

Mild Cognitive Impairment

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INTRODUCTION

The concept Mild Cognitive Impairment (MCI) has been introduced to describe cognitive impairment in nondemented subjects. The prevalence of MCI varies between 2 and 30% in the general population and between 6 and 85% in a clinical setting (average 40%) (Visser, 2000). Subjects with MCI are of major clinical importance because they have an increased risk of developing Alzheimer-type dementia. However, there is much confusion about the concept of MCI: there is no uniform definition, there is no single underlying cause, and the long-term outcome appears to be heterogeneous. In this chapter, definitions of MCI and terminology used, causes of MCI, outcome of MCI, and predictors of dementia will be discussed.

DEFINITIONS AND TERMINOLOGY OF MCI

MCI refers to the presence of cognitive impairment that is not severe enough to meet the criteria of dementia. It has been operationalized in many ways. In a review of the literature performed in 2004, we identified more than 40 definitions of MCI. On the basis of these different MCI definitions, six major concepts can be identified: MCI definitions based on cognitive complaints only, on the presence of mild functional impairment only, on the presence of impairment on cognitive tests only, on a combination of cognitive complaints and test impairment, on a combination of mild functional impairment and test impairment, and on mild functional impairment or test impairment (Table 1). Definitions that fall within the same concept can be further classified according to the cognitive domain that is impaired: impairment in at least the memory domain, in only the memory domain, in any domain, or in a combination of domains. Also, the definition of impairment on cognitive tests is variable and ranges from a score 1 standard deviation below the mean in healthy young subjects to a score 2 standard deviations below the mean in

age-matched control subjects. As can be seen in Table 1, the terminology is variable because different terms refer to similar MCI concepts and the same terms are used for different MCI concepts. The MCI definition that is most widely used is that of amnesic MCI (Petersen *et al.*, 1999). It requires a memory complaint, impairment on a memory test after correction for age and education, preserved general cognitive functioning, intact activities of daily living, and absence of dementia. However, due to a lack of detailed criteria, this definition has been operationalized in many different ways. Another common MCI definition is that of Age-Associated Memory Impairment (AAMI) (Crook *et al.*, 1986). It requires a complaint of memory impairment, a score on a memory test one standard deviation below the mean performance of healthy young adults, adequate intellectual functioning, absence of dementia, and absence of diseases that may cause memory impairment. This definition was common in the period 1986–1995, but it is presently less often used.

The lack of standardization is confusing and limits the interpretation of MCI studies. In the remaining part of the chapter, the term MCI will be used for cognitive impairment that do not meet criteria for dementia. It does not refer to any specific definition.

CAUSES OF MCI

One of the most important causes of MCI is Alzheimer's disease. However, all somatic, other neurological, or psychiatric disorders that influence brain functioning can also cause MCI. From a diagnostic perspective, these conditions can be classified in three groups (Visser, 2003). The first group of conditions are obvious causes for MCI. This means that they are a sufficient cause for the impairments and can be identified by clinical examination and/or ancillary tests like laboratory tests or neuroimaging (see Table 2 part A for examples). The second group of conditions are sufficient causes for the MCI that can presently not be diagnosed by

Table 1 Main MCI concepts

1.	Cognitive complaints Examples: MCI (Tei <i>et al.</i> , 1997), minor cognitive impairment (Visser <i>et al.</i> , 2002a), questionable dementia (Thompson <i>et al.</i> , 2002), memory impairment (Tierney <i>et al.</i> , 1996).
2.	Mild functional impairment Examples: MCI or questionable dementia (a score of 0.5 on the Clinical Dementia Rating scale) (Morris <i>et al.</i> , 2001), MCI (a score of 3 on the Global Deterioration Scale) (Reisberg <i>et al.</i> , 1982), Minimal dementia (Roth <i>et al.</i> , 1986).
3.	Impairment on cognitive tests Examples: MCI (Bennett <i>et al.</i> , 2002), CIND (Conquer <i>et al.</i> , 2000).
4.	Cognitive complaints and test impairment Examples: Aging-associated cognitive decline (Levy, 1994), age-associated memory impairment (Crook <i>et al.</i> , 1986), age-related cognitive decline (Celsis <i>et al.</i> , 1997), amnesic MCI (Petersen <i>et al.</i> , 2001).
5.	Mild functional impairment and test impairment Examples: MCI (Larrieu <i>et al.</i> , 2002), CIND (Wu <i>et al.</i> , 2002).
6.	Mild functional impairment or test impairment Examples: CIND (Ebly <i>et al.</i> , 1995), MCI (Albert <i>et al.</i> , 1999), Questionable dementia (Devanand <i>et al.</i> , 1997).

