UK National Screening Committee

Screening for dementia

External review against programme appraisal criteria for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Plain English summary

The term ’dementia’ covers a group of brain diseases that cause the gradual decline in thinking skills and the ability to perform everyday tasks such as washing and dressing. People with dementia may also develop problems with mental health and their behaviour that may be difficult for other people to manage or deal with.

Dementia is rarely diagnosed in younger people, but as people age, it becomes more common. About 10% of people over the age of 70 have dementia. In 2016, dementia was the most common cause of death for women and the second most common cause of death for men.

The aim of a screening programme for dementia in adults is to identify people with the condition as early as possible and offer them a treatment that would cure or delay the progression of their illness.

The UK NSC published its last review on screening for Alzheimer’s disease in 2009 and for dementia in 2014. For both these reviews, the evidence was limited. It was unclear whether screening tests could identify people with dementia in the early stages of the disease. Also, there was no evidence of effective treatments to cure or delay the condition from getting worse in a screened population.

This review will update the UK NSC’s recommendations from 2009 and 2014.

The main questions in this review are:

1. What are the early signs and risks that mean someone is likely to develop dementia when they have already developed some deterioration in thinking skills (known as mild cognitive impairment)?
2. Are there screening tests that can accurately identify people likely to have dementia?
3. Are there any treatments with better outcomes for people who have been diagnosed with dementia early?
4. Do the public, patients and health professionals think dementia screening is acceptable?

Recommendation

The main conclusions of this review are:

- in people whose thinking skills have already started to decline (known as mild cognitive impairment), the main signs and risks that they are likely to develop dementia are not clear;
- there are no screening tests that can accurately identify people in the general population with dementia who do not already have symptoms;
- there is no evidence of effective treatments in a screened population;
- there are mixed views by the public, patients and health professionals about the acceptability of dementia screening.

The UK NSC still cannot recommend population screening for dementia in adults. There is not enough new evidence to change the conclusions of the previous UK NSC reviews.

Executive summary

Purpose of the review

This review on screening for dementia will update 2 UK NSC recommendations; the 2009 ‘Screening for Alzheimer’s disease’ update and the 2014 ‘Screening for dementia’ review. The current review will assess the quality and volume of evidence published since 2008 for evidence of the prognosis of mild cognitive impairment, conversion to dementia, and the acceptability of dementia screening as well as evidence from 2013 for effective screening tests and interventions for dementia.

Background

Dementia is a clinical syndrome characterised by a progressive decline of brain functioning resulting in multiple cognitive and behavioural symptoms that worsen over time. This can include memory loss, problems with reasoning and communication, a change in personality, and a reduction in a person's ability to carry out daily activities, such as shopping, washing, dressing and cooking.

The progression of dementia will vary from person to person and each will experience dementia in a different way, so although people may often have some of the same general symptoms, the degree to which these affect each person will vary. People affected by dementia have a range of complex needs with high levels of dependency and morbidity, which hinder their ability to live independently and can challenge the skills and capacity of carers and health and social care services.

The most common types of dementia are: Alzheimer's disease (AD), vascular dementia, mixed dementia, dementia with Lewy bodies and frontotemporal dementia. Expert consensus suggests that in the UK approximately 62% of dementia is due to Alzheimer's disease.

Rates of dementia within the population vary by age and gender with higher rates observed in women and in people in older age groups. The overall prevalence of dementia in people over 70 years of age is 9.26%,

for women prevalence is 10.7% and men 7.4%. In 2016 dementia was the most common cause of death in the UK for women and for men it was the second most common cause of death after cardiovascular disease.

Mild cognitive impairment (MCI) differs from dementia in that although it affects brain functioning, it is not severe enough to impact on independence in daily life. People with MCI may go on to develop Alzheimer's disease or other types of dementia, but many individuals do not show progression of their cognitive deficits and may revert back to normal cognition. MCI is a recently defined condition and was introduced into the Diagnostic Statistical Manual 5th edition in 2013 as minor neurocognitive impairment. Prevalence of MCI varies considerably depending on how MCI criteria have been applied and the definition used.

Two major sub-types of MCI have been identified; these are amnestic (aMCI) involving episodic memory impairment (with or without other cognitive deficits) and non-amnestic (naMCI) involving cognitive impairment in cognitive domains other than memory. Amnestic MCI is considered more likely to progress to dementia than naMCI.

Focus of the review

The purpose of this review is to provide an evaluation of the volume and direction of the literature on key issues for screening for dementia published since the previous UK NSC reviews. Therefore, this review will focus on the following key questions:

1. what is the clinical prognosis of mild cognitive impairment (MCI), especially its association with dementia?
2. what is the accuracy of cognitive assessment tools as screening tests for any class of dementia and for MCI?
3. what is the accuracy of biomarkers and brain imaging as screening tools for any class of dementia and for MCI?
4. what is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of MCI?
5. what is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of dementia?
6. is screening for MCI and/or dementia clinically, socially and ethically acceptable to health professionals and the public?

Recommendation under review

The current UK NSC recommendation is that systematic population screening for dementia is not recommended in the UK.

A review of screening for Alzheimer's disease against the UK NSC criteria was completed in 2009. This was followed by another review in 2014 which included all types of dementia and MCI. The 2014 review found there was insufficient information on the epidemiology and natural history of mild cognitive impairment and its clinical progression to dementia.

The 2014 review concluded that cognitive assessment tools for dementia are not sufficiently accurate to be used in primary care or community care settings in the whole population. There was no validated test with agreed cut-off levels and all the cognitive assessment tools exhibited a wide range of sensitivity and specificity scores. The 2014 review did not examine evidence on the clinical utility and applicability of potential new biomarkers for routine screening, but this was briefly considered in the 2009 review for Alzheimer's disease. Evidence was confined to the use of biomarkers as confirmation testing of an AD diagnosis only when individuals have already manifested specific cognitive complaints.

Findings and gaps in the evidence of this review

The volume, quality and direction of new evidence published since 2008 for questions 1, 3 and 6 and since 2013 for questions 2, 4 and 5 do not indicate that the changes in the evidence base are sufficient to change the current recommendation not to screen for dementia in the UK. Key areas of concern relate to:

- uncertainties about the prognosis of MCI and sub-types of MCI in relation to dementia
- available cognitive screening tools for MCI and dementia lack evidence of clinical utility and that they would be effective as a screen detection method in the UK population
- no studies examining the clinical utility of biomarkers and brain imaging for the screen detection of MCI or dementia
- no studies examining pharmacological or non-pharmacological treatments in people with screen-detected MCI or dementia were identified

- the views reported in studies that examine perceptions, attitudes and views about screening for dementia described mixed views voiced by the general public and a lack of support for dementia screening by dementia specialists.

Recommendations on screening

The current recommendation not to introduce a systematic UK population screening programme for dementia should be retained.

Limitations

An important limitation of the evidence base is that MCI is a heterogeneous condition and diagnosis of people in the included studies are likely to be based on criteria from key studies and consensus of clinicians rather than an agreed definition. A clinical definition of MCI was introduced to the Diagnostic Statistical Manual 5th edition in 2013 but this will not have been used for most of the research studies included in this review.

This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by one information scientist, and further appraisal and study selection by one reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Evidence uncertainties

Research to determine homogenous sub-groups of MCI with clear aetiologies and trajectories is ongoing. Although there are some factors, such as the presence of the e4 allele of the gene APOE and multi domain cognitive impairments which are linked to aMCI and conversion to Alzheimer's disease, the evidence as a whole is inconsistent. Differences in research outcomes may well be down to how MCI diagnostic criteria have been operationalised, differences in setting where the criteria have

been applied, selection of subjects and length of follow up of longitudinal studies.

Based on current evidence there are uncertainties about whether cognitive screening tests for MCI and dementia would perform accurately in a large population-based screening program in the UK and their clinical utility has not been evaluated.

The lack of studies examining the effectiveness of interventions in a screen-detected population is partly a reflection of the limited evidence about what works for symptomatic patients. Overviews of pharmacological and non-pharmacological interventions report limited or no benefit of interventions for preventing or delaying the progression of MCI or dementia diagnosed through any clinical pathway.

As dementia has a relatively high prevalence in older age groups, future evidence needed to inform policy on screening for dementia should include large studies with homogenous populations and focus on the clinical utility of the tests.

Introduction and approach

Background

Dementia is a clinical syndrome characterised by a progressive decline of brain functioning resulting in multiple cognitive and behavioural symptoms that worsen over time. This can include memory loss, problems with reasoning and communication, a change in personality, and a reduction in a person's ability to carry out daily activities, such as shopping, washing, dressing and cooking[1].

The progression of dementia will vary from person to person and each will experience dementia in a different way so although people may often have some of the same general symptoms, the degree to which these affect each person will vary. People affected by dementia have a range of complex needs with high levels of dependency and morbidity, which hinder their ability to live independently and can challenge the skills and capacity of carers and health and social care services[2].

The most common types of dementia are: Alzheimer's disease (AD), vascular dementia, mixed dementia, dementia with Lewy bodies and frontotemporal dementia. Expert consensus suggests that in the UK approximately 62% of dementia is due to Alzheimer's disease. Table 1 shows the estimated proportions of each type of dementia in those aged over 65[2].

Table 1. Types of dementia

Type of dementia	Proportion of all dementias
Alzheimer’s disease	62%
Cerebrovascular disease	17%
Mixed aetiologies (combining symptoms of more than 1 type of dementia)	10%
Dementia with Lewy bodies	4%
Parkinson's disease dementia	2%
Frontotemporal dementia	2%
Other causes (e.g. alcoholism, Creutzfelt-Jacob disease, Picks disease, Acquired immunodeficiency Syndrome)	3%

Source: Prince et al (2014)[2]

Among people aged under 65 these proportions are different, with a lower contribution from vascular dementia and a greater relative incidence of frontotemporal dementia while in people aged 90 and over, mixed dementias are a larger proportion of the total[2].

Estimates of prevalence and incidence of dementia for the different countries in the UK come from different sources which are submitted to the global burden of disease (GBD) study[3]. This initiative aims to measure disability and death from a multitude of causes worldwide by collecting data from 195 countries. Using this data the GBD has estimated that the number of people with dementia in the UK in 2016 was 838,693 (95% CI: 708,801–995,493). There were 162,894 (95% CI: 135, 147–196,580)[3] new cases in 2016 and an estimated 60,525 (95% CI: 51,581 – 70,828)[3] deaths attributable to the condition.

Rates of dementia within the population vary by age and gender with higher rates observed in women and in people in older age groups. Table 2 shows the lowest prevalence rates per 100,000 population in men aged 65–69 (1,329; 95% CI: 1,011–1,734) whilst the highest are in women aged 90–94 (29,783; 95% CI: 23,664–36,799).

Table 2. Prevalence of Alzheimer's disease and other dementias per 100,000 population in the UK in 2016 by age and gender

	Both sexes	Females	Males
Age group	Rate per 100,000 pop (95%) CI	Rate per 100,000 pop (95% CI)	Rate per 100,000 pop (95% CI)
65 to 69	1429 (1086–1859)	1524 (1160–1975)	1329 (1011–1734)
70 to 74	3041 (2290–3974)	3147 (2364–4087)	2926 (2214–3806)
75 to 79	6038 (4608–7746)	6206 (4728–7957)	5845 (4443–7492)
80 to 84	11107 (8507–14506)	11718 (8933-15276)	10312 (7865–13499)
85 to 89	18074 (14211–22519)	19950 (15581–24804)	15100 (11884–19064)
90 to 94	26465 (21069–32748)	29783 (23664–36799)	19318 (15360–24035)
70+ years	9251 (7749–11086)	10686 (8955–12736)	7431 (6121–9011)
All Ages	1283 (1084–1523)	1602 (1358–1898)	955 (801–1135)

Source: Global Burden of Disease Study 2016 (GBD 2016)[3]

Table 3 shows percentage prevalence by age group and gender.

Table 3. Percentage prevalence of Alzheimer's disease and other dementias in the UK population in 2016 by age and gender

Age band	% prevalence both sexes	95% Upper and lower CI	% prevalence Females	95%Upper and lower CI	% prevalence Males	95% Upper and lower CI
65 to 69	1.43	1.09–1.87	1.53	1.16–1.98	1.33	1.02-1.74
70 to 74	3.05	2.29–3.98	3.15	2.37–4.1	2.93	2.22–3.82
70+	9.26	7.76–11.1	10.7	8.96–12.75	7.44	6.13–9.02
75 to 79	6.04	4.61–7.76	6.21	4.73–7.96	5.85	4.45–7.5
80+	16.46	13.46–20.1	18.63	15.34–22.56	13.14	10.56–16.2
80 to 84	11.11	8.51–14.52	11.72	8.94–15.28	10.32	7.87–13.51
85 to 89	18.08	14.22–22.53	19.96	15.59–24.81	15.11	11.89–19.07
90 to 94	26.47	21.08–32.76	29.79	23.67–30.41	19.32	15.37–32.76
95+	36.23	27.63–48.28	39.73	36.81–52.85	24.03	18.1–48.28

Source: Global Burden of Disease Study 2016 (GBD 2016)[3]

Table 4 shows that the lowest rates of new cases of dementia are in men aged 65–69 (247, 95%CI: 158–357) whist the rate is highest in women aged 90–94 (7,157, 95% CI: 4,591–10,468).

Table 4. Incidence of Alzheimer's disease and other dementias per 100,000 population in the UK in 2016 by age and gender

	Both sexes	Females	Males
Age group	Rate per 100,000 pop (95% CI)	Rate per 100,000 pop (95% CI)	Rate per 100,000 pop (95% CI)
65 to 69	256 (164–371)	265 (171–383)	247 (158–357
70 to 74	538 (350–760)	541 (350–764)	534 (351–750
75 to 79	1104 (710–1664)	1143 (731–1721)	1059 (687–1575)
80 to 84	2016 (1334–2852)	2254 (1484–3239)	1707 (1141–2394)
85 to 89	3442 (2336–4785)	4080 (2772–5688)	2432 (1650–3372)
90 to 94	6125 (3918–8971)	7157 (4591–10468)	3904 (2493–5720)
70+ years	1823 (1477–2222)	2226 (1797–2732)	1312 (1053–1620)
All Ages	249 (207–301)	328 (270–397)	169 (140–203)

Source: Global Burden of Disease Study 2016 (GBD 2016)[3]

For those aged ≥70 in the UK in 2016 Alzheimer's disease was ranked most common cause of death for women and second most common cause of death in men (Table 5)[3]. Between 1990 and 2016 there has been an increase of around 28% in the rate of deaths per 100,000 population from AD for both men and women[3]. Deaths attributable to AD in 1990 and 2016 in the UK found in women this has increased by 50.6% and in men by 78.3%. A combination of factors including a decrease in other causes of death such as cardiovascular disease over the same period, an aging population and increases in detection has meant that AD has become a more common cause of death in 2016 than in 1990.

Table 5. Death rate from Alzheimer's disease in 1990 and 2016 in the UK

	Death Rate per 100,000 pop (95% CI)	% Change of death rate 1990 - 2016	% Of total deaths (95% CI)	% Change in 1990 - 2016	Rank of cause of death
Female 1990	705 (594-841)		10.6% (9.0-12.6%)		3rd
Female 2016	902 (764 1049)		16.0% (13.6-18.7%)		1st
		27.9%		50.6%	
Male 1990	411 (339-507)		4.7% (3.9-5.8%)		6th
Male 2016	529 (441-639)		8.5% (7.0-10.2%)		2nd
		28.8%		78.3%	

Source: Global Burden of Disease Study 2016 (GBD 2016)[3]

Age is the strongest known risk factor for dementia, but it does not exclusively affect older people and early onset dementia (defined as the onset of symptoms before the age of 65 years) accounts for up to 9% of cases[4]. Other unmodifiable risk factors include gender and an inherited genetic predisposition. Growing evidence suggests a relationship between the development of cognitive impairment and life-style related risk factors that are shared with other non-communicable diseases such as cardiovascular disease, diabetes and cancer. These risk factors include physical inactivity, obesity, unhealthy diets, tobacco use and harmful use of alcohol. Additional potentially modifiable risk factors include mid-life depression, low educational attainment, social isolation, and cognitive inactivity[4].

A dementia preventative intervention model called World Wide Fingers is emerging out of a Finnish trial that showed that a multi component lifestyle intervention based on management of vascular and lifestyle risk factors for Alzheimer's disease and other dementias can prevent the decline of cognition in people aged 60 to 77[5]. Based on the theory that, as with other non-communicable diseases, modifying lifestyle factors may reduce incidence, the model will be tested in Europe, the US, China, Singapore, Japan and Canada. Counselling and group activities are the core components of the intervention with local adaptations to take account of geographical, ethnic and cultural differences between populations[6].

Mild cognitive impairment

Mild cognitive impairment (MCI) differs from dementia in that although it affects brain functioning, it is not severe enough to impact on independence in daily life. The construct of MCI is a recent development to define mild cognitive decline which is neither due to normal aging nor to dementia[7]. MCI has evolved to accommodate various outcomes and aetiologies through the development of sub-types with greater potential for clinical and prognostic value. A clinical definition of MCI was first included in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (2013)[8] and prior to this, diagnosis was by clinical consensus or criteria published in key research papers. Amnestic MCI (aMCI) involves episodic memory impairment, with or without the impairment in other cognitive domains and is most likely to progress to AD. Non-amnestic MCI (naMCI) involves impairment of other cognitive domains rather than memory and is considered more likely to progress to other types of dementia[7]. People with MCI of either type can remain stable with the same level of cognitive impairment, progress to dementia or revert to normal cognition[7,9]. The purpose of including questions about MCI in this review is to assess whether identifying people with MCI using a screening tool will effectively detect those who will go on to develop dementia within the context of a population based screening programme.

