

# Revised Criteria for Mild Cognitive Impairment: Validation within a Longitudinal Population Study

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## Key Words

Mild cognitive impairment, revised criteria • Cognition • Ageing, normal

## Abstract

**Background:** Mild cognitive impairment (MCI) refers to the transitional zone between normal ageing and dementia. Current criteria perform poorly within the general population setting. Revisions have been proposed based on results obtained from clinical and epidemiological studies. **Objective:** To evaluate revised diagnostic criteria for mild cognitive impairment (MCI-R) incorporating changes in activity level and non-mnesic cognitive functioning. **Method:** MCI-R subjects were recruited from a representative network of general practitioners in the south of France. A computerized neuropsychometric examination was given. At 2 years of follow-up, a diagnosis of dementia was made by a neurologist using DSM-III-R criteria and without knowledge of the results of the cognitive testing. Rates of conversion to incident dementia were assessed by receiver operating characteristics analysis. **Results:** The MCI-R prevalence was found to be 16.6% using revised criteria. A significantly better prediction of transition to dementia (AUC = 0.80, sensitivity: 95%, specificity: 66%) was obtained with MCI-R than with the previous MCI criteria (AUC = 0.48, sensitivity: 5%, specificity: 91%). The predictive power was found to increase when MCI subtypes

were combined. **Conclusion:** Incorporating the possibility of change in activity level and alteration of non-mnesic cognitive functions have been found to ameliorate the original algorithm and better define subjects converting to dementia. This definition may be applicable to both clinical and population research.

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The identification of cases of subclinical cognitive impairment at high risk of evolving towards dementia is important both for early treatment and protection of the individual. The concept of mild cognitive impairment (MCI) [1] is now widely used to describe this high-risk group [2–6], and numerous large-scale research programmes have now been undertaken with a view to providing treatment. As mild cases of cognitive disorder more commonly present initially to the general practitioner than to the specialist, it is important that diagnostic criteria perform adequately within this setting. Previous attempts to apply MCI criteria in general practice have been disappointing, the algorithm giving variable predictive validity with regard to the identification of dementia converters [7, 8]. A recent consensus conference held in Stockholm [9] provided an opportunity for clinicians and researchers working in the field of MCI to compare data sets and to propose modifications to the existing cri-

teria which might improve screening accuracy, especially in the general population setting. Essentially, the new criteria allow for the inclusion of cognitive deficits other than memory dysfunction, and also recognize that MCI may be associated with early and subtle changes in the ability to perform tasks of everyday living. The aim of the present study is to evaluate the performance of these revised criteria within a longitudinal population study.

## Methods

### Sample

The subjects included in the present study were over 60 years of age and were recruited from a representative general practitioner research network as part of the Eugeria longitudinal study of cognitive aging described in detail elsewhere [10]. The population-based network is representative of general practice in the Montpellier region in the south of France, and includes urban and rural areas and subjects living in institutions. An intensive training course in psychogeriatric screening and application of criteria for senile dementia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., revised (DSM-III-R) [11] was given to the 63 general practitioners in the network. 833 subjects representing all subjects without dementia over 60 were recruited into the study in the first year. At baseline, dementia cases were excluded by the general practitioners. A proxy questionnaire on cognitive functioning over the past year was sent to all subjects. This screening instrument, *Détérioration Cognitive Observée* (DECO), has been shown in a previous study to be highly sensitive to early changes in cognitive functioning due to various causes [12]. It is based on the degree of change in cognitive functioning over the last year, as estimated by a proxy who had at least monthly contact with the subject over the past 3 years. Of these subjects, 308 with cognitive complaints verified by proxies at baseline were identified. These persons were considered by an observer to have shown some degree of observable deterioration in at least one area of cognitive functioning over the past year and also to have a subjective cognitive complaint of declining ability (DECO score of less than 38).

These subjects were followed over a further 2 years along with a random sample ( $n = 64$ ) of the remaining subjects without cognitive complaints.

