

# Review: Diagnosing early cognitive decline - when, how and for whom?

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## ABSTRACT

Mild cognitive impairment (MCI) is a term to describe cognitive impairment in one or more cognitive domains that is greater than any expected age related changes, but not of the magnitude to warrant a diagnosis of dementia. This review considers how early cognitive decline is diagnosed, focusing on the use of neuropsychological tests and neuroimaging, as well as the differential diagnosis. Potential treatments, including secondary prevention, post-diagnostic support and self-help are discussed. Finally, medico-legal matters such as driving, lasting power of attorney and employment are outlined.

# CONTENT

<b>ABSTRACT .....</b>	<b>1</b>
<b>CONTENT .....</b>	<b>2</b>
<b>INTRODUCTION .....</b>	<b>3</b>
<b>METHODS .....</b>	<b>3</b>
<b>WHO SHOULD BE REFERRED AND WHEN? .....</b>	<b>3</b>
<b>DIAGNOSIS .....</b>	<b>3</b>
CONCEPT AND DIAGNOSTIC CRITERIA .....	3
ASSESSMENT .....	4
<i>Cognitive function</i> .....	4
<i>Activities of daily living (ADL)</i> .....	5
NEUROIMAGING .....	5
<i>Structural</i> .....	5
<i>Functional and Amyloid Imaging</i> .....	5
<b>DIFFERENTIAL DIAGNOSIS.....</b>	<b>6</b>
<b>TREATMENTS.....</b>	<b>7</b>
TREATMENT FOR MCI .....	7
SECONDARY PREVENTION .....	7
POST-DIAGNOSTIC SUPPORT .....	7
SELF-HELP .....	8
MEDICOLEGAL MATTERS .....	8
<i>Driving</i> .....	8
<i>Lasting power of attorney</i> .....	8
<i>Employment</i> .....	8
<b>CONCLUSIONS .....</b>	<b>9</b>
<b>CONFLICTS OF INTEREST .....</b>	<b>9</b>
<b>REFERENCES.....</b>	<b>10</b>

## INTRODUCTION

Mild cognitive impairment (MCI) describes cognitive impairment in one or more cognitive domains that is greater than any expected age related changes, but not of the magnitude and functional impact to warrant a diagnosis of dementia. Depending on the criteria used, the prevalence of MCI in the elderly (aged 75 and older) is found to be between 3 and 20% (1). The conversion rate of those with MCI to dementia is similarly hard to estimate, but may be between 23 and 47% over 2.6 years (1).

By the time dementia is diagnosed, substantial, irreversible neurological damage has occurred. Current therapies aim to slow further neurodegeneration. Developing a treatment for MCI, or identifying those who are likely to progress to dementia and starting treatment early, could confer huge health benefits for the population and is the focus of development of novel treatments. There is some evidence that secular changes, possible due to change in lifestyle or prophylaxis of cardiovascular disease has already had an impact on incidence of dementia (2).

This review considers how early cognitive decline is diagnosed, ramifications of the diagnosis and potential treatments.

## METHODS

We searched PubMed until October 2016, using the search terms [Mild cognitive impairment or MCI] and [diagnosis or neuropsychology or neuroimaging]; [Mild cognitive impairment or MCI] and [treatment or memantine or donepezil or cholinesterase inhibitor]; dementia and employment. We identified additional studies by hand-searching reference lists.

## WHO SHOULD BE REFERRED AND WHEN?

NICE advises that a referral to memory clinic should be considered for all people who show signs of mild cognitive impairment (3). Memory clinics are usually within secondary care, although increasingly GPs are taking an active role in the assessment and diagnostic process.

## DIAGNOSIS

### Concept and diagnostic criteria

The main aim when assessing patients presenting with early cognitive decline is to distinguish MCI from normal ageing and dementia and then, if possible, to identify the subgroup of patients with MCI, who will progress to dementia.