Published prevalence figures for MCI in the UK are limited although Sachdev et al (2015)[7] reported results from 11 cohort studies including one from the UK. Crude prevalence of MCI pooled from the studies was 5.9% (95% CI: 5.5–6.3) and increased with age from 4.5% among 60–69 year olds to 7.1% in 80–89 year olds. The average age and sex

standardised prevalence for people aged 60–89 was 5.8% (95%CI: 5.4–6.2). There were no significant differences between men and women in any of the age groups. The overall crude prevalence of aMCI pooled from 9 studies was 2.0% and naMCI 3.9%. Prevalence estimates of aMCI did not differ across age groups by sex but naMCI was greater in men aged 70–79 compared with those aged 60–69 (p= 0.024) and in women aged 80–89 compared with those aged 70–79 (p= 0.026)[7].

In contrast Petersen et al (2014)[9] reported MCI prevalence from 16 population based studies that range from 7.7% to 42.0% with an average of 18.9%. The studies found no strong agreement about differences in prevalence by gender although authors noted 2 studies reporting an association of higher prevalence of MCI in men.

Current policy context and previous reviews

A review of screening for Alzheimer's disease against the UK NSC criteria was completed in 2009[10]. This was followed by another review in 2014[11] which included all types of dementia and MCI. The evidence examined in these reviews informed the current recommendation from the UK NSC that systematic population screening for dementia should not be offered.

The 2014 review[11] found there was insufficient information on the epidemiology and natural history of mild cognitive impairment and its clinical progression to dementia. In particular, uncertainties remained with regard to the relationship between dementia and mild cognitive impairment. This is because while MCI could represent a potential early symptomatic stage of the condition it could also represent a significant source of over-diagnosis.

The 2014 review[11] concluded that cognitive assessment tools for dementia are not sufficiently accurate to be used in primary care or community care settings in the whole population. A single validated test with an agreed cut-off was not found and all the cognitive assessment tools exhibited a wide range of sensitivity and specificity scores. The 2014 review[11] did not examine evidence on the clinical utility[i] and applicability of potential new biomarkers for routine screening, but this was briefly

[i] The likelihood of improved outcomes from the use of the test

considered in the 2009 review[10] for Alzheimer's disease. Evidence was confined to the use of biomarkers as confirmation testing of an AD diagnosis only when individuals have already manifested specific cognitive complaints.

Detail about the findings of the 2014 review[11] in this update is given in the quality level synthesis for each key question below.

Objectives

The objective of this review is to provide an evaluation of the volume and direction of the literature on key issues for screening for dementia published since the previous UK NSC reviews. Therefore, this review will focus on the following key questions: the clinical prognosis of MCI and its relationship with dementia; the accuracy of dementia and MCI screening tools, including biomarkers and brain imaging; the effectiveness of pharmacological and non-pharmacological interventions after a diagnosis of dementia or MCI and the acceptability of a dementia screening pathway.

Table 6. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	1. What is the clinical prognosis of MCI, especially its association with dementia?	9
	THE TEST		
4 5	There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	2. What is the accuracy of cognitive assessment tools as screening tests for any class of dementia and for MCI?	4
		3. What is the accuracy of biomarkers and brain imaging as	0

	Criterion	Key questions	Studies Included
		screening tools for any class of dementia and for MCI?	
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	4. What is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of MCI?	0
		5. What is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of dementia?	0
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened		
	THE SCREENING PROGRAMME		
12	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	6. Is screening for MCI and/or dementia clinically, socially and ethically acceptable to health professionals and the public?	5

Methods

The current review was conducted by Solutions for Public Health (SPH) in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 11 May 2018 to identify studies relevant to the questions detailed in Table 6.

Eligibility for inclusion in the review

The following review process was followed:

1. each abstract was reviewed against the inclusion/ exclusion criteria by one reviewer. Where the applicability of the inclusion criteria was unclear from the abstract, the article was included at this stage in order to ensure that all potentially relevant studies were captured
2. full text articles required for the full text review stage were acquired
3. each full-text article was reviewed against the inclusion/ exclusion criteria by one reviewer, who determined whether the article was relevant to one or more of the review questions
4. any queries at the abstract or full text stage were resolved through discussion with a second reviewer
5. the review was quality assured by a second senior reviewer, not involved with the writing of the review in accordance with SPH's quality assurance process.

Eligibility criteria for each key question are presented in Table 7 below.
For questions 1, 3, and 6 only peer reviewed studies published in English between January 2008 and 11 May 2018 were eligible for consideration in the review. For question 2, 4 and 5, studies published between 12 August 2013 and 11 May 2018 were eligible for consideration in the review.

A total of 10,925 unique references were identified and sifted by an information scientist by title and abstract for potential relevance to the review. An SPH reviewer assessed 1,308 titles and abstracts for further appraisal and possible inclusion in the final review.

Overall, 112 studies were identified as possibly relevant during title and abstract sifting and further assessed at full text (see Appendix 2 for study flowchart).

Table 7. Inclusion and exclusion criteria for the review key questions

	Inclusion criteria							Exclusion criteria
Key question	**Population**	**Target condition**	**Intervention**	**Reference Standard**	**Comparator**	**Outcomes**	**Study type**	
1. What is the clinical prognosis of MCI, especially its association with dementia?	Adult population with MCI	MCI	N/A	N/A	N/A	Dementia Remission of symptoms and return to normal cognitive function Fluctuation of MCI symptoms Stable presence of MCI symptoms	Case-control studies, cohort studies and systematic reviews of any of the above	Case reports, case series, narrative reviews
2. What is the accuracy of cognitive assessment tools as screening tests for any class of dementia and for MCI?	Adults living in the community who are not already suspected of having dementia and/or MCI and do not have any	Dementia and MCI	Cognitive assessment tools such as the Mini-Mental State Examination (MMSE), clock drawing test, and any other screening tool/questionnair	Formal diagnosis of dementia and MCI consistent with UK recommendations or guidelines	N/A	Sensitivity, specificity, positive predictive value, negative predictive value	Randomised controlled trials, cross-sectional studies, cohort studies, systematic reviews	Case reports, case series, narrative reviews

	co-morbidity affecting cognitive performanc e		e that can be self-administered or delivered by a clinician in a primary care setting					
3. What is the accuracy of biomarkers and brain imaging as screening tools for any class of dementia and for MCI?	Adults living in the community who are not already suspected of having dementia and/or MCI and do not have any co-morbidity affecting cognitive performanc e	Dementia and MCI	Any biomarker used as a screening tool Brain imaging, including PET and MRI	Formal diagnosis of dementia and MCI consistent with UK recommendatio ns or guidelines	N/A	Sensitivity, specificity, positive predictive value, negative predictive value	Randomise d controlled trials, cross-sectional studies, cohort studies, systematic reviews	Case reports, case series, narrative reviews
4. What is the reported effectiveness of pharmacologica l and non-pharmacologica l interventions after a screen-detected diagnosis of dementia?	Adult population with screen-detected dementia	Dementia	Any pharmacological approach such as acetylcholineste rase inhibitors (donepezil, galantamine and rivastigmine) and memantine Any non-pharmacological	N/A	Any or none	Reduced cognitive decline Improved physical functions Reduced depression Reduced challenging behaviour e.g. aggression,	Randomise d controlled trials, cohort studies, and systematic reviews of any of the above	Case reports, case series, narrative reviews

			approaches including occupational therapy, social support, assistance with daily activities, home nursing, etc			restlessness and wandering Improved independence and general quality of life Reduced mortality		
5. What is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of MCI?	Adult population with screen-detected MCI		Any pharmacological approach such as acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) and memantine. Any non-pharmacological approaches such as cognitive rehabilitation, including the use of mnemonics, association strategies, and computer-assisted training programmes	N/A	Any or none	Reduced cognitive decline Prevention of the progression to dementia Improved physical functions Reduced depression Improved independence and general quality of life Reduced mortality	Randomised controlled trials, cohort studies, and systematic reviews of any of the above	Case reports, case series, narrative reviews
6. Is screening for MCI and/or dementia clinically,	Adult population	Dementia and MCI	Dementia and MCI screening	N/A	Usual care or none	Perceptions, views and/or attitudes and/or	Randomised controlled trials, cohort	Opinion based articles

socially and ethically acceptable to health professionals and the public?		experiences of patients and carers, and health and social care professionals Ethical, moral and cultural issues in the context of the perception of patients, carers and practitioners	studies, and systematic reviews of any of the above Qualitative, quantitative and mixed methods studies are all eligible for inclusion

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- meta-analysis: Center for evidence based management, critical appraisal of a meta-analysis or systematic review
- systematic reviews: Critical Appraisal Skills Programme (CASP) systematic review checklist
- cohort studies: Critical Appraisal Skills Programme (CASP) cohort Study Checklist
- qualitative studies: Critical Appraisal Skills Programme (CASP) qualitative research checklist.

Results of the quality assessments are presented in the summary and appraisal of individual studies in Appendix 3.

Databases/sources searched

A systematic search of 4 databases (Medline, Embase, PsycINFO and Cochrane) was conducted on 11 May 2018 to identify studies relevant to the questions detailed in Table 6. The search strategy is presented in Appendix 1.

Question level synthesis

Criterion 1 — Association between MCI and dementia

The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Question 1 – What is the clinical prognosis of mild cognitive impairment (MCI), especially its association with dementia?

The 2009 UK NSC evidence review[10] did not address the question of MCI and its prognosis in relation to dementia. The 2014 UK NSC evidence update[11] considered whether MCI was an early symptomatic phase of dementia and reported results from a key systematic review (Mitchell et al 2009[12]) suggesting that less than a quarter of people with MCI had gone on to develop dementia over periods between 3 and 10 years. The proportion of people with MCI who returned to normal cognition over time was reported as between 10 and 20% but there was no means of distinguishing between those people with MCI who would have a remission and those who would develop dementia.

Eligibility for inclusion in the review

Population: Adult population with MCI

Intervention: N/A

Outcomes:
- progression to dementia
- remission of symptoms and return to normal cognitive function
- fluctuation of MCI symptoms
- stable presence of MCI symptoms

Comparator: N/A

Study design: Case-control studies, cohort studies and systematic reviews of any of the above

Date and language: English peer reviewed publications from January 2008

Description of the evidence

Database searches yielded 10,925 results, of which 228 were judged to be relevant to this question and 20 abstracts met the criteria for full text review. After review of the full texts, 9 publications reporting prognosis of MCI and predictors of conversion to dementia were included. The remaining 11 studies were excluded after full text review either because they had been superseded by subsequent systematic reviews (n=4), they were focussed on risk factors of developing MCI (n=5), they were about modelling the trajectory of MCI (n=2).

Three systematic reviews and meta-analyses and 6 cohort studies examining rates of conversion of MCI to dementia and the factors which might predict conversion are included.

Discussion of findings

A study-level summary of data extracted from each included publication is presented in the summary and appraisal of individual studies in Appendix 3.

Of the included studies for question 1, 5 examine MCI (Canevelli et al 2016[13], Davis et al 2018[14], Cooper et al 2015[15] Clem et al 2017[16], and Diniz et al 2008[17]) and 4 examine aMCI (Jang et al 2018[18], Ferriera et al 2011[19], Scarabino et al 2016[20] and Santana et al 2018[21]).

Overall the evidence available about the prognosis and predictors of MCI converting to dementia is of moderate quality, with concerns being, small sample sizes, short or very varied follow up periods and the difficulty of standardising how an MCI diagnosis is made when a clinical definition has not been agreed. There are some concerns that publications included in meta-analyses and systematic reviews have not been assessed for quality. Much of the evidence is applicable to a UK population with all but one study having been carried out in Europe, the US and Canada.

An important limitation of the evidence base is that MCI is a heterogeneous condition with diagnosis based on criteria from key studies (Petersen et al 1999, 2014)[9 22] and consensus of clinicians prior to 2013 when more formal criteria for MCI were first published in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (2013)[8].

Predictors of conversion of MCI to dementia

The table below gives details of 6 studies that reported results of predictors of MCI conversion to dementia. Three small cohort studies[18,20,21] (n=88–338), from Europe and South Korea, report the presence and absence of different apolipoprotein E (APOE) alleles in people with MCI who develop dementia. People with either one or 2 APOE e4 alleles are more likely to convert from MCI to dementia than those without an e4 allele. The presence of APOE e4 allele increased the risk of conversion of single domain aMCI to multi domain aMCI or to AD compared with APOE e3/e3 and e3/e2 genotypes, (Odds Ratio (OR) 4.1, 95% Confidence Interval (CI): 1.2–13.6 p=0.02)[20].

One small cohort study (n=165)[21] from Portugal and one meta-analysis from 2008[17] examined differences in cerebral spinal fluid markers (CSF) in people with aMCI compared to healthy controls[17]and those with aMCI who converted to AD and those who did not[21]. The 3 biomarkers are total tau (T-tau), phosphorylated tau (P-Tau) and the β-amyloid 42 peptide (Aβ42). Higher levels of T-tau and P-tau indicate neurodegenerative pathology and low levels of Aβ42 indicate deposition of β amyloid protein in the brain.

There was a higher likelihood of conversion to AD with lower Aβ42 levels (OR 0.994, 95% CI: 0.991–0.998, p<0.001) and higher T-tau levels (OR 1.008 95% CI: 1.003–1.013, p<0.003) in CSF samples measured at baseline[21]. Of the sub-group of patients with abnormal Aβ42 and T-tau and/or P-tau levels, 27 (80%) converted to AD whereas only 5 (14%) of those with normal CSF biomarkers at baseline converted to AD (p<0.001). Follow up of patients was between 0.5 to 6.5 years, and in patients with shorter follow up periods there is less chance to detect a change in cognitive impairment in either direction.

Table 8. Predictors of conversion of MCI to AD from included studies for key question 1

Predictors of conversion of MCI to AD	Outcomes	Paper
APOE	APOE e4 alleles present (OR 4.71, 95%CI 2.12 -10.49) (n=338, follow up 3 years)	Jang et al (2018)[18] Longitudinal study South Korea
	APOE e4 more likely in group converted to AD versus the group that remained stable (58 vs 26%, p<0.001) (n=165, follow up 0.5 to 6.5 years)	Santana et al (2018)[21] Prospective cohort study Portugal
	At baseline (n=88, mean follow up 6.6 years) APOE e4/e4 homozygotes were present only in people with multi domain cognitive impairments and APOE e2 alleles were present only in people with single domain aMCI. People with multi domain aMCI were 3 times more likely to have APOE e4 alleles vs control group (p<0.001) and twice as likely as the single domain aMCI. APOE e4 allele increased risk of conversion of single domain aMCI to multi domain aMCI or to AD vs APOEe3/e3 and e3/e2 genotypes (OR 4.1, 95% CI 1.2-13.6 p=0.02). People at follow up who still had single domain aMCI (non-converters) had similar frequencies of APOE e2, e3, e4 to the control group (p=0.80). Participants who had converted to multi domain aMCI from single domain aMCI or AD at follow up had significantly different APOE e4 frequencies from the non-converters(p=0.014) and the controls (p<0.0001) Converted: APOE e3/e3 48%; APOE e3/e2 0; APOE e4/e3 71%; APOE e4/e4 75% Not converted: APOE e3/e3 52%; APOE e3/e2 100%; APOE e4/e3 29%; APOE e4/e4 25%	Scarabino et al (2017)[20] Prospective cohort study Italy
Biomarker CSF Aβ-42, CSF P-Tau, CSF T-Tau	Compared with people with normal cognition (n=142, n=157 and n=130) people with aMCI (n=130, n=169, and n=123) had significantly lower values of Aβ-42 (SMD -1.57, 95% CI: -2.30 to -0.84, zii= -4.23, p<0.0001); higher values of T-tau (SMD 1.52, 95%CI: 1.25 to 1.79, z= 11.06, p<0.0001) and higher values of P-tau (SMD 1.75, 95%CI: 0.99 to 2.51, z= 4.49, p<0.0001). (5 studies n= 326, follow up0.16 to 3 years)	Diniz et al (2008)[17] Meta-analysis
Biomarker CSF Aβ-	Lower CSF Aβ42 (OR 0.994, 95% CI 0.991 to 0.998, p<0.001)	Santana et al (2018)[21]

[ii] Z score enables a comparison of two scores that are from different normal distributions. A Z score of 0 indicates that the means of the two groups are similar, whereas a Z score of 2 indicates the intervention group is 2 standard deviations different to the mean