MCI, mild cognitive impairment; CIND, cognitive impairment no dementia.

Table 2 Causes of mild cognitive impairment

A. Disorders that have a strong relationship with mild cognitive impairment and that can often be easily recognized by clinical examination and/or ancillary tests Parkinson's disease, Huntington's disease, severe brain trauma, brain infections, large intracerebral tumors, cerebral bleeding, large cerebral infarcts, extensive white matter pathology, severe depression, psychotic disorders, longstanding and severe alcohol intoxication, drug intoxication (i.e. prolonged use of high doses of benzodiazepines), severe thiamine or vitamin B12 deficiency, unregulated diabetes mellitus or thyroid disorders.
B. Disorders that have a strong relationship with mild cognitive impairment, but that are difficult to recognize by clinical assessment and/or ancillary tests Predementia or prodromal stage of Alzheimer's disease, Lewy body disease, frontotemporal dementia, vascular dementia, Parkinson's disease, multiple system atrophy, or Huntington's disease.
C. Disorders that have a weak relationship with mild cognitive impairment Mild brain trauma, transient ischemic attack, epilepsy, disorders that chronically or temporarily impair brain perfusion (hyper/hypotension, stenosis of the carotid artery, generalized atherosclerosis, cardiac surgery), mild depression, bipolar disorders, anxiety disorders, regulated diabetes mellitus or thyroid disorders, mild thiamine or vitamin deficiency, heart failure, obstructive sleep apnea syndrome, chronic obstructive pulmonary diseases, anemia, severe liver or kidney disorders, hearing loss, "normal aging", fear of dementia, psychosocial problems in relation to work, relationships, life phase change, or somatic disorders.

clinical examination or ancillary tests (see Table 2 part B for examples). The third group of conditions have a weak relation with MCI, that is, subjects with such conditions may have MCI on a group level, but it is not clear whether

the disorder is the cause for MCI in individual patients (see Table 2 part C for examples). In most studies on MCI, which will be discussed below, subjects with MCI due to obvious causes have been excluded.

OUTCOME OF MCI

MCI is not a stable condition. Depending on the cause, subjects may progress to dementia, may continue to have MCI, or may improve. A meta-analysis of studies with a short to intermediate follow-up period (average 3.1 years, range 1.1–5 years) indicated that on average 10% (range 2–31%) of the subjects with MCI developed dementia at each year of follow-up (Bruscoli and Lovestone, 2004). The conversion rate to dementia appeared to be higher in a clinical setting than in a population-based setting. Similar data were obtained from another meta-analysis (Visser, 2000). This meta-analysis also showed that about 90% of the subjects who converted to dementia had Alzheimer-type dementia. Studies with a follow-up longer than 5 years indicated that subjects continued to convert to dementia at longer follow-up intervals. After 8–10 years, 50 to 80% of the subjects had become demented (Morris *et al.*, 2001; Petersen *et al.*, 2001). Figure 1 shows the long-term outcome of subjects older than 60 years with cognitive complaints and amnesic MCI from the Maastricht Memory Clinic. This figure shows that the conversion rate is dependent on the way MCI is defined. It is noteworthy that the annual conversion rates decline with longer follow-up intervals and that even after 10 years of follow-up a substantial number of subjects have not become demented.

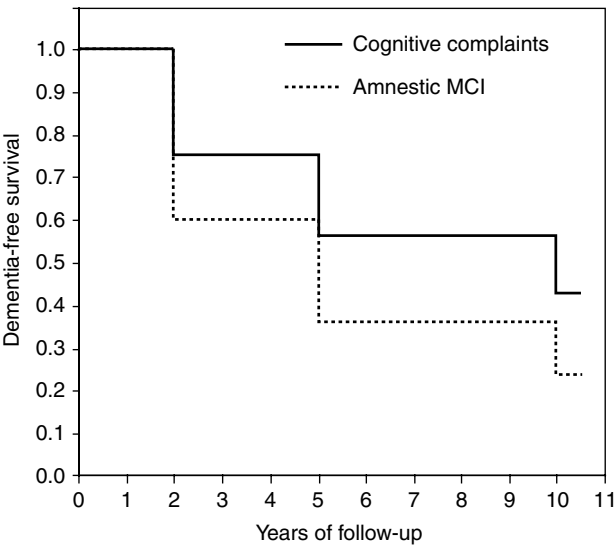


Figure 1 Long-term outcome of subjects older than 60 years with cognitive complaints ($N = 56$, straight line) and amnesic MCI ($N = 33$, dotted line) from the Maastricht Memory Clinic. Follow-up evaluations were performed after 2, 5, and 10 years. The average age at baseline was 69 years (range 60–84 years). 96% of the subjects with dementia had probable AD