### Instruments

#### Neuropsychological Assessment

Subjects were visited in their homes and given a computerized neuropsychometric examination, the ECO (Examen Cognitif par Ordinateur) [13]. The ECO assesses primary memory, verbal and visuospatial secondary memory, language skills (word and syntax comprehension, naming, verbal fluency), visuospatial performance (ideational, ideomotor and constructive apraxia, functional and semantic categorization of visual data, visual reasoning and form perception), and focused and divided attention (visual and auditory modalities). The development of the ECO and the theoretical basis for test selection is described elsewhere [13]. Response latencies were recorded using a tactile screen.

Ten summary scores representing 6 cognitive domains were used in the analysis:

- attention: response time on a dual task;
- primary memory: immediate recall of names;
- secondary memory: (i) delayed recall of names and (ii) their associated faces;
- visuospatial ability: (i) response time on a visual matching task and (ii) number of elements correct in the copying of meaningful and meaningless figures;
- language: (i) mean reaction time on word and syntax comprehension, (ii) naming and (iii) verbal fluency using both phonetic and functional cues;
- reasoning: completion of logical visual series.

#### Activity of Daily Living Assessment

A validated activity of daily living scale [14] with finely graded hierarchical subscales was used to assess alterations in everyday functioning in collaboration with both subjects and caregivers.

#### Definition of Cases

At 2 years of follow-up, a diagnosis of incident neurological disorders including dementia was carried out by a neurologist using a standardized neurological examination based on DSM-III-R [11] criteria and without knowledge of the results of the cognitive testing (computerized neuropsychometric examination).

A consent form describing the aims and methods of the study was completed by all subjects. Authorization for the study was also obtained from the National Data Protection and Ethics Committees.

#### Criteria for MCI and MCI-R Identification

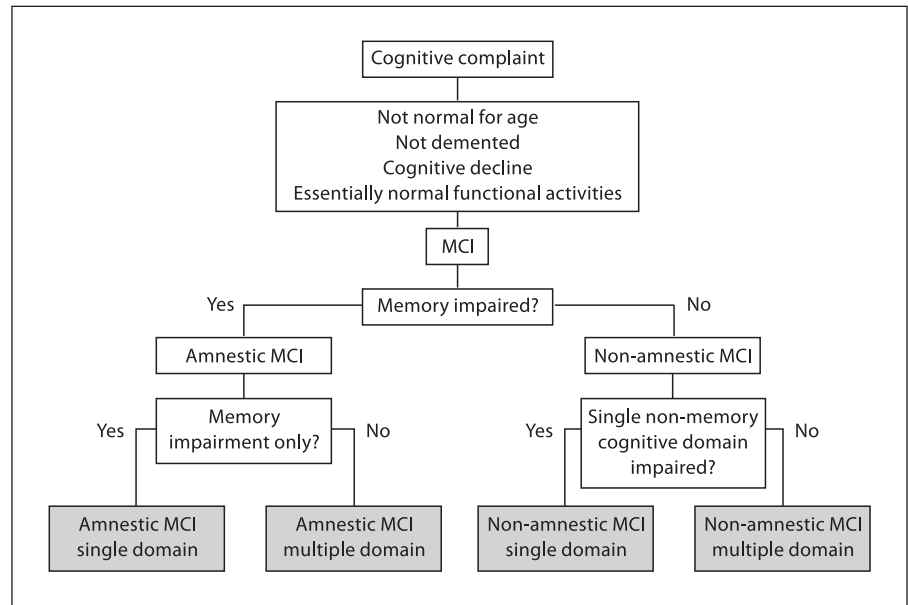
MCI and MCI-R criteria were applied to baseline data. The criteria for MCI are those previously proposed by Petersen et al. [1]: (i) presence of a subjective memory complaint; (ii) preserved general intellectual functioning (as estimated in this study by performance on a vocabulary test); (iii) demonstration of a memory impairment by cognitive testing; (iv) intact ability to perform activities of daily living; (v) absence of dementia.

MCI-R criteria are those proposed by the Stockholm consensus group [9]. They stipulate: (i) presence of a cognitive complaint from either the subject and/or a family member; (ii) absence of dementia; (iii) change from normal functioning; (iv) decline in any area of cognitive functioning; (v) preserved overall general functioning but possibly with increasing difficulty in the performance of activities of daily living.