42, CSF T-tau	Higher CSF T-tau levels vs lower levels (OR 1.008 95% CI 1.003 to 1.013, p<0.003) (n=165, follow up 0.5 to 6.5 years)	Prospective cohort study Portugal
Neuro-structural imaging	(6 studies n=429, follow up 12 to 36 months)Left hippocampus and para-hippocampal gyrus within the left medial temporal lobe reduced volume in aMCI patients who converted to AD vs those who did not (p<0.01cluster extent threshold of 100 mm^3)	Ferreira et al (2011)19 Meta-analysis
MCI type	Visual and verbal domains affected vs visual domain only affected MCI (OR 4.30, 95%1.95-9.47) Multiple cognitive domains affected vs a single domain affected (OR 3.60 95% CI 1.78 to 7.29) (n=338, follow up 3 years)	Jang et al (2018)[18] Longitudinal study South Korea
Age	Older vs younger people likely have stable MCI at follow up (p=0.003, Cohens d 0.18) (n=1029, follow up 3 years)	Clem et al (2017)[16] Retrospective cohort study US
	Older vs younger people with MCI more likely to convert to dementia (OR 1.10, 95% CI 1.05 to1.15) (n=338, follow up 3 years)	Jang et al (2018)[18] Longitudinal study South Korea
	Older vs younger people with MCI more likely to convert to dementia (OR 1.099 95% CI 1.031 to 1.171) p<0.004 (n=165, follow up 0.5-6.5 years)	Santana et al (2018)[21] Prospective cohort study Portugal
Diabetes	7 studies(n=4124 follow 1.5 – 9 years)) showed increased risk of people with MCI and diabetes converting to dementia pooled OR 1.65, (95% CI 1.12-2.43)	Cooper et al (2015)[15] Meta-analysis
Metabolic syndrome	1 study (n=2097, follow up 3.5 years) showed metabolic syndrome and prediabetes predicted all cause dementia in people with aMCI (HR 7.80,1.29-47.20) and any type dementia	Cooper et al (2015)[15] Meta-analysis
Neuropsychiatric symptoms	4 (n=2549, follow up 2 to 5 years) studies predicted those with presence of neuropsychiatric symptoms have higher risk of conversion to dementia (n=not reported) pooled odds ratio of 3.11(95% CI 1.38-7.02).	Cooper et al (2015)[15] Meta-analysis
Mediterranean diet	1 study(n=1393, follow up 4.3 years) those at the highest adherence to the Mediterranean diet tertile had a 48 % (HR, 0.52; 95% CI, 0.30 – 0.91; p=0.02) less risk of developing AD than those in the lowest adherence tertile	Cooper et al (2015)[15] Meta-analysis

APOE-Apolipoprotein E, e2,e3, e4 are alleles of APOE, aMCI-amnestic mild cognitive impairment, naMCI - non-amnestic mild cognitive impairment, AD-Alzheimer's disease, CSF Aβ-42 -cerebral spinal fluid beta amyloid 42 peptide, CSF T-tau – cerebral spinal fluid total tau, OR-odds ratio, HR-hazard ratio, n- number, p- probability, CI- confidence interval, SMD- standardised mean difference

Cooper et al (2015)[15] carried out a meta-analysis of modifiable predictors that increased MCI conversion to dementia. Diabetes was associated with an increased risk of conversion from aMCI to AD and from any type MCI to all cause dementia (OR 1.65, 95% CI: 1.12–2.43) in 7 studies (n=4,124 follow up 1.5 – 9 years). In one study (n=2,097, follow up 3.5 years) metabolic syndrome and prediabetes predicted all cause dementia in people with aMCI (Hazard ratio (HR) 7.80, 95% CI: 1.29–47.20) and any type dementia. The neuropsychiatric inventory was used in 4 studies (n=2,549, follow up 2 to 5 years) and people with one or more symptoms (including depression, apathy, anxiety and irritability) predicted conversion from any type MCI to all cause dementia (pooled OR 3.11, 95% CI: 1.38–7.02). One study of adherence to the Mediterranean diet (n=1,393, follow up 4.3 years) found a lower risk of aMCI converting to AD. Those at the highest adherence tertile had 48% (HR 0.52, 95% CI: 0.30–0.91; p=0.02) less risk of developing AD than those in the lowest adherence tertile. Hypertension, hypocholesteraemia, smoking, alcohol use, years of education and homocysteine serum levels were inconsistent or showed no increased prediction of conversion of any type of MCI to dementia or aMCI to AD. A quality assessment was carried out by the authors who included papers with variable follow up periods from 12 months to 10 years.

One fair quality meta-analysis (Ferreira et al 2011)[19] of 6 imaging studies (n=429, follow up 12 to 36 months) examined the neuro-structural predictors of patients with aMCI converting to AD which suggested that one area of the brain had significantly reduced volume in aMCI patients who converted to AD vs those who did not (p<0.01cluster extent threshold of 100 mm^3). This was located in the left hippocampus and para-hippocampal gyrus within the left medial temporal lobe. The quality of the included studies was not reported but on the whole, they were small (range 13–339) with short follow up periods.

Jang et al (2018)[18]developed a model of conversion to dementia risk in the form of a nomogram[iii] based on neuropsychological tests of 338 people with aMCI and:

- the presence or absence of APOE e4

[iii] A nomogram is a diagram representing the relationship between 3 or more variables by means of number scales.

- the number of cognitive domains affected,
- the type of cognitive domains affected (visual and verbal domains)
- the severity of memory impairment

The authors developed a scoring system to predict risk for dementia conversion within 3 years. Scores over 140 have a positive predictive value (PPV) for dementia conversion of 0.85 (without APOE e4 test result) and 0.89 (with APOE e4 test result). If total points are 73 or lower, negative predictive value (NPV) for conversion to AD in 3 years is 0.89 (without APOE e4 test result) and 0.87 (with APOE e4 test result).

Conversion rates of MCI to dementia

There were 6 studies that observed or estimated the transition from MCI to dementia. The table below give the percentage reversion from MCI to normal cognition or conversion to dementia extracted from the studies.

Table 9. Conversion rates extracted from included studies for key question 1 where reported

Paper	MCI stable	MCI revert to normal	MCI progress dementia	Other outcome
In people with MCI				
Canevelli et al (2016)[13] Meta-analysis 6 population based studies (n=not reported, follow up 2-5 years)		29% (95% CI 22-37)		
Clem et al (2017)[16] Retrospective Cohort study (n=1778, follow up 3 years)	34%(596)	26%(461)	26%(463)	14%(258)
aMCI and naMCI				
Santana et al (2018)[21] Longitudinal study of people with aMCI (n=165, follow up 0.5-6.5 years)	48%(80)		52%(85)	
Davis et al (2018)[14] (n=18,103) at age 75 with aMCI after 1 year	75%		23%	2%
Davis et al (2018)[14] (n=18,103) at age 75 with naMCI after 1 year	90%			10%
Jang et al (2017)[18] Longitudinal study of people with aMCI (n=338, follow up 3 years)	25.7%(87)	8.0%(27)	66% (208)	

A systematic review and meta-analysis by Canevelli et al (2016)[13] pooled data of 25 studies of people with MCI in the community (15 studies) and clinic settings (10 studies) with at least a 2 year follow up (n=6,914 in 25 studies range 22 to 1,843). An 18% (95% CI: 14–22) reversion rate to normal cognition was found with meta-analysis, but the studies were small and had a high degree of heterogeneity (I^2=96.1%, p<0.001[iv]). A sub-group analysis of 6 better quality population based studies was performed resulting in a rate of reversion to normal cognition of 29% (95% CI: 22–37).

Davis et al (2018)[14] carried out a retrospective analysis of 18,103 people with data on the National Alzheimer's coordinating centre dataset in the US between 2005 and 2014. Using the data to model the rates of conversion, 75% of people presenting with MCI at age of 75, are predicted to still have MCI a year later, 23% will have transitioned to mild AD and 2% will have died. For those people aged 75 with non-AD cognitive impairment, a year later 90% will still have the same diagnoses and 10% will have died.

Clem et al (2017)[16] used the same data source as Davis et al (2018)[14] and extracted longitudinal data for 1,778 patients with a 3 year follow up. People who had stable MCI were likely to be:

- younger (p=0.003, Cohens d[v] 0.18);
- have fewer years of education (p=0.007, Cohens d 0.18);
- have fewer APOE4 alleles (p<0.001, 0.20);
- have lower clinical dementia rating scale scores (p<0.001, Cohens d 0.80);
- have higher Mini-mental state examination (MMSE) scores (p<0.001, Cohens d 0.63);
- have lower functional activities questionnaire scores (p<0.001 Cohens d 0.61);
- have naMCI compared to aMCI (p<0.00, Cohens d 0.16).

There are some important limitations in the quality of the evidence identified that examines the prognosis of MCI and prediction of

[iv] I^2, ranging from 0-100%, measures the degree of inconsistency across studies in a meta-analysis with 0% = no heterogeneity.

[v] Cohen's d is effect size as a measure of the difference in the two groups' means divided by the average of their standard deviations(d=0.2 is small effect, d=0.5 is medium effect and d=0.8 is a large effect)

progression to dementia. Studies typically have small sample sizes and vary considerably in their range of follow up periods. The shorter the follow up period the less likely the study will capture the point at which MCI has reverted to normal or progressed to dementia. The differences between studies in age of population, severity of MCI, type of MCI and definition of MCI used for diagnosis, makes it difficult to draw firm overall conclusions from the evidence base.

Research to determine homogenous sub-groups of the condition with clear aetiologies and trajectories is ongoing and although there are some factors such as the presence of APOE e4, multi domain cognitive impairments and diabetes which are linked to MCI and conversion to AD, the evidence is inconsistent. Most evidence examines conversion to AD rather than non-AD dementias such as Lewy body dementia and frontotemporal lobe dementia. Overall, the natural history of MCI remains uncertain. There would be a benefit to carrying out larger studies with longer follow up periods to examine whether people with MCI who returned to normal cognition or remained stable over the short to medium term changed cognitive status over the long term.

Summary of Findings Relevant to Criterion 1: Criterion not met[vi]

The evidence included to address key question 1 is of moderate quality with concerns about consistency, size of studies and follow up period with which to capture changes in cognitive impairment. The lack of a clinical definition for MCI adds to the difficulty in determining aetiology, predictors of conversion to dementia and overall prognosis of the condition.
While dementia is an important health problem, current evidence does not support the clear cut role of MCI as an 'early predictor' of future dementia and therefore this element of criterion 1 is not met.

[vi] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criterion 4 and 5 — Accuracy of screening tools

4. There should be a simple, safe, precise and validated screening test.

5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Question 2 – What is the accuracy of cognitive assessment tools as screening tests for any class of dementia and for mild cognitive impairment (MCI)?

The 2014[11] review considered the evidence on several cognitive assessment tools that could be used for testing for dementia in a primary care setting whilst the 2009 review[10] only examined those to test for AD. The findings of the 2014 review suggest that in primary care most of these tools appear to have a reasonable test performance for detecting dementia but less good performance for detecting MCI. For dementia the tools with the best test performance to detect dementia included the Mini-Mental State Examination (MMSE), the Clock drawing test (CDT), the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and the Mini-cog. For MCI, the CDT was much less likely to detect the condition but the MMSE, IQCODE and the Montreal Cognitive Assessment (MoCA) showed the most promising results. However, although individual studies showed adequate test performance of many of the tests, there was a wide range of sensitivity and specificity scores. The optimal cut-off point to detect dementia or MCI also varied between studies. Since the prevalence rates for dementia vary for different age groups, this had an impact on the positive and negative predictive value of the screening tests. In particular, the review found that even for the best studied test, i.e. the MMSE, the positive predictive value of the screening tool in people under the age of 85 was under 40%. This meant that, on further evaluation, the majority of people below 85 years old with a positive screening test result would be found not to have dementia, resulting in a high proportion of unnecessary referrals.

Eligibility for inclusion in the review

Population: Adults living in the community who are not already suspected of having dementia and/or MCI and do not have any co-morbidity affecting cognitive performance

Intervention: Cognitive assessment tools such as the Mini-Mental State Examination (MMSE), clock drawing test, and any other screening tool/questionnaire that can be self-administered or delivered by a clinician in a primary care setting

Reference standard: Formal diagnosis of dementia and MCI consistent with UK recommendations or guidelines, e.g. criteria from the Diagnostic and Statistical Manual of Mental Disorders' (DSM)

Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value

Study design: Randomised controlled trials, cross-sectional studies, cohort studies, systematic reviews

Date and language: Peer reviewed studies published in English since 12 August 2013

Description of the evidence

Database searches yielded 10,925 results, of which 322 were judged to be relevant to this question and 24 abstracts met the criteria for full text review. After review of the full texts, 4 publications, all meta-analyses reporting the performance of a range of cognitive assessment tools, were included. Three of the meta-analyses were Cochrane Collaboration reviews examining the accuracy of different screening tools to detect dementia in people living in the community and one examined the accuracy of a screening tool to detect MCI.

The remaining 20 studies were excluded because:

- the population were not living in the community and were already suspected of having dementia and/or MCI (18 studies)
- the study focused on MCI risk (one study)
- the study was included in the 2014 NSC evidence review for dementia screening (one study).

Discussion of findings

The quality of the 4 meta-analyses[23,24,25,26] carried out to synthesise the evidence of test accuracy are good. The study populations within the meta-analyses were geographically, culturally and educationally heterogeneous and it is unknown how well these results would apply to a UK population. Studies were of variable quality and typically small in size with concerns about participant recruitment and the administration of the reference and index tests. All the screening tests had a cut-off point where good sensitivities and specificities were reported. When PPVs and NPVs were calculated there was considerable variation due to the range of prevalence reported by the studies. MCI prevalence has been reported in the literature with variable rates probably due to differences in how the criteria to diagnose MCI are applied. For dementia studies, some studies had a higher prevalence than might be expected, possibly due to participant selection, for example older age groups will have higher prevalence.

A study-level summary of data extracted from each included publication is presented in the summary and appraisal of individual studies in Appendix 3.

One good quality meta-analysis (Carson et al 2018)[26] examined the accuracy of the Montreal Cognitive Assessment Tool (MoCA), a screening tool for MCI developed to distinguish between normal cognitive aging and MCI (Table 10). A cut-off score of 23 offered the highest accuracy with a sensitivity of 0.89 (95% CI: 0.81–0.96) and a specificity of 0.90 (95% CI: 0.84–0.96). Due to the uncertainty about MCI prevalence an additional PPV calculation was undertaken based on 5.8% prevalence (reported by Sachdev et al (2015) [7] and resulted in a PPV and NPV of 0.35 and 0.99.

Table 10. Included studies for key question 2 – accuracy of MoCA to identify people with MCI (Carson et al 2018[26], n=799)

Cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (prevalence 35%)	NPV (prevalence 35%)	PPV (prevalence 5.8%)≈	NPV (prevalence 5.8%)≈
23	0.89(0.81-0.96)	0.90(0.84-0.96)	0.83	0.94	0.35	0.99
24	0.94(0.88-1.0)	0.65(0.48 -0.80)	0.59	0.95	0.14	0.99
25	0.88(0.83-0.93)	0.75(0.69-0.82)	0.66	0.92	0.18	0.99
26	0.93(0.89-0.97)	0.79(0.70-0.86)	0.71	0.95	0.21	0.99

≈ Prevalence reported by Sachdev et al (2015) 60 to 89 yrs[7]

The 3 meta analyses examining accuracy of screening tools for dementia looked at the Mini-cog brief screening test (Seitz et al 2018)[23], the MMSE (Creavin et al 2016)[24] and the IQCODE (Quinn et al 2014)[25]. Each meta-analysis comprised a range of typically small studies with moderate to good sensitivities (0.76 to 1.0) and specificities (0.70 to 0.90) across tests and cut-off thresholds. Calculations of PPV reported by the studies ranged from 0.13 to 0.72, probably varying in response to different prevalence rates in the different populations tested. Using a standard prevalence rate of 9.26% (population >70 years, GBD 2013)[3] the PPV varied from 0.22 to 0.46 indicating that regardless of test or cut-off, screening would result in a high proportion of people with a false positive test result (i.e. confirmation by diagnostic clinical interview would show they do not have dementia).

Table 11. Included studies for key question 2 – accuracy of screening tools to identify people with dementia

Screening test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	Prevalence from study	PPV§ from study	NPV¬ from study	PPV using 9.26%^ prevalence (≥70 years)	NPV using 9.26%^ prevalence (≥70 years)	Study
Mini-Cog-	Standard criteria*	1.00(0.84 to 1.00)	0.85(0.81-0.89)	5.0%	0.72	1.00	0.40	1.00	Fuchs et al (2012)[27] (n=423) in Seitz et al (2018)[23]
	Standard criteria*	0.76(0.53-0.92)	0.73(0.68-0.77)	5.5%	0.13	0.89	0.22	0.97	Holsinger et al (2012)[28] (n=383) in Seitz et al (2018)[23]
MMSE-	24	0.85(0.74-0.92)	0.90(0.80-0.95)	7.4%(5.5 to 20.1)	0.45	0.98	0.46	0.98	Creavin et al (2016)[24] (15 studies n=10,969)
	25	0.87(0.78-0.93)	0.82(0.65-0.92)	8.4%(6.0 to 19.6)	0.31	0.99	0.33	0.98	Creavin et al (2016)[24] (10 studies n=5,894)
	24or5	0.97(0.83-1.0)	0.70(0.5-0.85)	13.8%(2.4 to 27.4)	0.34	0.99	0.25	0.99	Creavin et al (2016)[24] (7 studies n=8,442)
IQCODE-	3.3	0.78 (0.69-0.85)	0.77(0.63 to 0.86)	14%	0.37	0.96	0.26	0.97	Quinn et al (2014)[25] (4 English language version studies, (n=1,553)
	3.4	0.84(0.70-0.93)	0.80(0.65-0.90	14%	0.41	0.97	0.30	0.98	Quinn et al (2014)[25] (3 studies, n=988)
	3.5	0.82(0.75-0.87)	0.84(0.80 -0.88)	16%	0.49	0.96	0.34	0.98	Quinn et al (2014)[25] (3 studies, n=1,144)
	3.6	0.78(0.68 -0.86)	0.87(0.71-0.95)	15%	0.51	0.96	0.38	0.98	Quinn et al (2014)[25] (3 studies, n=1,215)

*Mini-cog brief screening test has 2 elements. The first is a delayed 3 word recall task and the second is the clock drawing test. A positive test is assigned it the delayed word recall is 0 out of 3, or if delayed recall is 1 and 2 and the clock drawing is abnormal; § PPV – Positive predictive value; ¬NPV – Negative predictive value; ^ Prevalence estimate of Alzheimer's disease and other dementias for those aged ≥70 years of age in the UK for 2016 (Global burden of disease 2016)[3]

Overall the studies examining performance of screening tools for MCI and dementia reported by the 4 good quality meta-analyses are small with high heterogeneity due to cultural, social and geographical variations. These factors might have some bearing on the wide range of values reported, limiting confidence in the point estimates, that otherwise remain largely unexplained.