Differentiating MCI from cognitive ageing is challenging because health and pathology overlap. There is a significant heterogeneity in physical, as well as cognitive ageing, with people experiencing more or less severe trajectories of decline as they get older. It is increasingly understood that ageing per se does not cause decline and the observed changes are a result of cumulative pathology. The relationship between pathology and clinical symptoms, however, is not straightforward; the balance between factors conferring risk (age, lifestyle, vascular risk factors) and resilience (education, premorbid IQ) determines whether and how soon cognitive deficits develop in the presence of pathology.

More recently, the concept of 'pre-MCI' or 'subjective cognitive decline (SCD)' has been proposed; it is defined as a stage at which individuals perceive subjective changes in their cognitive abilities, but perform within normal limits on cognitive tests (4). SCD has been associated with an increased risk of AD biomarker abnormalities (4-6) and dementia (7, 8). Further research is required to investigate the heterogeneity in ageing and to confirm the validity of the 'SCD' construct.

The concept of MCI has evolved over the years. The original Mayo Clinic criteria for a diagnosis of MCI include self- or informant-reported memory complaints and objective memory impairment with essentially preserved general cognitive functioning (9). For the NIA-AA revised criteria, decline in memory is not mandatory for the diagnosis; impairment in executive function, attention, visuospatial skills, or language, with or without memory impairment also warrants a diagnosis of MCI (10). The key criteria that distinguish MCI from dementia are preservation of independence in functional abilities, and lack of significant impairment in social or occupational functioning (10). The US-American DSM-5 refers to this intermediate stage as 'mild neurocognitive disorder', but the criteria used to define it are essentially the same. The main difference between MCI and mild neurocognitive disorder is that the research that led to the construct of MCI primarily involved elderly subjects, while mild neurocognitive disorder includes acquired cognitive disorders at all ages (11).

## Assessment

All patients with suspected MCI should undergo a comprehensive assessment, including history, cognitive, mental state, physical and neurological examination, medication review and laboratory testing (3). Comprehensive assessment is required to identify potentially reversible forms of MCI due to other conditions (depression, B12 deficiency, medication effects). Although reversible causes have decreased over the last years, they remain an important cause of cognitive impairment and represent about 9 % of all dementia causes (12). As dementia, MCI can be due to one or more aetiologies, with Alzheimer pathology, vascular disease and Lewy body pathology being the three most common.

### Cognitive function

The first step in the assessment of cognitive function is obtaining a history of cognitive changes over time, confirmed by a reliable informant, if available. Onset, nature, and time-course of cognitive symptoms should be explored. The history provides information that can help to infer the likely primary aetiology. A chief complaint of progressive memory decline is suggestive of Alzheimer's type pathology, multiple vascular risk factors point towards vascular contribution, while fluctuating course, perceptual abnormalities, motor symptoms and REM-sleep behaviour disorder are associated with Lewy body pathology.

Objective evidence for impairment from neuropsychological tests is then required to confirm the diagnosis. Scores on cognitive tests for individuals with MCI are typically 1-1.5 standard deviation below the mean for their age and education, although these ranges are guidelines and not cut-off scores (13).

The neuropsychological test used should assess all cognitive domains, including executive function, visuospatial skills, attention, language, and memory. A systematic review of 26 studies of screening tools for MCI demonstrated that all four comprehensive screening tests (ACE-R, CAMCOG, MoCA, CERAD) and only three (DemTect, M@T, ABCS) of the eleven non-comprehensive screening tests had sensitivities over 80% for detecting MCI among healthy volunteers (14). Although brief cognitive screening tests can detect dementia, most of them are not suitable for detecting MCI due to their lower sensitivity.

MCI sub-types are defined by presence or absence of memory difficulties (amnesic vs. non-amnesic MCI (15)) and the number of affected cognitive domains (single-domain vs. multi-domain MCI (13)). Amnesic MCI is associated with AD, 10-15% of patients per year progress to a diagnosis of probable AD, compared with only 1% to 2% of the general elderly population (15). Patients with non-amnesic MCI more often develop dementias that are not related to AD, such as vascular, frontotemporal or dementia with Lewy bodies (15).

When interpreting the results of neuropsychological tests, it is important to consider that all are sensitive to differences in age, education and cultural background (13). In patients with subtle cognitive decline, formal neuropsychological testing or serial testing to detect intra-individual decline may be considered (3). Repeat cognitive assessments also decrease the risk that poor performance on a single assessment due to anxiety, fatigue or acute illness leads to a false positive diagnosis of MCI (16).