The definition of a significant change in cognitive performance is problematic in all studies of MCI, 1.5 standard deviations (SD) being most commonly used to define cognitive deficit within both a research and clinical context. We also found that this gave the best concordance with clinical judgement (the examining neurologist was also asked to clinically classify subjects as possible MCI cases on the basis of the standardized interview only). Subjects classified as having MCI and MCI-R demonstrated a decrement of more than 1.5 SD on a memory task (MCI) or on a cognitive task (MCI-R) compared to ECO standardization data matched by age and level of education.

#### MCI Subtypes

The MCI-R subjects may be subclassified according to the presence or absence of a memory impairment [15]. All test scores



**Fig. 1.** Flow chart: amnesic and non-amnesic MCI subjects.

were first converted to z-scores to permit across-test comparisons taking into account differences in the relative difficulty of tests. Subjects can be designated as having amnesic MCI if they have a prominent memory impairment either alone or with other cognitive impairments (multiple domain with amnesia) or non-amnesic MCI if a single non-memory domain is impaired alone or in combination with other non-memory deficits (multiple domain without amnesia; fig. 1).

#### Analysis of Data

Receiver operating characteristics (ROC) analysis has been used to analyse the relative predictive power of MCI and MCI-R identified to predict dementia onset in the following 2 years. We calculated the area under the curves (AUC) and the sensitivities and specificities for dementia for MCI, MCI-R and MCI-R subtypes.

Statistical analyses were performed using the SPSS (Statistical Package for Social Science) program version 13.0. The AUCs of the MCI groups were compared using the ROCcomp procedure of the STATA program version 9.0.

## Results

Of the 308 subjects (30% male; 70% female) included in the study at baseline with a subjective cognitive complaint, with a mean age of 75.7 years (SD = 7.8), 139 were classified as having MCI-R. The revised criteria provide an estimated prevalence of 16.6% and a yearly incidence of 0.06% in the general population. All MCI-R subjects were independent for activities of daily living but many had greater difficulty than non-cognitively impaired per-

sons in performing these activities when graded on subscales of performance. Approximately 32% of MCI-R subjects report increasing difficulty with at least one activity compared to 15.6% in cognitively stable subjects. The greatest difficulties reported by those MCI-R subjects with a later diagnosis of dementia are with instrumental activities of daily living, i.e. use of the telephone (36.8%), managing money (31%), use of household appliances (22%), and one basic activity of daily living, dressing (26.3%). While subjects were still able to dress appropriately, proxies reported increasing difficulty (14%; principally in time taken to dress or in deciding what to wear).

The mean cognitive test scores for the MCI-R are given in table 1. ROC analysis showed that significantly better prediction (AUC = 0.80) was obtained with MCI-R than with the previous MCI criteria (AUC = 0.48; table 2). 84% of the persons developing dementia had at least one functional deficit at baseline.

The subjects were classified according to MCI-R subtype. 76 subjects had a predominant memory deficit (the memory deficit alone being 1.5 SD greater than for age- and education-matched controls) and were classified as having amnesic MCI-R. 63 subjects had significantly lower scores (1.5 SD) on the non-memory tests or had multiple domain deficits in which numerous cognitive deficits of more than 1.5 SD were found. Given the small numbers in these two categories it was not feasible to examine the predictive validity of each of these subtypes, so

**Table 1.** Mean (SD in parentheses) cognitive test scores for normal and MCI-R groups 2 years before neurological diagnosis

	Normal group (n = 64)	MCI-R group (n = 139)
Attention		
Mean reaction time on double task	19.94 (4.49)	26.22 (8.28)
Primary memory		
Immediate recall of name list	5.42 (1.37)	3.95 (1.83)
Secondary memory		
Delayed recall of names	5.48 (1.80)	3.16 (2.22)
Delayed recall of faces recalled	7.96 (1.24)	6.57 (2.10)
Visuospatial ability		
Mean reaction time on total visual analysis	36.44 (6.60)	47.59 (11.57)
Copying tasks	23.95 (0.21)	21.95 (4.27)
Language		
Naming total correct	9.54 (0.68)	8.38 (1.79)
Fluency total	39.01 (10.98)	23.80 (11.36)
Reaction time of word and syntax comprehension	17.81 (4.92)	28.07 (10.34)
Reasoning		
Logical series total correct	1.45 (1.09)	0.57 (0.83)