In addition, the lack of evaluation of the clinical utility of the tests limits the conclusions that can be drawn about the applicability of the tests in the context of a UK screening programme.

The aim of identifying MCI with a screening tool would be to determine those people likely to develop dementia in the future. This tool is unlikely to be effective within a population based screening programme in detecting prodromal dementia due to uncertainties about:

- prevalence of MCI and its impact on performance of the MoCA tool
- the conversion rate of those people with MCI to dementia (i.e. with a positive screen for MCI, it is still not clear who would go on to develop dementia)
- the proportion of people who never have MCI but do develop dementia

Similarly, MCI detected as an incidental finding of a dementia screening tool would represent a potential source of overdetection, which has not been quantified.

Question 3 – What is the accuracy of biomarkers and brain imaging as screening tools for any class of dementia and for mild cognitive impairment (MCI)?

The 2009 evidence review[10] briefly considered potential new biomarkers for screening for Alzheimer's disease against the UK NSC criteria but found evidence was confined to the use of biomarkers as confirmation testing of an AD diagnosis only when individuals have already manifested specific cognitive complaints. The 2014 review[11] did not examine evidence on the clinical utility and applicability of potential new biomarkers and brain imaging for routine screening.

Eligibility for inclusion in the review

Population: Adults living in the community who are not already suspected of having dementia and/or MCI and do not have any co-morbidity affecting cognitive performance

Intervention: Any biomarker used as a screening tool such as brain imaging, including Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI)

Reference standard: Formal diagnosis of dementia and MCI consistent with UK recommendations or guidelines, e.g. criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM)

Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value

Study design: Randomised controlled trials, cross-sectional studies, cohort studies, systematic reviews

Date and language: Peer reviewed studies published in English from January 2008

Description of the evidence

Database searches yielded 10,925 results, of which 190 were judged to be relevant to this question and 30 abstracts met the criteria for full text review. After review of the full texts, no publications reporting performance about biomarker tests met the eligibility criteria for inclusion. The 30 studies were excluded after full text review because:

- the test described was not a potential screening test (7 studies)
- the population were not adults living in the community who are not already suspected of having dementia and/or MCI (18 studies)
- the test examined conversion of people with MCI to dementia (2 studies)
- the study was about assessing dementia risk (one study)
- the study was included in the 2014 NSC evidence review for dementia screening (2 studies).

In the absence of any studies examining the use of biomarkers and brain imaging as a method of screening patients who are not already suspected of having dementia, a brief general discussion of the evidence base for the use of biomarkers and brain imaging for the diagnosis of dementia is included.

Discussion of findings

No studies examining the accuracy of biomarkers and brain imaging as screening tools for any class of dementia in adults living in the community who are not already suspected of having dementia and/or MCI were identified.

The current evidence about biomarkers for dementia and MCI is focussed on using them as a method of confirming an already suspected diagnosis. Biomarkers of functional impairment, neuronal loss, and protein deposition that can be assessed by neuroimaging (i.e. MRI and PET) or CSF analysis are increasingly being used to diagnose dementia in research studies and specialist clinical settings. They are also used in combination to aid diagnosis as it is thought that higher accuracy can be achieved with a combination of markers (e.g. protein deposition and neuroimaging) despite inconsistent findings of performance (Noel-Storr et al 2013, Frisoni et al 2017)[29,30]

There is a large body of literature about biomarkers for dementia and MCI. However, the validation of the clinical usefulness of the tests is limited due to considerable variation in methodology and reporting, the selection of non-representative patients, blinding within studies and standardisation of laboratory tests (Noel-Storr et al 2013)[29.]

A strategic five-phase plan has been developed by the ‘Geneva taskforce for the strategic road map to the biomarker based diagnosis of Alzheimers disease’ to foster the clinical validation of biomarkers in Alzheimer's disease, adapted from the approach for cancer biomarkers (Frisoni et al 2017). Sufficient evidence of analytical validity is available for all biomarkers, but their clinical validity is incomplete and clinical utility largely unexamined. Research priorities include the standardisation of the readout of the assays and thresholds for normality, the evaluation of their performance in detecting early disease, the development of diagnostic

algorithms comprising combinations of biomarkers, and the development of clinical guidelines for the use of biomarkers in qualified memory clinics (Frisoni et al 2017)[30].

Summary of Findings Relevant to Criteria 4 and 5: Criteria not met[vii]

Question 2 and 3 considered for these criteria were about the effectiveness of screening methods to accurately detect people with dementia and/or MCI living in the community who are not already suspected of having the condition. Question 2 addressed cognitive screening tools whilst question 3 was focussed on the use of biomarkers and brain imaging.

There is good quality evidence from a small meta-analysis of validation studies that the MoCA screening tool may be able to detect MCI in a population but the variation between detection rates in studies are largely unexplained. In addition this tool is unlikely to be effective within a population based screening programme in detecting prodromal dementia due to uncertainties about:

- the conversion rate of those people with MCI to dementia (i.e. with a positive screen for MCI, it is still not clear who would go on to develop dementia)
- the proportion of people who never have MCI but do develop dementia

Similarly, MCI detected as an incidental finding of a dementia screening tool would represent a potential source of overdetection, which has not been quantified. More work on determining an accurate prevalence rate using the recently agreed clinical definition of MCI and larger studies of test accuracy and clinical utility of detecting MCI are needed to strengthen

[vii] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

the evidence.

There is good quality consistent evidence from a systematic review and meta-analysis that the MMSE may detect people with dementia in asymptomatic populations with a cut-off or 24 or 25. However, with the best PPV of 0.46 a significant proportion of those people who screen positive will not have dementia with confirmation testing at clinical assessment.

The study populations within the 4 meta-analyses for question 2 were geographically, culturally and educationally heterogeneous and, although this may have a bearing on the large variation in results, this variation is largely unexplained. It is unknown how well these results would apply to a UK population. Studies included in the meta-analyses are typically small and the clinical utility of the tests were not evaluated.

No studies were identified that examined the effectiveness of the use of biomarkers and brain imaging to detect MCI or dementia in adults living in the community who are not already suspected of having dementia and/or mild cognitive impairment.

These criteria are not met.

Criterion 9 and 11 — Effectiveness of interventions

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Question 4 – What is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of dementia?

The UK NSC's 2009 review did not identify any pharmacological or non-pharmacological treatments for people with screen-detected AD. The UK NSC's 2014 evidence review[11] identified a number of systematic reviews covering several potential treatments for dementia. Overall there was a lack of strong positive evidence for the benefit of the treatments considered for people with dementia or their families/carers. When statistically significant results were found, the effect sizes were generally small which raises questions about the clinical significance of the findings. The studies included people with mild to moderate dementia who were not screen-detected so the application of the findings to screen-detected cases was unclear.

Eligibility for inclusion in the review

Population: Adult population with screen-detected dementia

Intervention: Any pharmacological approach (e.g. acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine and memantine) and

any non-pharmacological approaches (e.g. occupational therapy, social support, assistance with daily activities and home nursing)

Comparator: Any or none

Outcomes:

- reduced cognitive decline
- improved physical functions
- reduced depression
- reduced challenging behaviour e.g. aggression, restlessness and wandering
- improved independence and general quality of life
- reduced mortality

Study design: Randomised controlled trials, cohort studies, and systematic reviews of any of the above

Date and language: English language published since 12 August 2013

Description of the evidence

Database searches yielded 10,925 results, of which after first pass sifting 394 were judged to be potentially relevant to this question. After abstract evaluation, 3 papers met the criteria for full text review. The three publications included 2 systematic reviews and one Lancet Commission[viii]. Of the systematic reviews, one was excluded because it was included in the UK NSC's 2014 evidence review about screening for dementia (Lin et al 2013)[31]. The second systematic review Kane et al (2017)[32] and the Lancet Commission (Livingstone et al 2017)[5] were excluded as there was no information about whether the included studies met the eligibility criteria agreed *a priori* for inclusion in this review, i.e. that populations should be screen-detected.

viii Lancet Commissions are landmark reports commissioned by the Lancet Global Health Journal for particular topics. The Lancet Commission on dementia comprised 24 experts from around the world led by University College London with the aim of reviewing the best available evidence and produce recommendations on how to best prevent, delay and manage dementia.

Therefore no studies met the inclusion criteria for question 4. A brief general discussion of the evidence base for people with non-screen-detected dementia is provided after the response to question 5.

Question 5 – What is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of mild cognitive impairment (MCI)?

The UK NSC's 2014 evidence review[11] identified a number of systematic reviews covering several potential treatments for MCI. Overall there was a lack of strong positive evidence for the benefit of the treatments considered for people with MCI or their families/carers. When statistically significant results were found, the effect sizes were generally small which raises questions about the clinical significance of the findings. The studies identified included people with MCI and the application of the findings to screen-detected cases was unclear.

Eligibility for inclusion in the review

Population: Adult population with screen-detected MCI

Intervention: Any pharmacological approach (e.g. acetylcholinesterase inhibitors, donepezil, galantamine and rivastigmine and memantine) and any non-pharmacological approaches (such as cognitive rehabilitation, including the use of mnemonics, association strategies, and computer-assisted training programmes)

Comparator: Any or none

Outcomes:
- reduced cognitive decline
- prevention of the progression to dementia
- improved physical functions
- reduced depression
- improved independence and general quality of life
- reduced mortality

Study design: Randomised controlled trials, cohort studies, and systematic reviews of any of the above

Date and language: English language published since 12 August 2013

Description of the evidence

Database searches yielded 10,925 results, of which 123 were judged to be relevant to this question and 17 abstracts met the criteria for full text review.

All 17 publications were systematic reviews or meta-analyses but none provided information about whether the included studies met the eligibility criteria agreed *a priori* for inclusion in this review, i.e. that populations should be screen-detected.

Therefore no studies met the inclusion criteria for question 5.

In the absence of evidence from known screen-detected cohorts, current evidence from non screen-detected cohorts from Kane et al (2017)[32] is presented to give a brief overview of the current evidence of the effectiveness of interventions to prevent, delay and treat dementia and MCI.

Kane et al (2017)[32] is a comparative effectiveness systematic review of randomised controlled trials produced by the US Agency for Health Research and Quality examining evidence for interventions to prevent or delay age-related cognitive decline, MCI and clinical Alzheimer's type dementia. Key question 1 in Kane et al (2017)[32] assessed the evidence for effectiveness of treatments to prevent, slow or delay the progression from normal cognition to dementia (excluding Lewy body dementia or dementia caused by stroke, traumatic brain injury, infectious diseases, substance misuse, Parkinson's disease and Huntingdon's disease). Key question 2 assessed the evidence for effectiveness of treatments on preventing, delaying and slowing progression from MCI to the same types of dementias as key question 1.

Discussion of findings for questions 4 and 5

Kane et al (2017)[32] examined evidence of 12 types of interventions for the potential to delay or prevent cognitive decline. These include: cognitive training; physical activity; nutritional interventions (e.g. omega 3 fatty acids, Ginkgo biloba extract) dietary changes; vitamin supplements (e.g.

folic acid and B vitamins), multimodal interventions (e.g. a combination of cognitive training, physical activity and dietary changes); anti dementia medication and non-steroidal anti-inflammatory medication (NSAIDs) and hormone therapy. They also examined the evidence of the use of pharmacological interventions including anti-hypertensive medication, cholesterol lowering medication and diabetes medication that lower the risk or delay the progression of other non-communicable diseases such as cardiovascular disease and diabetes that are the focus of an increasing number of dementia studies.

Overall the authors found low strength evidence that the wide range of interventions examined had little or no benefit for preventing or delaying the progression of MCI or dementia. There was moderate strength evidence that cognitive training improved performance in the trained cognitive domains (e.g. memory, processing speed) but this did not have an effect on the cognitive domains not trained and was not considered clinically significant. There was a mix of positive and negative outcomes from low strength evidence for physical activity, anti-hypertensives, NSAIDS, nutritional interventions, B vitamin supplements and multimodal interventions. Physical activity and the use of combined folic acid and vitamin B12 showed promising outcomes.

The authors noted that taken as a whole the evidence was inconclusive which was attributed to the use of different cognitive outcomes, short follow up periods and high attrition rates in the included studies.

Summary of Findings Relevant to Criteria 9 and 11: Criteria - not met[ix]

The 2 questions considered for these criteria were about the effectiveness of interventions to manage MCI and dementia following a screen-detected diagnosis. No studies were identified that specifically examined the effectiveness of interventions in a screen-detected population.

In the absence of evidence of the effectiveness of either pharmacological or non-pharmacological interventions in screen-detected populations, these criteria are not met.

[ix] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criterion 12 — Acceptability of screening for MCI and/or dementia

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

Question 6 – Is screening for MCI and/or dementia clinically, socially and ethically acceptable to health professionals and the public?

The NSC's 2009 review[11] identified some studies from the US about the acceptability of cognitive tests to the general public for screening for AD. Some qualitative studies reported that, despite 50% of people found screening for AD acceptable, there were concerns that it would impact on people's ability to hold a driver licence, live independently and obtain health insurance policies. Results from one study indicated that if people received a screen positive result, subsequently a high proportion of them would not continue for further assessment and diagnosis (50% of 450 screen positive older adults refused further assessment).

The NSC's 2009 review[10] did not identify any literature on whether screening for AD using neuroimaging, taking CSF or blood samples was acceptable to the general public.

The NSC's 2014 evidence review did not identify studies that directly addressed the question of the acceptability of screening for MCI or dementia amongst health professionals and the public.

Eligibility for inclusion in the review

Population: Adult population

Intervention: N/A

Comparator: N/A

Outcomes: Perceptions, views and/or attitudes and/or experiences of patients and carers, and health and social care professionals.
Ethical, moral and cultural issues in the context of the perception of patients, carers and practitioners

Study design: Randomised controlled trials, cohort studies, qualitative, quantitative and mixed methods studies and systematic reviews of any of the above

Date and language: English language published since 2008

Description of the evidence

Database searches yielded 10,925 results, of which 61 were judged to be relevant to this question and 18 abstracts met the criteria for full text review. After review of the full texts, 5 publications, including 2 systematic reviews, one mixed methods study, one national survey and one qualitative study were included. The remaining 13 studies were excluded after full text review either because they had been superseded by subsequent systematic reviews (n=5) or they were focussed on attitudes and preference of disclosure of a diagnosis of MCI or dementia rather than attitudes towards screening for those conditions (n=8).

Discussion of findings

A study-level summary of data extracted from each included publication is presented in the summary and appraisals of individual studies in Appendix 3.

The 2 systematic reviews[33,34] identified for question 6 are of good quality; however, the evidence they identify is limited to the concept of screening for dementia rather than the acceptability of cognitive or biomarker tests. A proportion of the publications in the 2 systematic reviews are the same; however, the scope of the earlier systematic review by Martin et al (2015a)[34] is directly relevant to question 6 whereas the Smith et al (2017)[33] review has a wider remit and covers other aspects of dementia screening (such as who should screen people). Both systematic reviews assessed the quality of their included studies which were all rated as either moderate or high quality. The 2 systematic reviews included studies from exclusively high income countries such as Canada, the US, Australia and Europe that are analogous to the UK in this respect. Groups consulted for their views included adults, older adults and caregivers from the general public, health care workers, general practitioners and dementia specialists from the health sector. No other characteristics of the studies were described such as ethnic mix, gender, economic status

and education. The qualitative study by Martin et al (2015b)[35], and mixed methods studies by Tang et al (2017)[36], and Fowler et al (2015)[37] had small sample sizes and the groups consulted were not representative of the wider UK population.

The qualitative study by Martin et al (2015b)[35] is an analysis of responses by members of the public and members of the Alzheimer's Society (n=44) in the UK to the themes emerging from the systematic review by the same authors (Martin et al 2015a)[34]. The views were gathered at a public and patient involvement event in a set up as a quasi-focus group. It is not published as a standalone piece of qualitative research and has significant sources of bias including a small number of participants, recruited from the public and from research partners.

Mixed methods studies from the US by Tang et al (2017)[36] and Fowler et al (2015)[37] add some quantitative analysis to these themes.