#### Activities of daily living (ADL)

Standardised instruments are available for assessment of everyday functioning (e.g. the Bristol activities of daily living scale). People with MCI remain independent in daily life, although they often have mild difficulties performing complex tasks. A recent review demonstrates consistent deficits in global or specific ADL in MCI, with financial capacity being affected in most studies. Performance-based measures were found to be more sensitive than informant-reported. Compared to healthy controls, patients with MCI needed longer to complete tasks and made more mistakes (17). Functional deficits in MCI were also found to predict the likelihood of dementia (18).

## Neuroimaging

#### Structural

In individuals with MCI, structural imaging is useful not only to exclude other causes of cognitive impairment, such as space occupying lesions, but also provides information about the possible underlying pathology and prognosis. MRI evidence of disproportionate medial temporal lobe atrophy (MTA), which is the most characteristic neuroimaging feature of AD, suggests underlying Alzheimer's type pathology (19, 20). The probability of converting from MCI to AD increases with greater baseline MTA scores; e.g. after three years, fewer than 40% of patients with an MTA score of 0 (i.e. normal) converted to AD, compared with more than 75% with baseline MTA score of 3 (i.e. severe atrophy) (21).

Structural MRI can also show evidence of vascular pathology, with small-vessel disease being the most common (22). Small-vessel disease is defined as lesions involving >25% of the white matter, and appears on MRI as white matter hyperintensities (WMH), small subcortical infarcts, lacunes and microbleeds (23). Depending on the study, WMH are found in 10-90% of cognitively healthy elderly and are clinically and pathologically heterogeneous (24). However, as WMH become more extensive, they are more likely to be clinically significant (25). Mixed pathologies are common, and the presence of WMH does not exclude other possible pathologies.

#### Functional and Amyloid Imaging

Changes in function and molecular composition of brain tissue typically precede atrophy detectable by structural imaging. The dynamic biomarkers model of AD proposes that at first, markers of amyloidosis become positive, followed by markers of cortical hypometabolism on FDG-PET, and last, markers of brain atrophy (26). In MCI with AD pathology, perfusion abnormalities on SPECT or reduced metabolism on FDG-PET are seen in the frontal association-, posterior cingulate- and temporoparietal cortex (27, 28), and they predict conversion from MCI to AD (29). In vascular cognitive impairment, the pattern is different, with focal hypometabolism observed in sensorimotor cortex and subcortical areas, while the association cortex is relatively spared (30, 31).

Amyloid imaging provides direct evidence of the presence of Alzheimer's type pathology and in patients with MCI has a very good predictive value for conversion to AD (32, 33). More than 90% of patients with AD show increased cortical binding (34), and false-negative cases are reported only rarely (35). Amyloid deposition, however, increases with age; up to 30 % of healthy controls aged 80

had positive scan, compared with 0% below the age of 50 (36). Negative scans do not discount progression, as neurodegenerative diseases without amyloidosis such as FTD cannot be excluded.

When considering the use of imaging in the evaluation of cognitive impairment, particularly some of the newer techniques, the limitations of each test and the possible benefits and harms of ‘knowing’ must be considered in advance (37). There is substantial overlap between pathology and health and a large proportion of cases have mixed pathologies, implying that a combination of tests will be required.

## DIFFERENTIAL DIAGNOSIS

Diagnosis of MCI requires a confirmation of cognitive impairment that is beyond that which is to be expected with normal ageing, but not as marked or progressive as to be classified as one of the dementia subtypes. Any identifiable underlying process or pathology that may contribute to the cognitive impairment should be considered in the differential diagnosis (see Table 1).