**Table 2.** ROC analyses of the discriminability of MCI, MCI-R and MCI-R subtypes (amnestic and non-amnestic) for the prediction of dementia after 2 years

Classification	n	AUC	SE	Asymptotic significance	95% CI	Sensitivity, %	Specificity, %
MCI	23	0.48	0.07	0.84	0.34–0.62	5	91
MCI-R	139	0.80	0.04	0.001	0.71–0.89	95	66
Subtypes							
Non-amnestic MCI-R	63	0.26	0.07	0.005	0.11–0.40	23	30
Amnestic MCI-R	76	0.73	0.07	0.005	0.59–0.88	77	70

SE = Standard error; CI = confidence interval.

they have been classified together as non-amnestic MCI-R. ROC analysis shows that whereas taken alone both groups have worse predictive power (AUC = 0.73 amnestic; AUC = 0.26 non-amnestic), the highest prediction of dementia is obtained when the subtypes are combined (AUC = 0.80; table 2, appendix).

The AUCs of the MCI and MCI-R groups are significantly different ( $\chi^2 = 50.19$ ,  $p < 0.00001$ ); the AUCs of the MCI and amnestic MCI-R groups are also significantly different ( $\chi^2 = 17.75$ ,  $p < 0.00001$ ).

## Discussion

In a previous study we have shown that currently used MCI criteria emphasizing a relatively isolated memory impairment applied to general population research have poor predictive validity for the onset of dementia within the general practice setting [2]. However, this previous study also found that subjects with a cognitive complaint verified by a proxy have a higher conversion rate to senile dementia (18% incidence over 3 years) than that observed in the general population. This suggests that mild cognitive dysfunction is an important risk factor for dementia, but that MCI criteria require modification if they are to

have a high prognostic value within the general population setting.

This study has applied revised MCI criteria proposed by an international expert group in Stockholm in 2003 within a longitudinal population study of subclinical cognitive deficit. The revised criteria perform significantly better than the original algorithm due to the inclusion of a criterion relating to increasing difficulty in performance of everyday tasks without loss of autonomy. The study furthermore suggests that these changes are most likely to be observed in predementia in the areas of use of telephone, dressing, use of money and household appliances and that future diagnostic interviews should focus on these areas, noting however that these activities are not lost but performed with increasing difficulty. Previous studies have suggested that MCI subjects show mild impairments of everyday functioning when using sensitive measures [16–19].

Secondly, the revised criteria include cognitive deficits other than memory allowing us to classify MCI subjects as predominantly in the amnesic multiple domain and non-amnesic groups as given in figure 1. While non-amnesic MCI was found to be a poor predictor of 2-year dementia conversion, combined with amnesic MCI-R it gives maximum predictive validity. It is thus clear that extension of the original MCI criteria to a larger range of cognitive functions gives higher sensitivity and better dementia prediction (using the former criteria 63 subjects would not have been detected). Amnesic difficulties are, however, clearly both more common and less likely to be benign. The validity of this type of subclassification will depend of the course of the tests used – it being generally accepted that the more tests one uses, the more one sees multiple domain deficits and specialist judgement is clearly required to make this discrimination with clinical accuracy. Previous studies have shown that cognitive deficits other than memory were involved in the detection of presenile dementia [6, 20–23].

There is a fragility of the MCI concept when one attempts to operationalize it strictly in terms of test performance. Numerous attempts have been made to develop MCI screening tests which may screen independently of comprehensive clinical assessment, and not surprisingly their discriminability is relatively poor [2, 7].

The aim of the paper has been to establish a global definition which may be applicable for both clinical and population research, and not to validate a clinical dementia prediction instrument. While modifications to the original algorithm have been found to better define subjects converting to dementia, results also point to the

complexity of operationalizing this definition in terms of neuropsychological tests. Collectively results point to certain cognitive domains as being particularly vulnerable; however, individual subjects show wide variation in patterns of deficit and rates of change across time such that it is difficult to diagnose MCI in the absence of a specialist review of the cognitive data. Further research is needed to examine the relationship across time between neuropsychological and functional test performance and clinical diagnosis of MCI. This new MCI algorithm functions only at a syndrome level, permitting the early identification of persons at risk of cognitive decline without being able to specify the nature of the underlying neurocognitive disorder. At the present levels of knowledge, it would seem unwise to attempt detection of Alzheimer's disease specifically, or to differentiate Alzheimer's disease from other diseases such as Lewy body disease given the heterogeneity of these disorders.