For patients, key factors that impact on the acceptability of screening for dementia include:

1. existing health issues — people who are less healthy tend to view dementia screening as more acceptable (n=318, 39% vs 54.5%, p=0.008) although there was a view that if someone perceived their current care as low quality they would be less likely to attend screening
2. lack of awareness of the screening test and the reasons to be screened and what the results mean
3. people who had partners tested for dementia using the MMSE noted that it was a particularly 'stressful' tool for people to complete
4. concerns about how confidential the result would be
5. the unavailability of a cure and perceptions that current management was inadequate
6. awareness of the disease and perceived stigma of taking the test and the judgement of other people of having a positive screen
7. role of the family in terms of support
8. the role and relationship of the clinician to the patient
9. some people preferred to know the diagnosis and be able to plan for the future.

Tang et al (2017)[36] reported that from a sample of 4,033 respondents women were more likely to be more worried about developing dementia than men (15% vs 10.5%, p<0.001) and were more likely to agree to being screened (52% vs 41.9%, p<0.001). Older adults aged 60+ were more likely to agree to be screened than younger adults (18–29= 42.9%,

30–44= 46%, 45–59= 48%, 60+= 50.8%, p=0.011). The survey responses were weighted by 9 factors, gender, age, household income, race/ethnicity, household size, education, census region, metro status and prior internet access to match the US current population.

Fowler et al (2015)[37] contacted 400 people by phone and asked them their views of screening for dementia and following the questionnaire during the same phone call they were offered a screening test. Participants who refused screening (37%) were significantly less likely to perceive any benefit compared with those who accepted screening (p<0.001). People were not asked why they chose to refuse screening. Participants were aged over 65, predominantly female (69%), Caucasian (84%) and educated for greater than 12 years (93%).

Concerns about the methodology of the study include a lack of clarity regarding at what point during the telephone call, participant consent to screening was obtained. This could have been before or after the questionnaire was administered and may have had an impact on participants' response. In addition, asking for people's views and soon afterwards asking them if they would act in accordance with their own views, could have introduced social desirability bias[x] where people might think 'if I have just said I think dementia screening is acceptable then I should probably go ahead and carry out the test even if I do not actually want to'.

One study reported in Smith et al (2017)[33] found a high acceptance of screening with 86% (n=345) and 90% (n=554) reporting that they would be happy to be screened whilst Martin et al (2015a)[34] reported that in one study (n=748), half those who screened positive refused a further diagnostic assessment.

Martin et al (2015a)[34] described one study (n=not reported) where patients could not consistently recollect the screening test or results, which raises ethical issues around consent and disclosure.

[x] A tendency of some respondents to report an answer in a way they feel to be more socially acceptable than what they consider is the 'true' answer

For health professionals there were a wide range of factors that impacted on the acceptability of dementia screening. Key factors include:

1. the perception that screening tools were inaccurate. In one study in Martin et al (2015a)[34] (n= not reported) both generalists and specialists in the UK reported screening inaccuracy as the most important reason for not undertaking screening at age 65
2. the management and treatment interventions available for dementia were limited and the prognosis was difficult to communicate with the clinical view that nothing could be done for patients (3 studies n=1,105; 2 studies n= not reported). There was also reluctance by some clinicians to follow up on a positive dementia screen with a full diagnostic assessment
3. an undecided or negative perception by clinicians that screening would lead to better outcomes for those screen-detected with dementia (one study n=55, 3 other studies n= not reported)
4. the recognition that there was stigma associated with a dementia diagnosis
5. disclosure of a diagnosis was perceived as potentially harmful to some patients and linked to other factors such as other existing health issues and duration of their relationship with the clinician (one study n=245, 5 studies n= not reported).
6. increased detection was mentioned as a positive benefit in that it would support planning of services, and would give time to the family to plan care, avert crises and come to terms with the diagnosis.

Other concerns raised by both the adults, older adults, care givers and health professionals were: the cost of implementing a screening programme; that there was not adequate support for all the people that might be screen-detected; that there might be a financial motive for putting screening in place (benefitting insurance companies or clinicians); and the time it would take for primary care staff to be trained and to screen people in already busy surgeries

Overall health professionals tended to be more sceptical about the benefits of screening compared to the public[34] and specialists in dementia were less likely to support dementia screening compared to general practitioners.

Studies reported here and included in the systematic reviews were carried out in the UK or other high income countries such as the US, Canada and Europe so in this respect they are analogous to the UK population. However other characteristics may lead to differences in attitudes, views and perceptions about dementia screening between countries such as cultural differences, ethnic mix and mechanism of

health and social care funding. None of the studies consulted a large sample of people who were representative of the wider UK population.

Summary of Findings Relevant to Criterion 12: Criterion not met[xi]

The 5 small studies included for question 6 describe the evidence about the perceptions and views of the public, caregivers and health professionals about screening for dementia. The 2 systematic reviews described good or moderately good evidence about the public, patients and health professionals, attitudes, views and perceptions about screening for dementia. None of the evidence was focussed on a particular type of screening test such as cognitive or biomarker tests. Studies not carried out in the UK have largely been carried out in high income countries such as the US, Canada and Europe so are analogous in this respect to the UK population. However other characteristics may lead to differences in attitudes, views and perceptions about dementia screening between countries such as cultural differences, ethnic mix and mechanism of health and social care funding. None of the studies consulted a large sample of people who were representative of the wider UK population.

Pooling results has not been possible due to the methodological inconsistency of the studies, however common themes have emerged.

There were a wide range of factors that determine the acceptability of a screening programme for both the public and professionals but the most important were: accuracy of the screening test, the availability of an effective treatment, the benefit of screening, the stigma surrounding dementia and awareness of screening and what the test result means. The perceived positive benefits to screening were limited to the time it

[xi] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

would give people to plan for the future and get used to a diagnosis.

Overall the studies that examine perceptions, attitudes and views about screening for dementia described mixed views voiced by the general public and a lack of support for dementia screening by dementia specialists.

Overall this criterion is not met.

Review summary

Conclusions and implications for policy

This report is an update review on systematic population screening for dementia against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

The volume, quality and direction of new evidence published since 2008 for questions 1, 3 and 6 and since 2013 for questions 2, 4 and 5 do not indicate that the changes in the evidence base are sufficient to alter the current recommendation not to screen for dementia in the UK. Key areas of concern relate to:

- uncertainties about the prognosis of MCI and sub-types of MCI in relation to dementia
- available cognitive screening tools for MCI and dementia lack evidence of clinical utility and that they would be effective as a screen detection method in the UK population
- no studies examining the clinical utility of biomarkers and brain imaging for the screen detection of MCI or dementia
- no studies examining pharmacological or non-pharmacological treatments in people with screen-detected MCI or dementia were identified
- the studies that examine perceptions, attitudes and views about screening for dementia described mixed views voiced by the general public and a lack of support for dementia screening by dementia specialists.

The current recommendation not to introduce a UK systematic population screening programme for dementia should be retained.

Limitations

An important limitation of the evidence is that MCI is a heterogeneous condition and diagnosis of people in the studies included are likely to be based on criteria from key studies and consensus of clinicians rather than an agreed definition. A clinical definition of MCI was introduced to DSM

5th edition in 2013, but this will not have been used for most of the research studies included in this review.

This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 4 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by one information scientist, and further appraisal and study selection by one reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of Medline, PsycINFO, Cochrane and Embase databases shown in Table12.

Table 12. Summary of electronic database searches and dates

Database	Platform	Date of search	Date range of search
Medline	Ovid SP	May 11th 2018	2008 to Present(Q1,6) 2013 to present (Q2,3,4,5)
Embase	Ovid SP	May 11th2018	2008 to present (Q1,6) 2013 to present (Q2,3,4,5)
PsycINFO	Ovid SP	11th May 2018	2008 to present (Q2,3,4,5) 2013 to present (Q1.6)
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL) - Database of Abstracts of Reviews of Effects (DARE)	Wiley Online	11th May 2018	2008 to present (Q1,6) 2013 to present (Q2,3,4,5)

Search Terms

Search terms for each key question for Medline are shown in Tables 13 to 17. Search terms included combinations of free text and subject headings.

Table 13. Medline search terms for key question 1

# ▲	Searches	Results
1	*Cognitive Dysfunction/	6923
2	(mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.	5901
3	(cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)	5806
4	1 or 2 or 3	13426
5	*Prognosis/	2206
6	exp *disease progression/	6076
7	"recovery of function"/	43539
8	(prognos* or progress*).ti.	261438

9	((symptom* adj3 (remission or fluctuat* or chang* or stable or stability)) or "return to normal*").ti,ab.	25079
10	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/	101693
11	(dementia*1 or alzheimer*2 or lewy body).ti,ab.	182160
12	10 or 11	192138
13	Risk Factors/	720536
14	biological phenomena/	6426
15	(risk? or predictor? or factor?).mp.	6088383
16	(biolog* adj3 process*3).ti,ab.	46180
17	13 or 14 or 15 or 16	6127445
18	12 and 17	61714
19	5 or 6 or 7 or 8 or 9 or 18	392534
20	4 and 19	3916
21	limit 20 to "reviews (maximizes specificity)"	184
22	Epidemiologic studies/	7669
23	exp case control studies/	912142
24	exp cohort studies/	1736381
25	Case control.tw.	107441
26	(cohort adj (study or studies)).tw.	153829
27	Cohort analy$.tw.	6165
28	(Follow up adj (study or studies)).tw.	44934
29	(observational adj (study or studies)).tw.	80629
30	Longitudinal.tw.	203421
31	Retrospective.tw.	423779
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2275919
33	20 and 32	1809
34	(case reports or comment or editorial or letter or news or "review").pt.	5703744
35	33 not 34	1681
36	exp animals/ not humans.sh.	4450651
37	35 not 36	1681
38	21 or 37	1847
39	limit 38 to (english language and yr="2008 -Current")	1566

Table 14. Medline search terms for key question 2

# ▲	Searches	Results
1	*Cognitive Dysfunction/	6923
2	(mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.	5901
3	(cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)	5806
4	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/	101693
5	(dementia*1 or alzheimer*2 or lewy body).ti.	98056
6	1 or 2 or 3 or 4 or 5	128612

7	mass screening/ or multiphasic screening/	94635
8	early diagnosis/	22451
9	(screen*3 or detect*3 or test*3 or question*5 or instrument*2 or exam*1 or examination*1 or surveillance).ti,ab.	5264153
10	(early adj2 diagnos*3).ti,ab.	86256
11	diagnos*3.ti.	527331
12	7 or 8 or 9 or 10 or 11	5698589
13	exp Neuropsychological Tests/	161863
14	((cognitive assess* or neuropsycholog*) adj2 (tool? or toolkit? or question* or instrument? or interview? or screen*3)).ti,ab.	1364
15	("general practitioner assessment of cognition" or gpcog or "memory impairment screen" or mis or mini-cog or "short form of the informant questionnaire on cognitive decline in the elderly" or short 1qcode or "eight-item informa interview to differentiate aging and dementia" or ad8 or "mini-mental state*exam" or mmse or clock drawing).ti,ab.	19358
16	13 or 14 or 15	176620
17	"Sensitivity and Specificity"/	325706
18	(sensitiv* or specific*).ti,ab.	3580631
19	((false or true) adj (negative* or positive*)).ti,ab.	71696
20	"Predictive Value of Tests"/	180589
21	(predictive value* or ppv or npv).ti,ab.	99090
22	17 or 18 or 19 or 20 or 21	3899972
23	6 and 12 and 16 and 22	4816
24	limit 23 to "reviews (maximizes specificity)"	94
25	(case reports or comment or editorial or letter or news or "review").pt.	5703744
26	23 not 25	4418
27	exp animals/ not humans.sh.	4450651
28	26 not 27	4413
29	24 or 28	4488
30	limit 29 to (english language and yr="2013 -Current")	1427

Table 15. Medline search terms for key question 3

# ▲	Searches	Results
1	*Cognitive Dysfunction/	6963
2	(mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.	5918
3	(cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)	5811
4	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/	101794
5	(dementia*1 or alzheimer*2 or lewy body).ti.	98159
6	1 or 2 or 3 or 4 or 5	128776
7	mass screening/ or multiphasic screening/	94737
8	early diagnosis/	22485

9	(screen*3 or detect*3 or test*3 or question*5 or instrument*2 or exam*1 or examination*1 or surveillance).ti,ab.	5811751
10	(early adj2 diagnos*3).ti,ab.	86332
11	diagnos*3.ti.	527585
12	7 or 8 or 9 or 10 or 11	6213697
13	exp Biomarkers/	647672
14	exp Neuroimaging/	152727
15	Brain/ and (magnetic resonance imaging/ or exp tomography, emission-computed/)	74553
16	(biomarker? or biological marker?).ti,ab.	193457
17	((brain or neurolog*) adj5 (magnetic resonance imaging or mri or pet or tomogra*)).ti,ab.	40796
18	(neuroimag* or neuro-imag*).ti,ab.	40894
19	13 or 14 or 15 or 16 or 17 or 18	1002778
20	"Sensitivity and Specificity"/	325879
21	(sensitiv* or specific*).ti,ab.	3583423
22	((false or true) adj (negative* or positive*)).ti,ab.	71761
23	"Predictive Value of Tests"/	180781
24	(predictive value* or ppv or npv).ti,ab.	99172
25	20 or 21 or 22 or 23 or 24	3902976
26	6 and 12 and 19 and 25	3427
27	limit 26 to "reviews (maximizes specificity)"	69
28	(case reports or comment or editorial or letter or news or "review").pt.	5707534
29	26 not 28	2757
30	exp animals/ not humans.sh.	4452508
31	29 not 30	2691
32	27 or 31	2741
33	limit 32 to (english language and yr="2013 -Current")	1322

Table 16. Medline search terms for key questions 4 and 5

# ▲	Searches	Results
1	*Cognitive Dysfunction/	6963
2	(mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.	5918
3	(cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)	5811
4	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/	101794
5	(dementia*1 or alzheimer*2 or lewy body).ti.	98159
6	1 or 2 or 3 or 4 or 5	128776
7	mass screening/ or multiphasic screening/	94737
8	early diagnosis/	22485
9	(screen*3 or detect*3 or test*3 or question*5 or instrument*2 or exam*1 or examination*1 or surveillance).ti,ab.	5811751
10	(early adj2 diagnos*3).ti,ab.	86332

11	diagnos*3.ti.	527585
12	7 or 8 or 9 or 10 or 11	6213697
13	Cognitive Dysfunction/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy]	1078
14	dementia/dh, dt, rh, th or alzheimer disease/dh, dt, rh, th or exp dementia, vascular/dh, dt, rh, th or lewy body disease/dh, dt, rh, th	27150
15	cholinesterase inhibitors/ or galantamine/ or rivastigmine/	20142
16	Memantine/	2033
17	(((cholinesterase or acetylcholinesterase) adj inhibitor?) or donepezil or galantamine or rivastigmine or memantine).ti,ab.	12728
18	((pharmacolog* or drug?) adj2 (therap* or treatment)).ti,ab.	128119
19	exp Rehabilitation/	272450
20	exp Home Nursing/	9128
21	exp social support/	63575
22	(rehabilitation or ((occupational or art or dance or music) adj therap*)).ti,ab.	147211
23	(("activity of daily living" or "activities of daily living" or adl) adj3 (support or service? or intervention? or program*)).ti,ab.	423
24	"social support".ti,ab.	31479
25	home nurs*.ti,ab.	1516
26	((nonpharmacolog* or non-pharmacolog*) adj2 (treatment or therap*)).ti,ab.	3839
27	(therap* or treatment or management or intervention).ti.	2066478
28	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	2540164
29	6 and 12 and 28	11090
30	limit 29 to "reviews (maximizes specificity)"	430
31	limit 29 to "therapy (best balance of sensitivity and specificity)"	2247
32	30 or 31	2441
33	limit 32 to (english language and yr="2013 -Current")	869

Table 17. Medline search terms for key question 6

# ▲	Searches	# ▲
1	*Cognitive Dysfunction/	1
2	(mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.	2
3	(cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)	3
4	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/	4
5	(dementia*1 or alzheimer*2 or lewy body).ti.	5
6	1 or 2 or 3 or 4 or 5	6
7	mass screening/ or multiphasic screening/	7
8	early diagnosis/	8
9	(screen*3 or detect*3 or test*3 or question*5 or instrument*2 or exam*1 or examination*1 or surveillance).ti.	9