*Table 1- Differential Diagnosis of Mild Cognitive Impairment*

Differential Diagnoses	Notes
Dementia (including Alzheimer’s disease, Frontotemporal lobe dementia, Dementia with Lewy Bodies, Parkinson’s Disease Dementia, Vascular dementia etc.)	Chronic, progressive impairment in multiple cognitive domains with impairment in everyday functioning
Delirium	Acute and fluctuating presentation. Evidence of other symptoms of delirium (e.g. clouding of consciousness, sleep disturbance)
Depression	May present as subjective cognitive impairment with objective cognitive slowing. Look for other symptoms of depression, including biological symptoms (sleep and appetite disturbance)
Other neurodegenerative conditions or brain tumour	For example: Multiple Sclerosis, Huntington’s Disease, CJD. Other neurological symptoms likely to be present
Iatrogenic	Medication, particularly those with a high anticholinergic burden or polypharmacy may lead to cognitive blunting
Endocrine disturbance	For example: hypothyroidism, hyperthyroidism, hypopituitarism, Cushing’s disease. Other systemic symptoms likely to be present
B12 deficiency	May have other neurological symptoms too. Reversible with B12 therapy
Normal Pressure Hydrocephalus	Classic triad of cognitive impairment, urinary incontinence and gait disturbance
Korsakoff Syndrome	Severe vitamin B1 deficiency, usually associated with alcohol abuse
Traumatic brain injury	Positive history
Transient global amnesia	Discrete period of amnesia

## TREATMENTS

### Treatment for MCI

There is no randomised controlled trial evidence that treatment for MCI can improve cognition, function, global outcomes, quality of life or incident dementia (38). There is no evidence that anti-cholinesterase drugs are beneficial in MCI (38, 39). The lack of effective treatments for MCI is disappointing and has led some to question the value of early diagnosis. There is putative evidence for nor-adrenergic based therapies, polyphenolic compounds (e.g. Ginkgo biloba, green tea, wines) which have anti-oxidant and anti-inflammatory activity, B-vitamins, and Vitamin E, but there are no large randomised controlled trials to support use of these compounds (38-40).

It is well recognised that depressive disorder may influence the onset and course of cognitive decline, and increases the risk of conversion to dementia (40, 41). Therefore, where there is evidence of low mood, treating this may improve cognitive symptoms or reduce the risk of incident dementia (42).

There is no clear evidence for use of non-pharmacological approaches to the treatment of MCI. Social interventions, such as exercise, may have a small benefit for cognition in patients with MCI, but further studies are needed to establish this with greater confidence (43). Psychological approaches to treatment for MCI have been proposed. Randomised controlled trials have shown that cognitive training may promote small improvements in selected cognitive abilities, activities of daily living and mood (44, 45), but have little overall effect on quality of life (46). Methodological limitations, such as lack of long-term clinical follow-up and significant differences between study criteria, further reduce confidence in these findings.

### Secondary prevention

Although there is no effective treatment for MCI, there has been much interest in developing interventions for secondary prevention, i.e. to prevent disease progression from MCI to dementia. Anti-dementia drugs have been trialled in MCI, but there is currently no clear evidence that use of these can reduce the risk of conversion from MCI to Alzheimer's disease (38, 39, 45). Other therapies have been proposed, but there is no evidence that compounds, such as statins, non-steroidal anti-inflammatories, ginkgo biloba or vitamin E have a significant effect in reducing incident Alzheimer's disease (39).

A systematic review of modifiable risk factors for incident dementia in MCI identified a number of predictive and protective factors (42). Diabetes, pre-diabetes and metabolic syndrome increased the risk of conversion from amnesic MCI to Alzheimer's and other types of dementia, including vascular dementia (42). This provides an additional reason to promote careful attention to avoidance of diabetes and metabolic syndrome, and close attention to diabetic control. Other predictors of incident dementia were neuropsychiatric symptoms, lower serum folate levels, no Mediterranean style diet, and possibly depressive symptoms (42). Therefore, focus on dietary interventions and treatment of neuropsychiatric symptoms, including depression, may reduce conversion to dementia. Hypertension, hypercholesterolaemia and smoking were not identified as predictive risk factors (42).