### Acknowledgements

Financial support for the Euseria project has been given by the French Social Security (CNAM-TS), the Fondation de France, the Regional Government of Languedoc-Roussillon and the Direction Générale de la Santé. We thank Isabelle Jausset for her helpful assistance in statistical analysis.

### Appendix

Subject number in each group (MCI-R, non-MCI-R, no baseline cognitive complaint) used in the ROC analysis

	MCI-R	Non-MCI-R	No baseline cognitive complaint	Total
Converted to dementia	18	1	0	19
Not converted to dementia	121 <sup>1</sup>	168 <sup>2</sup>	64 <sup>3</sup>	353
Total	139	169	64	372

<sup>1</sup> 15 dead, 6 unable.

<sup>2</sup> 3 dead.

<sup>3</sup> 1 unable.



## References

- 1 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–308.
- 2 Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC: Mild cognitive impairment: prevalence and predictive validity according to current approaches. *Acta Neurol Scand* 2003;108:71–81.
- 3 Fisk JD, Merry HR, Rockwood K: Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology* 2003;61:1179–1184.
- 4 Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR: Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology* 2006;66:828–832.
- 5 Larrieu S, Letenneur L, Orgogozo JM, et al: Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology* 2002;59:1594–1599.
- 6 Palmer K, Backman L, Winblad B, Fratiglioni L: Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study. *BMJ* 2003;326:245.
- 7 Ritchie K, Artero S, Touchon J: Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology* 2001;56:37–42.
- 8 Ritchie K, Touchon J: Mild cognitive impairment: conceptual basis and current nosological status. *Lancet* 2000;355:225–228.
- 9 Winblad B, Palmer K, Kivipelto M, et al: Mild cognitive impairment – Beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;256:240–246.
- 10 Ritchie K, Ledesert B, Touchon J: The Eugeria Study of cognitive ageing: who are the 'normal' elderly? *Int J Geriatr Psychiatry* 1993;8:969–977.
- 11 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), ed 4. Washington, American Psychiatric Association, 1994.
- 12 Ritchie K, Fuhrer R: A comparative study of the performance of screening tests for senile dementia using receiver operating characteristics analysis. *J Clin Epidemiol* 1992;45:627–637.
- 13 Ritchie K, Allard M, Huppert F, et al: Computerized cognitive examination of the elderly (ECO): the development of a neuropsychological examination for clinic and population use. *Int J Geriatr Psychiatry* 1993;8:899–914.
- 14 Ritchie K, Ledesert B: The measurement of incapacity in the severely demented elderly: the validation of a behavioural assessment scale. *Int J Geriatr Psychiatry* 1991;6:217–226.
- 15 Petersen RC, Doody R, Kurz A, et al: Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985–1992.
- 16 Perneckzy R, Pohl C, Sorg C, et al: Complex activities of daily living in mild cognitive impairment: conceptual and diagnostic issues. *Age Ageing* 2006;35:240–245.
- 17 Tabert MH, Albert SM, Borukhova-Milov L, et al: Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology* 2002;58:758–764.
- 18 Perneckzy R, Pohl C, Sorg C, et al: Impairment of activities of daily living requiring memory or complex reasoning as part of the MCI syndrome. *Int J Geriatr Psychiatry* 2006;21:158–162.
- 19 Nygard L: Instrumental activities of daily living: a stepping-stone towards Alzheimer's disease diagnosis in subjects with mild cognitive impairment? *Acta Neurol Scand Suppl* 2003;179:42–46.
- 20 Tierney MC, Szalai JP, Snow WG, et al: Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. *Neurology* 1996;46:661–665.
- 21 Artero S, Tierney MC, Touchon J, Ritchie K: Prediction of transition from cognitive impairment to senile dementia: a prospective, longitudinal study. *Acta Psychiatr Scand* 2003;107:390–393.
- 22 Rapp MA, Reischies FM: Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). *Am J Geriatr Psychiatry* 2005;13:134–141.
- 23 Amieva H, Letenneur L, Dartigues JF, et al: Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. *Dement Geriatr Cogn Disord* 2004;18:87–93.