PREDICTORS OF DEMENTIA IN SUBJECTS WITH MCI

It is of major importance to identify subjects with MCI who become demented, in order to give them a prognosis and to allow for starting treatment in an earlier phase than is possible now. Many variables have been tested as predictors of dementia in subjects with MCI (DeCarli, 2003). Since the majority of the subjects with dementia have Alzheimer's Disease-type (AD-type) dementia, these predictor variables can be regarded as predictors of AD-type dementia, rather than of dementia in general. Most of the studies discussed below had a follow-up period of 5 years or less (3 years on average). We will first discuss studies that tested predictive accuracy of single variables and then studies that tested predictive accuracy of a combination of variables.

Predictive Accuracy of Single Variables

Predictors Tested in More than Four Studies with a Similar Design

Age, mini-mental state examination (MMSE) score, functional impairment, memory impairment, medial temporal lobe atrophy, and the apolipoprotein E (APOE) genotype have been tested as predictor in more than four studies with a similar design. We have pooled data from these studies (Table 3). Age, the MMSE score, medial temporal lobe atrophy, and the APOE genotype were weak predictors with the odds ratios between 2 and 5 (the odds ratio is a global measure of diagnostic accuracy – an odds ratio of 25 or more indicates a good diagnostic accuracy). Functional impairment and memory impairment were moderately strong predictors with odds ratios between 5 and 8. None of the variables combined a high sensitivity (i.e. the percentage of subjects with dementia at follow-up in whom the predictor was present) with a high positive predictive value (PPV) (i.e. the percentage of subjects in whom the predictor was present and who had dementia at follow-up).

Other predictor Variables

Cognitive predictors. Impairments on neuropsychological tests in domains other than memory such as language

function (as measured for example by the Boston Naming Test or verbal fluency), executive functions (as measured for example by the Stroop Color Word test card 3 or the Trail Making Test B), or attention (as measured for example by the Symbol Digit Substitution Test) were also predictors for dementia, but the predictive accuracy was generally less compared to that of tests of memory (Visser, 2003).

Neuroimaging predictors. One study found that the presence of white matter lesions was predictive of dementia (Wolf *et al.*, 2000), but this finding was not replicated in other studies (Korf *et al.*, 2004; Maruyama *et al.*, 2004). Several studies have shown that Single-Photon Emission Computed Tomography (SPECT) hypoperfusion in the parietal-temporal region or posterior cingulate gyrus may be predictive for dementia, but findings have been conflicting (Celsis *et al.*, 1997; McKelvey *et al.*, 1999; Huang *et al.*, 2002; Okamura *et al.*, 2002; Encinas *et al.*, 2003). Also, hypometabolism in the posterior cingulate gyrus or parietal-temporal area as measured with Positron Emission Tomography (PET) scanning was associated with an increased risk for dementia although not in all studies (Berent *et al.*, 1999; Arnaiz *et al.*, 2001; Chetelat *et al.*, 2003; Drzezga *et al.*, 2003; Nestor *et al.*, 2004).

Electrophysiological predictors. A combination of different background frequencies accurately identified subjects with dementia at follow-up with an overall accuracy of 82% in one small study (Jelic *et al.*, 2000). Another small study showed that event-related potentials may be useful for the prediction of dementia with an overall diagnostic accuracy of 85% (Olichney *et al.*, 2002).

Biochemical predictors. The most promising biochemical predictors of dementia are the levels of tau protein (either total tau or phosphorylated tau) and β -amyloid ending at amino acid 42 (A β 42) in the cerebrospinal fluid. These proteins are thought to reflect the neurodegeneration caused by AD (Blennow and Hampel, 2003). An elevated concentration of total tau protein had a high sensitivity for detecting subjects with Alzheimer-type dementia at follow-up (Arai *et al.*, 1997; Maruyama *et al.*, 2004). The sensitivity of the combination of an elevated concentration of total tau protein and a decreased concentration of A β 42 for AD-type dementia at follow-up was about 90% (Andreasen *et al.*, 1999; Riemenschneider *et al.*, 2002). The odds ratio

Table 3 Pooled estimates of predictive accuracy for dementia

	OR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Age (>75 versus 60–75)	2.0	47	70	54	67
Functional impairment (mild versus very mild)	6.8	77	66	51	86
MMSE (<27 versus >26)	3.8	57	73	49	81
Memory (impairment yes versus no)	7.6	74	73	59	85
MTL atrophy (yes versus no)	4.6	59	79	61	81
APOE (e4 allele carrier versus no e4 allele carrier)	3.4	61	67	45	81

OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; MMSE, mini-mental state examination; MTL, medial temporal lobe; APOE, apolipoprotein E genotype.