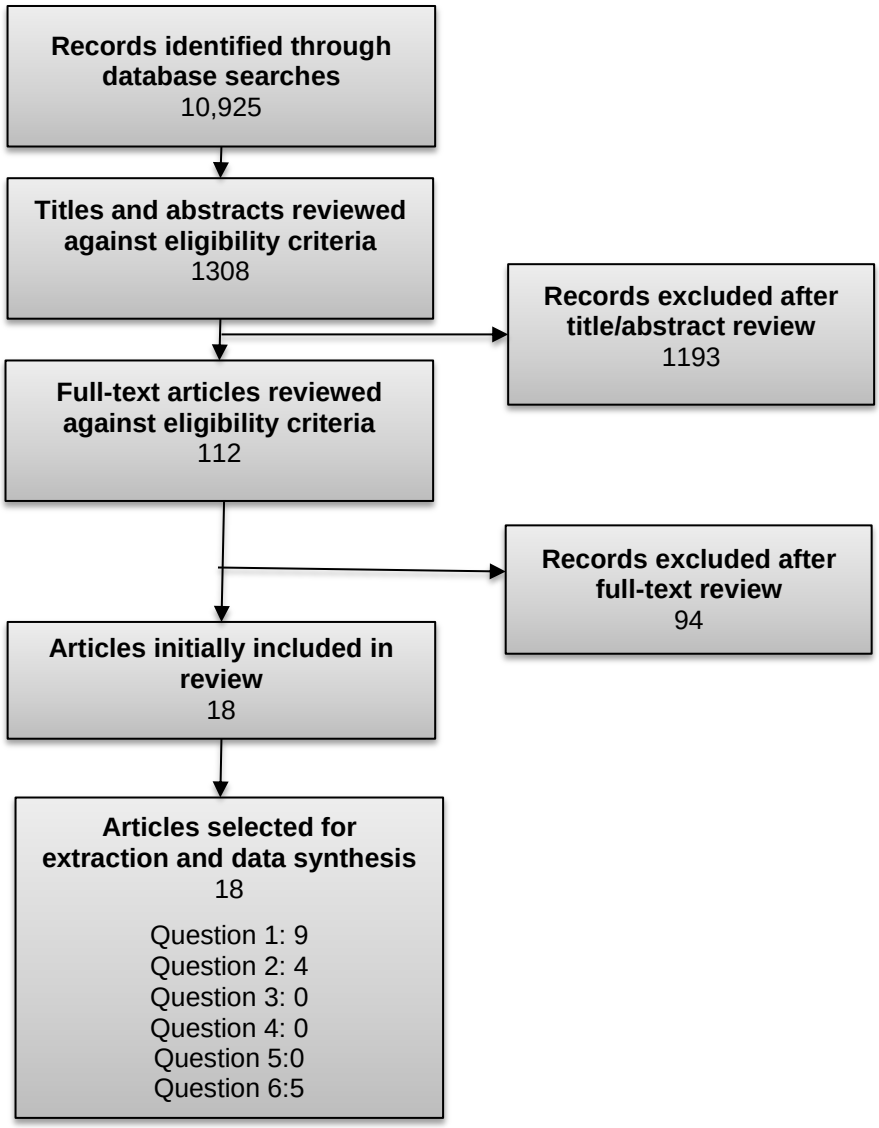
10	(early adj2 diagnos*3).ti,ab.	10
11	diagnos*3.ti.	11
12	7 or 8 or 9 or 10 or 11	12
13	exp *ETHICS/	13
14	Public Opinion/	14
15	exp Attitude/	15
16	(ethic* or moral* or cultural or culture or religion or religious).ti.	16
17	(attitude? or view* or opinion? or perspective? or perception?).ti.	17
18	((patient? or carer? or caregiver? or professional? or physician? or doctor? or nurse? or specialist?) adj3 (attitde? or view* or opinion? or perspective? or perception?)).ti,ab.	18
19	13 or 14 or 15 or 16 or 17 or 18	19
20	6 and 12 and 19	20
21	limit 20 to "reviews (maximizes specificity)"	21
22	(case reports or comment or editorial or letter or news or "review").pt.	22
23	20 not 22	23
24	21 or 23	24
25	limit 24 to (english language and yr="2008 -Current")	25

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. 18 publications were ultimately judged to be relevant to one or more review questions and were considered for extraction.

Figure 1. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

The 18 publications included after review of full texts are summarised in Table 18 below.

Table 18. Summary of publications included after review of full text articles, and the question(s) each publication was identified as being relevant to.

Study	The condition	The test	The intervention	The screening programme
Davis (2018)[14]	Q1			
Jang (2018)[18]	Q1			
Santana (2018)[21]	Q1			
Clem (2017)[16]	Q1			

Canevelli (2016)[13]	Q1		
Scarabino (2016)[20]	Q1		
Cooper (2015)[15]	Q1		
Ferriera (2011)[19]	Q1		
Diniz (2008)[17]	Q1		
Carson (2018)[26]		Q2	
Seitz (2018)[23]		Q2	
Creavin (2016)[24]		Q2	
Quinn (2014)[25]		Q2	
Tang (2018)[36]			Q6
Smith (2017)[33]			Q6
Martin (2015a)34			Q6
Martin (2015b)[35]			Q6
Fowler (2015)[37]			Q6

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

- Systematic reviews and meta-analyses would be considered the highest quality of evidence if any were found. Following this, study designs would be prioritised for each question in the order listed in table 7 respectively.
- Studies relating to epidemiology would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK.

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Key question 1: What is the clinical prognosis of mild cognitive impairment (MCI), especially its association with dementia?

Table 19. Canevelli et al (2016)

Publication	Canevelli M, Grande G, Lacorte E, Quarchioni E, Cesari M, Mariani C, et al. Spontaneous Reversion of Mild Cognitive Impairment to Normal Cognition: A Systematic Review of Literature and Meta-analysis. Journal of the American Medical Directors Association. 2016;17(10):943-8.
Study details	Systematic review and meta-analysis
Study objectives	Systematically review and analyse studies with the aim of estimating the proportion of people with MCI that revert to normal cognition
Inclusions	Longitudinal studies from 1999 to November 2015
Exclusions	Studies with follow up <2 years
Population	25 longitudinal studies with 6914 people with MCI(range 22 to 1843) follow up 2 to 5 years
Intervention	N/A
Comparator	N/A
Outcomes	15 studies were population based and 10 studies were clinic based • A total of 1243 (18.0%) of people with MCI reverted to normal cognition • Meta-analysis of studies resulted in 18% (95%CI 14-22) reversion rate with high degree of heterogeneity (I^2=96.1%,p<0.001) • A significant association was observed between effect size and setting (p=0.011) • Sub-group analysis using setting showed reversion rate of 10% (95%CI 6-13) in the clinic setting and 23% (95%CI 18-29) in the population based studies • Effect size observed in the population based studies ranged from 0.04 (95%CI 0.01-0.15) to 0.41 (95%CI 0.29-0.55)

	• Effect size in the studies based in clinic settings ranged from 0.03(95%CI 0.02-0.06) to 0.40(95%CI 0.28 – 0.52) • Following assessment of quality of the studies, meta-analysis of 6 better quality population based studies was performed resulting in a reversion rate of 29% (95%CI 22-37)
Quality appraisal	The CASP checklist for systematic reviews was used to assess the quality of this review and there were no concerns. In terms of the studies included in the review they varied in size and inclusion was over a period of time when the definition and diagnosis of MCI was uncertain. Only 6 of the higher population based studies have been included.

Table 20. Clem et al (2017)

Publication	Clem MA, Holliday RP, Pandya S, Hynan LS, Lacritz LH, Woon FL. Predictors That a Diagnosis of Mild Cognitive Impairment Will Remain Stable 3 Years Later. Cognitive & Behavioural Neurology. 2017;30(1):8-15.
Study details	Retrospective cohort study
Study objectives	To identify predictors of MCI staying stable over time
Inclusions	Data about people in the US with an MCI diagnosis from the National Alzheimer's Coordinating Centre Uniform Dataset between September 2005 and July 2013 with complete demographic information who undertook 3 annual on-site clinic follow up visits each within 18 months of each other
Exclusions	None stated
Population	1778 participants
Intervention	N/A
Comparator	N/A

Outcomes	• 596 (34%) people were MCI stable as they had an MCI diagnosis at all 3 visits
	• 463 (26%) had converted to dementia
	• 461 (26%) had reverted to normal cognition
	• 258 (14%) were categorised as impaired/not MCI as the cognitive impairment did not fully meet MCI or normal cognition for age
	• People were more likely to be MCI stable if they were
	  ○ younger (p=0.003, Cohens d 0.18)
	  ○ had fewer years of education (p=0.007, Cohens d0.18)
	  ○ had fewer ApoE4 alleles (p<0.001, 0.20)
	  ○ had lower clinical dementia rating scale scores(p<0.001, Cohens d 0.80)
	  ○ had higher MMSE scores (p<0.001, Cohens d 0.63)
	  ○ had lower functional activities questionnaire scores (p<0.001 Cohens d 0.61)
	  ○ had non amnestic MCI compared to amnestic MCI (p<0.00, Cohens d 0.16)

Quality	The CASP checklist for cohort studies was used to assess the quality of this review and there were generally no

appraisal	concerns although there is an inevitable sample selection and recording bias due to it being retrospective. The diagnosis of MCI has evolved over time and it is likely that different clinicians submitting data to the national dataset operationalised the MCI criteria differently as a clinical definition had not been agreed during that period.

Table 21. Cooper et al (2015)

Publication	Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. American Journal of Psychiatry. 2015;172(4):323-34.
Study details	Systematic review and meta-analysis
Study objectives	Synthesize evidence from longitudinal studies examining modifiable risk factors that predict conversion to dementia
Inclusions	Longitudinal studies reporting modifiable risk factors for incident dementia in people with MCI
Exclusions	None stated
Population	30 studies
Intervention	N/A
Comparator	N/A
Outcomes	Diabetes – 10 studies - 7 studies pooled (n= 4124) follow up 1.5 to 9 years • 7 studies pooled OR 1.65, (95% CI 1.12-2.43) suggest diabetes increases risk of Alzheimer's dementia in people with aMCI and increases risk of all cause dementia in people with naMCI. Studies not included (n=3) in meta-analysis show consistent trend Metabolic syndrome 1 study (n=2097) 3.5 years follow up • Shows metabolic syndrome and prediabetes predicted all cause dementia in people with aMCI (Hazard ratio (HR) 7.80,1.29-47.20) and any type dementia Any neuropsychiatric symptoms 5 studies • 4 studies(n=2549), 2 to 5 years follow up (pooled OR 3.11(95% CI 1.38 to 7.02)) showed people with one or more symptoms on neuropsychiatric inventory associated with risk of conversion of any MCI and all cause dementia. Mediterranean diet 1 study (n=1393) 4.3 years follow up • Showed those at the highest adherence to the Mediterranean diet tertile had a 48% (HR, 0.52; 95% CI, 0.30 – 0.91; p=0.02) less risk of developing AD than those in the lowest adherence tertile
Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this review and there were no concerns. A quality assessment was carried out by the authors who included papers with follow up from 12 months onwards which is a relatively short time for capturing the point at which MCI develops into dementia.

Table 22. Davis et al (2018)

Publication	Davis M, O Connell T, Johnson S, Cline S, Merikle E, Martenyi F, et al. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. Current Alzheimer Research. 2018;18:18.
Study details	Retrospective cohort study
Study objectives	To estimate annual progression rates from normal cognition to MCI to AD and to model the impact of a delay in MCI due to AD on the trajectory of AD, dementia and clinical outcomes
Inclusions	Data about people ≥65 years in the US with an MCI diagnosis from the National Alzheimer's Coordinating Centre Uniform Dataset between 2005 and 2014 with complete demographic information with more than 1 visit to a clinic.
Exclusions	None stated
Population	18,103 patients
Intervention	N/A
Comparator	N/A
Outcomes	Relative to people with normal cognition patients with MCI that converted to AD were: • older ($p<0.0001$) • displayed behavioural disturbances ($p<0.0001$) • took medication for AD symptoms ($p<0.0001$) • possessed APOE e4 alleles ($p<0.0001$) • were more likely to have diabetes ($p<0.01$) • were more likely to have hypercholesterolemia ($p<0.0001$) • were more likely to have hypertension ($p<0.0001$) • were more likely to have depression ($p<0.0001$) Using the data to model the rates of transition, authors predict for people with normal cognition at age 65 within the next year 92% will still have normal cognition, 4% will have transitioned to MCI, 3% will have transitioned to non-Alzheimer's disease cognitive impairment and 1% will have died. For people with MCI at age 75, 75% will have MCI a year later, 23% will have transitioned to mild AD and 2% will have died. For people with normal cognition at age 65 who go on to develop MCI-related AD the transition probabilities predict an average age of onset of MCI due to AD of 74.0 and of AD at 77.1 years with an average lifespan of 81.6 years.
Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this review and there were generally no concerns although there is an inevitable sample selection and recording bias due to it being retrospective. The diagnosis of MCI has evolved over time and it is likely that different clinicians submitting data to the national

	dataset operationalised the MCI criteria differently as a clinical definition had not been agreed during that period.

Table 23. Diniz et al (2008)

Publication	Diniz BSO, Pinto Junior JA, Forlenza OV. Do CSF total tau, phosphorylated tau, and beta-amyloid 42 help to predict progression of mild cognitive impairment to Alzheimer's disease? A systematic review and meta-analysis of the literature. World Journal of Biological Psychiatry. 2008;9(3):172-82.
Study details	Systematic review and meta-analysis
Study objectives	To determine the usefulness of the CSF biomarkers Aβ42, T-tau and P-tau to predict the progression of MCI patients to Alzheimer's disease.
Inclusions	Studies where patients had a diagnosis of MCI with clearly described criteria, there was information about the conversion to dementia or AD starting from MCI diagnosis, time of follow up was included, baseline levels for Aβ42, T-tau and P-tau were included. Papers should be in English and published between 1999 and April 2007.
Exclusions	See above
Population	5 studies for meta-analysis (n=326)
Intervention	N/A
Comparator	N/A
Outcomes	A comparison of people from 4 studies who converted from MCI to AD (n=130) and controls (n=130) with normal cognition had significantly lower values of CSF Aβ-42 (SMD -1.57, 95% CI -2.30 to -0.84, z=-4.23, p<0.0001). A comparison of people from 5 studies who converted from MCI to AD (n=169) and controls (n=157) with normal cognition had significantly higher values of CSF T-tau (SMD 1.52, 95%CI 1.25 to 1.79, z=11.06, p<0.0001). A comparison of people from 3 studies who converted from MCI to AD (n=123) and controls (n=130) with normal cognition had significantly higher values of CSF P-tau (SMD 1.75, 95%CI 0.99 to 2.51,z=4.49, p<0.0001).
Quality appraisal	The CASP checklist for systematic reviews was used to assess the quality of this review. There was no evaluation of the quality of the included studies. The samples sizes of the individual studies were small and the follow up period varied from 4 to 80 months. Studies with shorter follow ups are less likely to capture the point at which people convert from aMCI to AD.

Table 24. Ferreira et al (2011)

Publication	Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neuro-structural predictors of Alzheimer's disease: A meta-analysis of VBM studies. Neurobiology of Aging. 2011 October;32(10):1733-41.
Study details	Meta-analysis
Study objectives	To carry out meta-analysis of voxel-based morphometry(VBM) studies of neuro-structural predictors of conversion from aMCI to Alzheimer's disease

Inclusions	Studies included if they: • performed baseline structural brain MRI of normal subjects or MCI patients • followed up subjects to determine who converted to AD and who did not • compared baseline MRI of normal or MCI participants who converted to AD with those who did not • performed whole brain analysis • followed particular VBM protocols
Exclusions	None stated
Population	6 studies with a total of 429 aMCI participants of which 142 converted to AD
Intervention	N/A
Comparator	N/A
Outcomes	Comparison of brain neurostructure of aMCI participants who converted to AD vs those who did not showed no significant difference in age, gender or educational level. One area of the brain had a significantly reduced volume in aMCI patients who converted to AD vs those who did not ($p<0.01$cluster extent threshold of $100mm^3$). This was located in the left hippocampus and para-hippocampal gyrus within the left medial temporal lobe.
Quality appraisal	The CASP checklist for systematic reviews was used to assess the quality of this review. The quality of the included studies was not reported and the studies included were small with short follow up periods.

Table 25. Jang et al (2018)

Publication	Jang H, Ye BS, Woo S, Kim SW, Chin J, Choi SH, et al. Prediction Model of Conversion to Dementia Risk in Subjects with Amnestic Mild Cognitive Impairment: A Longitudinal, Multi-Center Clinic-Based Study. Journal of Alzheimer's Disease. 2018;61(2):825.
Study details	Longitudinal cohort study
Study objectives	Develop a nomogram to predict dementia conversion in aMCI participants using neuropsychological profiles
Inclusions	Patients followed for at least 3 years after baseline neuropsychological tests
Exclusions	Patients with secondary causes of cognitive deficit and those with non-AD type dementia
Population	338 aMCI patients from 2 hospital–based cohorts in South Korea
Intervention	N/A
Comparator	N/A
Outcomes	Patients grouped into sub-groups by modality, severity and number of cognitive domains affected. Modality • Visual memory dysfunction • Verbal memory dysfunction • Both visual and verbal memory dysfunction

Severity

- Mild memory dysfunction
- Severe memory dysfunction

Cognitive domains affected:

- Single domain affected
- Multiple domains affected

Of 338 aMCI patients 208 (61.5%) converted to AD during 3 year follow up. Non converters included those who remained stable (n=87) those who reverted to normal (n=27) or those who converted to non-memory type cognitive impairment (n=16).

People that were significantly predictive of converting to AD were:

- Older (OR 1.10, 95% CI 1.05-1.15)
- Had both visual and verbal MCI (OR 4.30, 95%1.95-9.47)
- Had more severe memory impairment (OR 2.15 95% CI 1.06-4.36) although this became non-significant when presence of APOE e4 alleles was added to the model
- Had multiple cognitive domains affected (OR 3.60 95% CI 1.78 to 7.29)
- Had APOE e4 alleles(OR 4.71 95%CI 2.12 -10.49)

An overall risk score nomogram was constructed from the results to develop a risk prediction model.