### Post-diagnostic support

Systematic follow-up of patients with MCI is a contentious issue. From an individual perspective, regular follow-up and repeat cognitive testing may help to determine the tipping point from MCI to dementia accurately and, therefore, to initiate treatment. However, service pressures mean that many patients diagnosed with MCI are discharged back to primary care and are re-referred when more significant problems have developed. Given this approach to follow up, it is even more vital that patients and their carers are well educated about their diagnosis, the signs and symptoms that may

indicate deterioration, and that they have good access to support from third sector organisations, such as Age UK or the Alzheimer's Society.

## Self-help

Given the lack of medication available for those with mild cognitive impairment, people with a diagnosis of MCI may seek out “self-help” methods of maintaining their cognitive function and reducing likelihood of developing dementia. “Brain-training” and similar cognitive interventions have been found to confer some benefits (improved immediate and delayed verbal recall) but these benefits are not specific to cognitive interventions and were also seen in an “active control” group (47). Physical exercise improves cardiovascular health, which in turn is associated with cognitive health, but there is no substantial evidence to demonstrate that exercise has any effect on the outcomes for people with MCI (38). Weak evidence supports a Mediterranean diet and social activity for preservation of cognitive function (16).

## Medicolegal matters

### Driving

Patients diagnosed with dementia have a duty to inform the Driver and Vehicle Licensing Agency (DVLA) in the UK, regardless of whether they are deemed fit to drive. Patients with MCI are not required to inform the DVLA, unless there is a possible driving impairment. In some cases, the DVLA may request that patients with MCI who may not be safe to drive undergo a driving assessment (48). A patient's fitness to drive will be regularly reviewed, particularly if the patient subsequently develops dementia.

### Lasting power of attorney

In England and Wales individuals can choose to nominate a “Lasting Power of Attorney” (LPA) to make decisions on their behalf, should a time come when the individual lacks the capacity to make such decisions. A diagnosis of MCI may provide the impetus for individuals to plan, creating LPAs while they still have capacity to appoint attorneys and complete the paperwork.

Separate LPA forms are required for “health and welfare” and “property and affairs”. An individual completing the form may nominate a single attorney or more than one and specify if the attorneys must act jointly, severally or a combination of both. Completion of LPA paperwork does not require a solicitor but the paperwork must be signed by a professional or someone who has known the applicant for at least two years and is independent of the process. LPA forms must be registered with the Office of the Public Guardian before they can be used, but the attorneys have no right to make any decision until the individual is found to lack capacity to make such a decision. When making decisions, attorneys must demonstrate they are following the principles of the Mental Capacity Act 2005 (49), by acting in the person's best interests and taking into account the person's former wishes and beliefs.

### Employment

With the increase in statutory retirement age in the UK, there is likely to be an increase in the number of people in employment with a diagnosis of MCI or dementia, conditions which occupational health physicians are currently not accustomed to manage (50). As with any disability, the Equality Act 2010 (51) requires employers to make “reasonable adjustments” for an employee to be able to maintain his job. What such adjustments may be in the case of employees with dementia depends on the job and is largely uncharted water for most employers, with early evidence suggesting that adjustments are not being made (52); the application of this legislation to employees with cognitive impairment may be further clarified by case law in the future.



## CONCLUSIONS

Diagnosis of MCI can be made by specialists following a thorough assessment including use of neuropsychological tests and neuroimaging. At present, there is no specific treatment available for MCI, and the advantage of knowing the diagnosis is centred around understanding the cause of clinical symptoms, the potential for risk factor modification (particularly vascular risk factors and diabetes), and enabling patients to engage in advance decision making at a point when they are likely to have the capacity to do so. One significant advantage of making a diagnosis of MCI is yet to be fully realised: the potential for starting disease modifying treatments that can prevent or delay the development of dementia. Further research needs to focus on use of biomarkers to diagnose subtle cognitive changes with high specificity and sensitivity, and to understand the factors that predict decline from MCI to dementia. The development of effective treatments for MCI that prevent further deterioration in cognitive impairment would radically change the outlook for patients and for services, offering a major incentive for early diagnosis.

## CONFLICTS OF INTEREST

CLA has attended an educational seminar on Amyloid Imaging sponsored by Eli Lilly. The other authors declare no interests.

## AUTHOR CONTRIBUTION

All authors contributed to the writing of the review and reviewed the final version.

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