Data are based on a meta-analysis of prospective MCI studies from a clinical setting with a follow-up of on average 3 years (Visser *et al.*, unpublished data).

of this combination for AD-type dementia at follow-up was between 18 and 64 and the positive predictive value between 60 and 94% (Riemenschneider *et al.*, 2002; Zetterberg *et al.*, 2003). In one study, the level of tau phosphorylated at threonine 231 was predictive of dementia (Buerger *et al.*, 2002). Preliminary data indicate that an elevated level of F2-isoprostane 8,12-iso-iPF_{2 α} -VI in cerebrospinal fluid, plasma, or urine and the level of sulfatide in cerebrospinal fluid may be predictors of dementia as well (Pratico *et al.*, 2002; Han *et al.*, 2003).

It can be concluded that there is no single variable that can accurately identify subjects with dementia at follow-up from among subjects with mild cognitive impairment that will not become demented. The meta-analysis of variables that have been investigated in at least five studies indicated that no variable has an Odds Ratio (OR) higher than 8. Several new promising predictors of dementia have been investigated in small studies, but larger studies are needed to further assess the diagnostic value of these predictors.

Predictive Accuracy of a Combination of Variables

In the previous section, we showed that there is no single variable that can accurately predict progression to dementia. Several studies have suggested that a combination of variables may have a higher accuracy for Alzheimer's disease in subjects with MCI than a single variable (Okamura *et al.*, 2002; Visser *et al.*, 2002b). In the present section, we will

discuss one of these multivariable approaches in more detail: the Predementia Alzheimer's disease Scale (PAS) (Table 4) (Visser *et al.*, 2002b). The PAS combines six markers for Alzheimer's disease: age, MMSE score, degree of functional impairment, cognitive test performance, medial temporal lobe atrophy, and the apolipoprotein E genotype. Each variable is scored on a three- to four-point scale and the total sum score indicates the risk for predementia Alzheimer's disease. A retrospective validation study of the PAS in two samples of subjects with MCI who were older than 55 years indicated that the best cutoff score was 6 for the full PAS and 5 for the PAS without the neuroimaging variable. The odds ratio at the best cutoff score was 25, the sensitivity 82% and the positive predictive accuracy 75%. Subjects with a score of 7 or higher had a very high risk (93%) for Alzheimer's disease in both samples, subjects with a score lower than 4 had a very low risk (7%) for Alzheimer's disease, while subjects with a score between 3 and 7 had an intermediate risk for Alzheimer's disease (46%). These intermediate scores were seen in 38% of the subjects. This means that the diagnosis remains uncertain in a substantial number of subjects.

CONCLUSIONS

MCI is a heterogeneous condition. The risk for dementia, typically Alzheimer-type dementia, is high but at longer follow-up intervals, a subset of patients do not develop dementia.

Table 4 Predementia Alzheimer's disease scale (PAS)

	−1	0	1	2	Score
A. Age	≤59	60–64	65–74	≥75	
B. MMSE ^a	–	≥28	26,27	≤25	
C. Functional impairment ^b					
C.1 GDS					
C.2 CDR	–	GDS 1	GDS 2	GDS 3	
C.2.1. Total box score	–	<0.5	0.5–1	≥1.5	
C.2.2. Final score	–	CDR = 0	–	CDR = 0.5	
C.3 CAMDEX	–	–	–	Min Dem	
D. Neuropsychological tests ^c	Memory ≥50 perc	Other	1 test impaired	2 tests impaired	
E. MTL atrophy ^d					
E.1 Qualitative rating					
Age <75 years	–	0	1	2	
Age ≥75 years	0	1	2	3	
E.2 Volumetry	≥66 perc	33–66 perc	10–33 perc	≤10 perc	
F. ApoE genotype	–	Other	e2e4/e3e4	e4e4	
					TOTAL SCORE

The table indicates which score corresponds with the test result. The total score is an indication for the risk of predementia AD. More information can be found in (Visser *et al.*, 2002b), and at www.np.unimaas.nl/scales/pas.

MMSE, mini-mental state examination; GDS, Global Deterioration Scale (Reisberg *et al.*, 1982); CDR, Clinical Dementia Rating scale (Morris, 1993); MTL, medial temporal lobe; ApoE, apolipoprotein E; Min Dem, minimal dementia; perc, percentile; CAMDEX, Cambridge Mental Disorders of the Elderly Examination (Roth *et al.*, 1986).