Low risk profile of conversion to dementia (<5%)

- Age – 45 years
- Visual aMCI
- Early stage aMCI
- Single cognitive domain affected

Intermediate risk profile of conversion to dementia (50%)

- Age 65 years
- Verbal aMCI
- Late stage aMCI
- Multiple cognitive domains affected

High risk profile of conversion to dementia (>95%)

- Age – 90 years
- Both visual and verbal aMCI
- Late stage aMCI
- Multiple cognitive domains affected

Using these variables authors developed a scoring system using a nomogram to predict dementia risk for dementia conversion within 3 years. Scores over 140 have a positive predictive value for dementia conversion of 0.85 (without APOE e4 test result) and 0.89 (with APOE e4 test result). If total points are 73 or lower negative predictive value for conversion to AD in 3 years is 0.89 (without APOE e4 test result) and 0.87 (with APOE e4 test

	result).
Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this study. The applicability of the study results to a UK population is limited as it was carried out in South Korea, however the approach could be replicated in the UK. This was a relatively small study with wide confidence intervals reducing the confidence in the results.

Table 26. Santana et al (2018)

Publication	Santana I, Baldeiras I, Santiago B, Duro D, Freitas S, Pereira MT, et al. Underlying Biological Processes in Mild Cognitive Impairment: Amyloidosis Versus Neurodegeneration. Journal of Alzheimer's Disease. 2018;16:16.
Study details	Prospective cohort study
Study objectives	To investigate the underlying biological processes and of amyloidosis and neurodegeneration and their relevance for progression to AD from aMCI
Inclusions	People with aMCI who underwent CSF biomarker tests for Aβ42, T-tau and P-tau and followed up for 2 years and remained stable or developed AD
Exclusions	None stated
	217 patients with aMCI at baseline (dropping to 165 at follow up) in Portugal. Follow up 0.5 to 6.5 years)
Intervention	N/A
Comparator	N/A
Outcomes	At follow up 165 patients classed as stable aMCI (n=80, 48%) or converted to AD (85, 52%). Variables that contributed to a greater likelihood of converting to AD were : • Age (OR 1.099 95% CI 1.031 to 1.171) p<0.004 • CSF Aβ42 (OR 0.994, 95% CI 0.991 to 0.998, p<0.001) • T-tau (OR 1.008 95% CI 1.003 to 1.013, p<0.003)) APOE e4 was much more represented in the group that converted versus the group that remained stable (58 vs 26%, p<0.001) but it did not emerge as a significant predictor. Table showing different levels of CSF biomarkers in aMCI patients and proportion converting to AD

aMCI patients	Proportion at baseline	Proportion converting to AD
Group A -All CSF markers normal(Aβ42, T-tau and/or P-tau)	37(22%)	5(14%)
Group B - All CSF markers were abnormal (Aβ42, T-tau and/or P-tau)	69(42%)	27(80%)***
Group C-CSF marker Aβ42 is abnormal and T-tau and/or P-tau is	17(10%)	8(47%)* +

	normal		
	Group D -CSF marker Aβ42 is normal and T-tau and/or P-tau is abnormal	42(26%)	17(40%)* $^{+++}$
	***p<0.001 versus Group A $^{+++}$p<0.001 versus Group B *p<0.05 versus group A $^{+}$p<0.05 vs Group B		
Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this study. The study was small with a variation in follow up from 0.5 to6.5 years. Detecting a change in cognitive impairment in the shorter follow up periods is less likely.		

Table 27. Scarabino et al (2016)

Publication	Scarabino D, Broggio E, Gambina G, Maida C, Gaudio MR, Corbo RM. Apolipoprotein E genotypes and plasma levels in mild cognitive impairment conversion to Alzheimer's disease: A follow-up study. American Journal of Medical Genetics. 2016;Part B, Neuropsychiatric Genetics:the Official Publication of the International Society of Psychiatric Genetics. 171(8):1131-8
Study details	Prospective cohort study
Study objectives	To examine the role of APOE gene in aMCI development and progression to AD in people with aMCI
Inclusions	Patients referred to a clinic for assessment by their GP
Exclusions	Patients with a history of head injury, psychiatric disorders, neurological disease or severe sensorial deficits
Population	88 people consecutively admitted to the Alzheimer's Disease Centre of Neurology and diagnosed with aMCI and 164 controls with no cognitive impairment in Italy.
Intervention	N/A
Comparator	N/A
Outcomes	There were significant difference in APOE genotype (p=0.03) and allele frequencies (p=0.005) among aMCI participants and controls. At baseline APOE e4/e4 homozygotes were present only in people with multi domain cognitive impairments and APOE e2 alleles were present only in people with single domain aMCI. People with multi domain aMCI were 3 times more likely to have APOE e4 alleles than the control group (p<0.001) and twice as likely as the single domain aMCI. Carrying the APOE e4 allele significantly increased the risk of conversion of single domain aMCI to multi domain aMCI or to AD as compared to the APOEe3/e3 and e3/e2 genotypes (OR 4.1, 95% CI 1.2-13.6 p=0.02).

	Distribution of APOE allele frequencies at follow up showed that people who still had single domain aMCI (non-converters) had similar frequencies of APOE e2,e3,e4 to the control group (p=0.80) and participants who had converted to multi domain aMCI or AD had significantly different frequencies from the non-converters(p=0.014) and the controls(p<0.0001). Table 1: Proportion of patients with aMCI converting to multi domain MCI or AD by APOE allele frequency

	APOE e3/e3	APOE e3/e2	APOE e4/e3	APOE e4/e4
Converted	48%	0	71%	75%
Not converted	52%	100%	29%	25%

Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this study and there were generally no concerns although the sample size is small.

Key question 2: What is the accuracy of cognitive assessment tools as screening tests for any class of dementia and for mild cognitive impairment (MCI)?

Table 28. Carson et al (2018)

Publication	Carson N, Leach L, Murphy KJ. A re-examination of Montreal Cognitive Assessment (MoCA) cut off scores. International Journal of Geriatric Psychiatry. 2018 February;33(2):379-88.
Study details	Meta-analysis of validation studies
Study objectives	Carry out meta-analysis of MoCA validation studies to statistically determine the optimal cut-off score for differentiating normal aging from MCI.
Inclusions	Diagnostic validity studies distinguishing between cognitively normal adult and those with MCI, diagnoses of MCI or normal aging must have been made independently of MoCA
Exclusions	Specific populations with known medical problems such as cardiovascular disease.
Population	9 studies of which 5 used the English version of the screening tool
Intervention	N/A
Comparator	N/A
Outcomes	Validation study results for use of MoCA to identify MCI

MoCA test cut off	Control n	MCI n	Sensitivity	Specificity	PPA	NPA
23	90	62	0.89(0.81-0.96)	0.90(0.84-0.96)	0.86	0.92
24	36	53	0.94(0.88-1.0)	0.65(0.48 -	0.80	0.87

				0.80)		
25	156	164	0.88(0.83-0.93)	0.75(0.69-0.82)	0.79	0.85
26	106	132	0.93(0.89-0.97)	0.79(0.70-0.86)	0.84	0.90

MoCA test cut off	True p	True n	False p	False n	Prevalence	Classification accuracy
23	55	81	9	7	0.41	0.90(0.85-0.94)
24	50	23	13	3	0.60	0.82(0.74-0.90)
25	144	118	38	20	0.50	0.82(0.78-0.86)
26	123	83	23	9	0.55	0.86(0.82-0.91)

Quality appraisal	The Center for Evidence Based Medicine check list was used to assess quality of this review. The quality of each study including risk of bias was not evaluated and a calculation of heterogeneity across the studies was not performed. Sample sizes were small, studies are culturally and educationally heterogeneous and it is unknown how well these results would apply to a UK population.

Table 29. Seitz et al (2018)

Publication	Seitz DP, Chan CC, Newton HT, Gill SS, Herrmann N, Smailagic N, et al. Mini-Cog for the diagnosis of Alzheimer's disease dementia and other dementias within a primary care setting. Cochrane Database of Systematic Reviews. 2018;2:CD011415.
Study details	Systematic review
Study objectives	To determine diagnostic accuracy of the Mini-Cog for diagnosing Alzheimer's disease dementia in a primary care setting
Inclusions	Studies in primary care using Mini-Cog
Exclusions	None stated
Population	4 studies, n=1517
Intervention	Index test was Mini-Cog
Comparator	Reference test: clinical diagnosis of dementia using any recognised classification system
Outcomes	Screen positive = delayed word recall score is 0 or delayed recall score is 1 or 2 plus an abnormal clock drawing test. Of 4 studies 2 were assessing adults with no suspicion of dementia with a: Specificity range 0.76 to 1.00 Sensitivity range 0.27 to 0.85
Quality appraisal	The Center for Evidence Based Medicine check list for systematic reviews and meta analyses was used to assess the quality of this review and there were no concerns. The study authors assessed risk of bias using QUADAS 2.

	Sampling methodology was a source of bias for 2 studies that did not select either random or consecutive populations with no known dementia diagnosis.

Table 30. Creavin et al (2016)

Publication	Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database of Systematic Reviews. Meta-analysis 2016;(1):CD011145.
Study details	Systematic review and meta-analysis
Study objectives	To determine diagnostic accuracy of the MMSE in primary care and community dwelling populations in people over age 65 with no prior suspicion of cognitive impairment
Inclusions	Population was in community or primary care, the MMSE was the index test and a reference standard was reported
Exclusions	Case control studies and studies where the index test is only administered to cases or controls
Population	28 community studies (n=12,110)
Intervention	Index test - MMSE
Comparator	Reference test: clinical diagnosis of dementia using any recognised classification system
Outcomes	Meta-analysis of 28 community studies (n=12,110)

Cut-off	Sensitivity (95% CI)	Specificity(95% CI)	Number of studies
24	0.85 (0.74-0.92)	0.90(0.80-0.95)	15 studies
25	0.87(0.78-0.93)	0.82(0.65-0.92)	10 studies
MMSE adjusted for education at either a cut off of 24 or	0.97(0.83-1.0)	0.70(0.5-0.85)	7 studies

Quality appraisal	The Center for Evidence Based Medicine check list for systematic reviews and meta analyses was used to assess the quality of this review and there were no concerns

Table 31. Quinn et al (2014)

Publication	Quinn TJ, Fearon P, Noel-Storr AH, Young C, McShane R, Stott DJ. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within community dwelling populations. Cochrane Database of Systematic Reviews. 2014;(4):CD010079.
Study details	Systematic review and meta-analysis
Study objectives	Determine diagnostic accuracy of the IQCODE questions for detection of all cause dementia in community dwelling adults with no previous cognitive assessment compared with a clinical diagnosis of dementia (reference

	standard).
Inclusions	Studies in community settings that used IQCODE to assess for presence of dementia and where it was confirmed with clinical assessment.
Exclusions	None stated
Population	10 studies with 2644 participants (range 37 to 684 of whom 379 (14%) received a clinical dementia diagnosis.
Intervention	Index test was IQCODE
Comparator	Reference test: clinical diagnosis of dementia using any recognised classification system
Outcomes	

Cut-off	Sensitivity (95% CI)	Specificity(95% CI)	Participants (n)
3.3	0.78 (0.69-0.85)	0.77 (0.63 to 0.86	4 English language version studies, n=1553
3.4	0.84(0.70-0.93)	0.80(0.65-0.90	3 studies, n=988
3.5	0.82(0.75-0.87)	0.84(0.80 -0.88)	3 studies, n=1144
3.6	0.78(0.68 -0.86)	0.87(0.71-0.95)	3 studies, n=1215

No difference in accuracy between 26 item version and 16 item version with relative sensitivity of 1.00 (95%CI 0.91 to 1.11) and relative specificity of 0.94 (95% CI 0.82 to 1.09)

Using these figures authors calculate that if the over 65 population were tested 87,120 people with dementia would be detected and a further 1,314,660 would screen positive but not have dementia

Quality appraisal	The Center for Evidence Based Medicine check list for systematic reviews and meta analyses was used to assess the quality of this review and there were no concerns. Risk of bias was assessed by the authors using QUADAS 2 (a check list of potential sources of bias for assessing studies that report accuracy of screening and diagnostic tests against a reference standard). No study was graded low risk for all areas. Participant sampling was a concern as few papers used a true consecutive sampling methodology.

Key question 6: What is the reported effectiveness of pharmacological and non-pharmacological interventions after a screen-detected diagnosis of dementia?

Table 32. Martin et al (2015a)

Publication	Martin S, Kelly S, Khan A, Cullum S, Dening T, Rait G, et al. Attitudes and preferences towards screening for dementia: a systematic review of the literature. BMC Geriatrics. 2015;15:66
Study details	Systematic review
Study objectives	To examine the attitudes and preferences of the general public, health care professionals, people with dementia and their carers towards population screening for dementia.

Inclusions	Studies where the primary or secondary objectives were to explore, describe or explain the attitudes and preferences of screening for dementia.
Exclusions	Studies examining the use of biomarkers or genetic tests as the screening method. Studies where screening was for MCI rather than dementia.
Population	29 studies that included 2,575 people with dementia, 331 carers, 1,977 members of the public and 5,132 health care professionals
Intervention	N/A
Comparator	N/A
Outcomes	• 1 study (n=318) found that being healthier was associated with less willingness to be screened (39% vs 54.5%, p=0.008) • Lack of awareness of the screening test and the reasons to be screened and what the results mean was reported in 3 studies (for 2 studies n=364, n =not reported for 3rd study) • Two studies (n=364) reported that the role of the clinician was important in leading the patient through the screening process • One study (n=not reported) described uncertainties about the test and were unable to recollect that screening had been explained to them. They also reported the test being strenuous and stressful as they felt under pressure to do well. • 6 studies (4 studies n= unreported in 2 studies n=287) reported that caregivers and the general public thought there were benefits to screening for dementia including treatment and financial benefits. One further study (n=748) reported that half those who screened positive for cognitive impairment refused a diagnostic evaluation. • Patients existing health and comorbidities was reported in 4 studies to be prioritised over dementia screening or assessment (n= not reported in the 4 studies) • Lack of awareness of dementia by healthcare professionals was reported by 2 studies (n= not reported).It was suggested that attitudes of clinicians rather than knowledge was a barrier to screening. In one European study UK clinicians were consulted and: o 68% said there was not enough funding of treatment o 50% felt the government is a barrier to those seeking medication o 0% agreed that Alzheimer's disease was over treated. • Clinicians were undecided or negative about the acceptability of screening in 4 studies when asked if it would lead to better outcomes (for 1 study n=55, 3 other studies n= unreported). • In 2 studies (n=913) clinicians who had little or not relationship with patients were more apprehensive about screening was reported • The lack of an acceptable and accurate screening tool was an important barrier to the acceptability of screening by clinicians in 4 studies (n=871 in 1 study, 3 studies n=unreported). In one study (n= unreported) both generalists and specialists in the UK reported screening inaccuracy as the most

	important reason for not undertaking screening at age 65 (44%). In a UK sample of clinicians more specialists than generalists (50% vs 38%, p<0.001) agreed screening tests are not accurate. • Cost concerns in 1 study (n= not reported) were related to implementation, disruption to current working practices, and additional infrastructure. • Disclosure of a diagnosis was perceived as potentially harmful to some patients and linked to other factors such as other existing health issues and duration of their relationship (6 studies, 1 study n=245, 5 studies n= not reported). • Lack of time to screen patients was a common theme that emerged in 4 studies (3 studies n=1979, 1 study n= not reported). In a single study that examined screening intervention on practice staff did n'ot report significant disruption. • Limited treatment options and a difficult to communicate prognosis with the view that nothing could be done for patients was an important barrier for clinicians (6 studies for 3 studies n=1105, 2 studies n= not reported). There was also a reluctance to follow up on a positive dementia screen with a full diagnostic assessment. • Clinicians recognised that stigma is associated with a dementia diagnosis.
Quality appraisal	The CASP checklist for systematic reviews was used to assess the quality of this review and there were no concerns.

Table 33. Martin (2015b)

Publication	Martin S, Fleming J, Cullum S, Dening T, Rait G, Fox C, et al. Exploring attitudes and preferences for dementia screening in Britain: contributions from carers and the general public. BMC Geriatrics. 2015;15:110.
Study details	Qualitative output of patient and public involvement event in quasi focus group format
Study objectives	To gauge public opinion about the acceptability of population screening for dementia as a consultation during the final stages of a systematic review on attitudes and preferences towards screening for dementia.
Inclusions	N/A
Exclusions	N/A
Population	A representative sample of the people of Cambridge (based on the 2011 census) were recruited (n=44)
Intervention	N/A
Comparator	N/A
Outcomes	Themes: Pre-screening • Existing care – attendees receiving care for existing conditions are more likely to take up the offer of screening if the care is good than if it is poor • Experiences of other screening tests and programmes may impact on the likelihood of an individual taking up screening for dementia

Screening

- Concerns were expressed about the screening tool and its accuracy
- Concerns that there was insufficient agreement within the health profession to be a viable programme
- There was no strong preference for who should administer the test but a strong rapport with a health professional would mean that it was more likely to be acceptable
- There was no consensus on whether there was a higher likelihood of attending screening if an individual had a good understanding and awareness of dementia.

Post screening.