^aThe MMSE should be corrected for age and education: if age is 75 or higher or if the period of education has been 8 years or less, one point should each time be added to the observed score; if the period of education has been 14 years or more, one point should be subtracted from the observed score. ^bOne option should be used. The CDR can be scored using the Sum of Boxes score (preferred) or the final rating. ^cAt least two and maximal four tests including one memory test for delayed recall or learning. An impairment is a score below the 10th percentile or above the 90th percentile (for speed related tasks) after correction for age, sex, and education. ^dOne option should be used. A qualitative score can be performed on a CT scan or a MRI scan (Scheltens *et al.*, 1992; de Leon *et al.*, 1993). Volumetry should measure the hippocampus (preferred), parahippocampal gyrus, or entorhinal cortex. The percentile score is relative to age, sex, and intracranial volume.

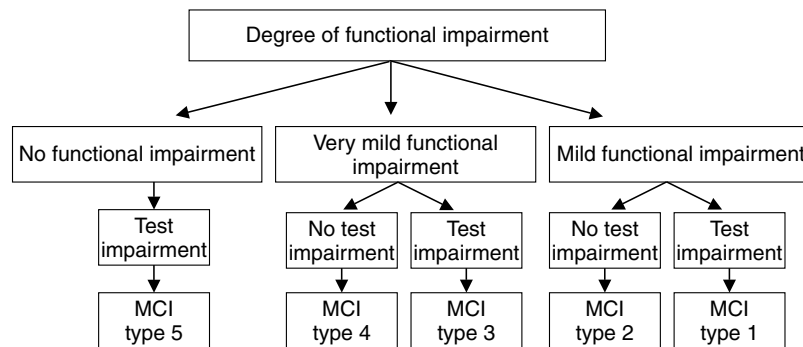


Figure 2 Classification scheme for subjects with mild cognitive impairment. The classification should be performed for each cognitive domain separately (examples of cognitive domains are memory, language, executive function, abstract reasoning/problem solving, and attention). See also www-np.unimaas.nl/scales/cirs. The functional rating is based on a clinical assessment of the performance in daily living. Very mild functional impairments mean that complaints are present and that more effort may be needed to perform tasks. The overall presentation, however, is not impaired and there is no notable deficit in employment or social situation as observed by colleagues or family members. Mild functional impairments mean that complaints are present, impairments are noticeable to colleagues, family members, or the physician, impairments may slightly affect social or occupational functioning, but does affect self-care and does not cause need for assistance from others. The impairment indicates a decrease in functioning that cannot be attributed to normal aging. Test impairment means that performance on cognitive tests is not normal as evidenced by a mild but consistent impairment on a number of tests or a severe impairment on one or more tests

Therefore, MCI should be considered as a description of the severity of cognitive impairment rather as a specific disease.

The lack of standardization of MCI definitions and terminology is confusing and makes it difficult to compare studies. In clinical practice, it may be more informative to classify subjects within the MCI spectrum instead of using a specific MCI definition. An approach for such a classification is shown in Figure 2. More information regarding this classification system can be found at www-np.unimaas.nl/scales/cirs.

There is no single predictor of Alzheimer's disease, but a multivariable approach such as the PAS may provide good diagnostic accuracy. Low-risk and high-risk subjects can be accurately identified by a multivariable approach, but there remains a substantial group of subjects with an intermediate risk for Alzheimer's disease in whom the diagnosis remains uncertain. It is expected that the diagnostic accuracy for these subjects will increase if new predictors for Alzheimer's disease such as the concentration of tau and Aβ42 in cerebrospinal fluid are included in the multivariable approach.

In clinical practice, it seems advisable to keep subjects at intermediate or high risk for dementia under clinical supervision. There is no evidence that subjects at high risk for dementia will benefit from pharmacological treatment. Preliminary data from trials that aimed to prevent progression from MCI to Alzheimer-type dementia with acetylcholine esterase inhibitors, vitamin E, piracetam, or rofecoxib showed lack of efficacy (data presented at the 9th International Conference on Alzheimer's Disease and related disorders in Philadelphia, 19–22 July 2004).

Since subjects continue to develop dementia at longer follow-up studies, studies that investigate predictors of long-term outcome are needed to improve the identification of subjects with MCI who will become demented.

KEY POINTS

- There are no standard criteria for MCI.
- MCI is not related to one specific disorder.
- Subjects with MCI have a high risk for Alzheimer-type dementia, but even in the long term, a substantial number of subjects do not develop dementia.
- A combination of variables may be useful to identify subjects with MCI who are at high risk for Alzheimer-type dementia.
- MCI should be considered as a syndrome rather than as a disease.

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