- Negative social impact with friends family and employers
- Anxiety about knowing or not knowing the result and what it meant
- Lack of effective treatment and prognosis
- Stigma from having a positive test result

Cross cutting themes

- Personal circumstances such as having young children were an important determinant in the decision to be screened
- The role of the family in supporting someone who wants to be screened and a positive diagnosis was important as was the role the individual had in the family. Those with less support or a more pivotal role in the family may be less likely to be screened
- The provision of support for people with dementia was important
- There was concern that a screening programme would be of financial benefit to someone (GPs, pharmaceutical companies or insurance companies)
- There was no agreement on who should be targeted for screening which was a possible reflection of the lack of awareness of the factors that might determine a target group within the participants.
- There were concerns over the logistics of offering screening through primary care including taking time from already busy GPs for screening and training
- Some participants viewed the time after a screen positive test result to be when they would plan for the future such as putting in place a lasting power of attorney
- Concerns were expressed about the cost of a screening programme which would be of questionable benefit when the money could be used elsewhere in the NHS or for dementia research.

Participants were asked to complete a questionnaire before and after the workshop. Changes in responses included between the pre and post workshop questionnaire include:

- Fewer delegates said they would like to know if they had a problem with their memory
- Fewer delegates said they would like to know they had a greater risk of dementia
- Fewer delegates said they would like to know if they had a problem with dementia
- Fewer delegates said people should be tested for dementia
- Fewer delegates said they thought screening was harmless.

Quality appraisal	This qualitative public and patient involvement study was a workshop event set up as a quasi focus group in England to explore the themes emerging from the systematic review by Martin et al (2015a). It is not published as a standalone piece of qualitative research and has significant sources of bias including a small number of participants, recruited from the public and from research partners.

Table 34. Smith et al (2018)

Publication	Smith T et al Systematic review MDT approach to early diagnosis of dementia and screening in primary care. Positive and negative effects and who should deliver it? 2018 Current Alzheimer's research 15 5-17.
Study details	Systematic review
Study objectives	To examine the potential positive and negative effects of early diagnosis or screening programmes for dementia in primary care
Inclusions	Studies conducted in primary care to October 2015
Exclusions	Where cohort was ≥80% less than 65 years of age
Population	People ≥65 years of age undergoing early diagnosis or screening for dementia
Intervention	N/A
Comparator	N/A
Outcomes	Outcomes extracted from the full paper below relate only to perceptions and views of health professionals, caregivers, patients and the general population. Improved long and shorter term outcomes: • Two studies from the US reported that in older adults there was acceptance of dementia screening with 86% (n=345) and 90% (n=554) reporting that they would be happy to be screened. However in a similar population when actually invited to be screened only 63% (n=400) of people took up the offer. • Health professionals may not be convinced that dementia detection improves outcomes. One study of 249 Canadian GPs suggested 35% were undecided whether dementia screening would improve outcomes for patients • There is variability in the confidence of professionals to screen for dementia. One study reported community mental health nurses felt most confident to assess people for dementia (87%) a similar figure to GPs (81%) compared to community nurses (46%) and nurse practitioners (42%). However only 11% of community mental health nurses were confident about assessing people for MCI. • Concern by the public and professionals about the uncertainty of the accuracy of the screening test and subsequent impact for those screen detected who are false positives (which may be difficult to ascertain in the short term). • Lack of treatment options following detection – there was a perception that treatment and management of dementia was ineffective and a diagnosis of dementia was perceived as a 'death sentence'. • Social consequences following detection such as employment status, options for health insurance and life insurance, social isolation due to stigma surrounding the disease.

	• Psychological consequences and development of depression and anxiety due to detection of dementia • Concern by health care providers that resources are not available to support all those who would be screen detected with dementia • Concern that primary care health professionals would need additional training to be able to deliver a screening programme as they don't currently have the skills • Increased detection was mentioned as a positive benefit in 7 papers as it would support planning of services, and time for the family to plan care; avert crises and come to terms with the diagnosis.
Quality appraisal	The CASP checklist for systematic reviews was used to assess the quality of this review and there were no concerns.

Table 35. Tang et al (2018)

Publication	Tang W, Kannaley K, Friedman DB, Edwards VJ, Wilcox S, Levkoff SE, et al. Concern about developing Alzheimer's disease or dementia and intention to be screened: An analysis of national survey data. Archives of Gerontology and Geriatrics. 2017 01 Jul;71:43-9.
Study details	Survey
Study objectives	Using randomly recruited panel members from the Porter Novellis Summer Styles 2013 online survey in the US the authors aimed to examine people's worries about developing Alzheimer's disease or dementia, their intention to be screened and concerns about sharing diagnostic information with others.
Inclusions	6015 people were randomly recruited from 50,000 survey panellists
Exclusions	NA
Population	6015 sample of US survey panellists representing the general population
Intervention	N/A
Comparator	N/A
Outcomes	4033 adults completed the entire survey • Women (15%) were significantly more worried about getting AD/dementia than men (10.5%, p<0.001) • Adults over 45 were more worried about getting AD/Dementia compared to younger adults especially those aged 45-59 (15.5% vs12.8% aged 30-44 and 11.4% aged 18 to 29, p<0.001) • Care givers (18.4%) more worried than non-caregivers (11.4%) about getting AD/dementia (p=0.004) • Women (52%) were more likely to agree to be screened than men (41.9%, p<0.001) • Older people aged 60+ (50.8%) were more likely to agree to be screened than younger adults(18-29=42.9%, 30-44=46%,45-59=48%, p=0.011) • Caregivers (54.8%) were more likely to agree to be screened than non-caregivers (45.9%, p= 0.005) • Women (33.9%) were more concerned than men (27.6%) about sharing their diagnostic information with family and friends (p=0.003) • Concerns about sharing information included concerns about being left out of activities, being treated differently and having to give up driving.

	Gender		Age				Care giver status	
	Women N(%)	Men N(%)	18-29 N(%)	30-44 N(%)	45-59 N(%)	60+ N(%)	Caregiver N(%)	Non-caregiver N(%)
Level of worry about getting Alzheimer's disease/dementia								
Very worried or worried	337(15.0)	219(10.5)	64(11.4)	156(30.8)	200(45.7)	65(12.1)	113(18.4)	443(11.9)
Somewhat worried	1005(45.3)	831(38.2)	127(12.8)	389(38.5)	306(36.8)	85(11.8)	308(44.3)	1524(41.5)
Not at all worried	599(30.1)	706(41.1)	208(15.5)	621(43.1)	449(32.1)	102(9.3)	178(29.9)	1121(36.2)
Don't know	164(9.6)	155(10.1)	157(11.0)	670(52.9)	350(29.4)	67(6.7)	47(7.4)	271(10.3)
Likelihood of agreeing to be tested								
Very likely or likely	1100(52.0)	874(41.9)	211(42.9)	450(46.0)	690(48.0)	623(50.8)	359(54.8)	1612(45.9)
Somewhat likely	655(27.8)	641(33.2)	140(28.3)	276(29.4)	438(31.6)	442(31.9)	187(28.3)	1106(30.8)
Not at all likely	181(10.4)	222(13.6)	62(13.3)	96(13.0)	141(11.1)	104(10.7)	58(11.2)	343(12.0)
Don't know	174(9.8)	170(11.3)	73(15.5)	87(11.7)	109(9.3)	75(6.6)	42(5.7)	299(11.3)
Concerns about sharing diagnostic information								
Very concerned or concerned	757(33.9)	573(27.6)	161(29.7)	326(34.5)	505(33.8)	338(24.6)	240(34.3)	1088(30.3)
Somewhat concerned	763(35.9)	686(34.2)	171(35.5)	308(32.7)	467(32.3)	503(40.3)	220(36.3)	1226(34.9)
Not at all concerned	427(20.9)	488(26.0)	93(21.6)	176(20.5)	318(24.6)	326(26.4)	147(22.4)	763(23.5)
Don't know	152(9.3)	160(12.2)	54(13.3)	96(12.2)	88(9.2)	74(8.7)	38(7.0)	273(11.3)

Data were weighted by gender, age, household income, race/ethnicity, household size, education, census region, metro status and prior internet access.

Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this review and there were no concerns

Table 36. Fowler et al (2015)

Publication	Fowler NR, Perkins A J, Turchan HA, Frame A, Monahan P, Gao S et al. Older primary care patients attitudes and willingness to screen for dementia. J Aging Res 2015:423265(2015).
Study details	Mixed methods study
Study objectives	To understand older primary care patient's perceptions of the risks and benefits of dementia screening and to measure the association between attitudes and screening behaviours
Inclusions	People were community dwelling ≥65 years of age and had no diagnosis of dementia and had seen their primary care physician in the past 12 months.
Exclusions	Patients who did not speak English, had hearing loss that precluded them from communicating via telephone or had severe mental illness.
Population	400 participants from 2 US primary care sites
Intervention	Researchers' contacted people by phone and after consent administered the questionnaire Perceptions Regarding Investigational Screening for Memory in Primary Care (PRISM-PC) and asked participants to undergo screening for dementia. If participants agreed to screening this would be carried out in the same phone call using the Telephone Instrument for Cognitive Screening. Participants who scored ≤30 were referred to a specialist.
Comparator	N/A
Outcomes	Following questionnaire completion a similar proportion of people refused screening at both sites, (37.7% and 36.1% p=0.746). For both sites participants who refused screening had significantly ($p<0.001$ and $p=0.002$) lower questionnaire scores (67.7 and 65.6) on the perceived benefits of screening compared to those who accepted screening (73.8 and 72.1).
Quality appraisal	The CASP checklist for cohort studies was used to assess the quality of this review. It was not clear at what point during the telephone contact with participants that they were asked if they would consent to be screened. This could have been before or after the questionnaire was administered and may have had an impact on their response. In addition by asking for people's views then asking them if they would act in accordance with their views almost immediately this could introduce social desirability bias (a tendency of some respondents to report an answer in a way they feel to be more socially acceptable than what they consider is the 'true' answer) i.e. 'if I have just said I think dementia screening is acceptable then I should probably go ahead and carry out the test even if I might have second thoughts later'.

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in

Table 37. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1 TITLE AND SUMMARIES			
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	7
2 INTRODUCTION AND APPROACH			
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	12
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	21

2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	25
3 SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)			
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	60
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	60
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	20,26,35,40 ,45,51
4 STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)			
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	69
5 QUESTION LEVEL SYNTHESIS			
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	27,36,41,46 ,48,52,
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	27,37,42,48 ,52
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question,	34,43,50,56

		with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	
6 REVIEW SUMMARY			
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	58
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	58

References

[1] NICE Dementia: Assessment, management and support for people living with dementia and their carers 2018 NICE Guideline 97.

[2] Prince, M, Knapp, M, Guerchet, M, McCrone, P, Prina, M,Comas-Herrera, A, Wittenberg, R, Adelaja, B, Hu, B, King, D,Rehill, A and Salimkumar, D. Dementia UK: Second edition – Overview 2014 Alzheimer's Society 2014.

[3] Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016. (http://www.healthdata.org/gbd).

[4] World Health Organisation 2017 Global action plan on the public health response to dementia 2017-2025 Switzerland.

[5] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet.2017. [PMID: 28735855] doi:10.1016/S0140-6736(17)31363-6.

[6] Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Tuomilehto, Soininen H, Kivipelto M. A 2 year multi-domain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet 2015;vol 385 ISSUE 9984; 2255-2263.

[7] Perminder S. Sachdev; Darren M. Lipnick; Nicole A. Kochan; John D. Crawford et al The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration PLoS One. 2015; 10(11): e0142388.

[8] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders 5th ed. Washington DC American Psychiatric Association 2013.

[9] Petersen RC, Caracciolo B, Brayne C et al. Mild cognitive impairment a conception in evolution Journal of internal medicine 2014;275:214-228.

[10] Public Health Resource Unit. Appraisal for screening for Alzheimer's Disease 2009 PHRU. Oxford

11 Solutions for Public Health. Screening for dementia: can screening bring benefits to those with unrecognised dementia, their carers and society? An appraisal against UK NSC criteria. A report for the UK National Screening Committee. 2014.SPH, Oxford.

[12] Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatrica Scandinavica. 2009;119(4):252-65.

[13] Canevelli M, Grande G, Lacorte E, Quarchioni E, Cesari M, Mariani C, et al. Spontaneous Reversion of Mild Cognitive Impairment to Normal Cognition: A Systematic Review of Literature and Meta-Analysis. Journal of the American Medical Directors Association. 2016;17(10):943-8

[14] Davis M, O Connell T, Johnson S, Cline S, Merikle E, Martenyi F, et al. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. Current Alzheimer Research. 2018;18:18

[15] Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. American Journal of Psychiatry. 2015;172(4):323-34.

[16] Clem MA, Holliday RP, Pandya S, Hynan LS, Lacritz LH, Woon FL. Predictors That a Diagnosis of Mild Cognitive Impairment Will Remain Stable 3 Years Later. Cognitive & Behavioral Neurology. 2017;30(1):8-15

[17] Diniz BSO, Pinto Junior JA, Forlenza OV. Do CSF total tau, phosphorylated tau, and beta-amyloid 42 help to predict progression of mild cognitive impairment to Alzheimer's disease? A systematic review and meta-analysis of the literature. World Journal of Biological Psychiatry. 2008;9(3):172-82

[18] Jang H, Ye BS, Woo S, Kim SW, Chin J, Choi SH, et al. Prediction Model of Conversion to Dementia Risk in Subjects with Amnestic Mild Cognitive Impairment: A Longitudinal, Multi-Center Clinic-Based Study. Journal of Alzheimer's Disease. 2018;61(2):825

[19] Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural predictors of Alzheimer's disease: A meta-analysis of VBM studies. Neurobiology of Aging. 2011 October;32(10):1733-41.

[20] Scarabino D, Broggio E, Gambina G, Maida C, Gaudio MR, Corbo RM. Apolipoprotein E genotypes and plasma levels in mild cognitive impairment conversion to Alzheimer's disease: A follow-up study. American Journal of Medical Genetics. 2016;Part B, Neuropsychiatric Genetics:the Official Publication of the International Society of Psychiatric Genetics. 171(8):1131-8

[21] Santana I, Baldeiras I, Santiago B, Duro D, Freitas S, Pereira MT, et al. Underlying Biological Processes in Mild Cognitive Impairment: Amyloidosis Versus Neurodegeneration. Journal of Alzheimer's Disease. 2018;16:16.

[22] Peterson RC, Smith GE, Waring SC et al Mild cognitive impairment: clinical characterisation and outcome. Arch Neurol Psychiatry 1999;56:303-308.

[23] Seitz DP, Chan CC, Newton HT, Gill SS, Herrmann N, Smailagic N, et al. Mini-Cog for the diagnosis of Alzheimer's disease dementia and other dementias within a primary care setting. Cochrane Database of Systematic Reviews. 2018;2:CD011415.

[24] Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated

people aged 65 and over in community and primary care populations. Cochrane Database of Systematic Reviews. 2016;(1):CD011145.

[25] Quinn TJ, Fearon P, Noel-Storr AH, Young C, McShane R, Stott DJ. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within community dwelling populations. Cochrane Database of Systematic Reviews. 2014;(4):CD010079.

[26] Carson N, Leach L, Murphy KJ. A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. International Journal of Geriatric Psychiatry. 2018 February;33(2):379-88

[27] Fuchs A, Wiese B, Altiner A Wollny A Pentzek M. Cued recall and other cognitive tasks to facilitate dementia recognition in primary care. Journal of the American Geriatrics Society 2012 60;130-5

[28] Holsinger T, Plassman BL, Stchuchak KM, Burke JR, Coffman CJ, Williams JW. Screening for cognitive impairment: comparing instruments in primary care Journal of the American Geriatrics Society 2012;60: 210-7

[29] Noel-Storr AH, Flicker L, Ritchie CW, Nguyen GH, Gupta T, Wood P, et al. Systematic review of the body of evidence for the use of biomarkers in the diagnosis of dementia. Alzheimer's & Dementia. [Review]. 2013;9(3):e96-e105.

[30] Frisoni G, Boccardi M Barkhof F, Blennow K, et al Strategic roadmap for an early diagnosis of Alzheimers disease based on biomarkers The Lancet Neurology, 201716(8);661-676

[31] Lin JS, O'Connor E, Rossom R, Perdue LA, Burda BU, Thompson M, Eckstrom E. Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force. Evidence Report No. 107. AHRQ Publication No. 14-05198-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013.

[32] Kane RL, Butler M, Fink HA, Brasure M, Davila H, Desai P, Jutkowitz E, McCreedy E, Nelson VA, McCarten JR, Calvert C, Ratner E, Hemmy LS, Barclay T. Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. Comparative Effectiveness Review No. 188. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I.) AHRQ Publication No. 17-EHC008-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017.

[33] Smith T et al Sustematic review MDT approach to early diagnosis of dementia and screening in primary care. Positive and negative effects and who should deliver it? 2018 Current Alzheimers research 15 5-17

[34] Martin S, Kelly S, Khan A, Cullum S, Dening T, Rait G, et al. Attitudes and preferences towards screening for dementia: a systematic review of the literature. BMC Geriatrics. 2015;15:66.

[35] Martin S, Fleming J, Cullum S, Dening T, Rait G, Fox C, et al. Exploring attitudes and preferences for dementia screening in Britain: contributions from carers and the general public. BMC Geriatrics. 2015;15:110.

[36] Tang W, Kannaley K, Friedman DB, Edwards VJ, Wilcox S, Levkoff SE, et al. Concern about developing Alzheimer's disease or dementia and intention to be screened: An analysis of national survey data. Archives of Gerontology and Geriatrics. 2017 01 Jul;71:43-9

[37] Fowler NR, Perkins A J, Turchan HA, Frame A, Monahan P, Gao S et al. Older primary care patients attitudes and willingness to screen for dementia. J Aging Res 2015:423265(2015).