PAPER

Mild cognitive impairment: a cross-national comparison

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Objective: The main aim of this collaborative study was to assess the comparability of the most commonly used criteria for mild cognitive impairment (MCI) by comparing the cognitive performance of patients with MCI from the Mayo Clinic (USA) and the Karolinska Institutet (Sweden).

Methods: Standardised neuropsychological test scores were used to compare the two samples from the two institutions with regard to the number of cognitive domains in which performance was below 1.5 SD. Possible predictors for the conversion from MCI to Alzheimer's disease (AD) were assessed.

Results: When the two institutions were considered together in the Cox proportional hazard model, the number of affected cognitive domains below 1.5 SD was a significant predictor of time to AD diagnosis with age, education, and *APOE* ε4 genotype entered into the same model as covariates. The number of affected cognitive areas remained as a significant predictor when the institutions were considered separately. The logistic regression model of conversion to AD showed that only tests assessing learning and retention were predictors of developing AD.

Conclusions: Differences in population as well as in methodology of case ascertainment as well as other aspects may account for the observed variability between samples of patients with MCI. The number of impaired cognitive factors at baseline can predict the progression from MCI to AD. Furthermore, tests assessing learning and retention are the best predictors for progression to AD.

In recent years, the concept of mild cognitive impairment (MCI) has become increasingly popular.[1] MCI refers to a transitional state between normal ageing and early Alzheimer's disease (AD) whereby the subjects have intermediate cognitive impairments, usually involving memory but of insufficient magnitude to constitute the diagnosis of dementia or AD.[2] While there is good agreement on the concept of MCI, there is considerable variability concerning the specific diagnostic criteria and the rates of progression of subjects from MCI to AD.[3][4]

While most studies have documented an increased rate of progression in subjects with MCI, there is considerable variability in the literature.[5–7] Several possible explanations for this variability have been proposed including the sources of recruitment of the subjects and the specific diagnostic criteria employed. A recent international conference on MCI highlighted the heterogeneity of the term.[1] In particular, there have been notable differences in the outcomes of subjects studied in the USA and Europe, and thus far, there has been no cross-national comparison of subjects with MCI.

This study aimed to address two of the major issues involved in the variability among the results of studies reported in the literature: subject population and diagnostic criteria. A group of subjects with MCI from the Mayo Clinic (MC) in Rochester, MN, USA, who have been studied for up to 15 years was compared with a group of subjects with MCI recruited by an academic medical centre, the Karolinska Institute (KI), in Stockholm, Sweden. The KI has a long history of studying subjects with intermediate stages of cognitive impairment and has extensive longitudinal data on the outcome of these subjects. The nature of the subject groups varies between these two institutions and served as a basis for investigating the difference in diagnostic criteria. This comparison allowed an evaluation of the role of source of recruitment of the subject population and varying of the criteria to assess the core features of the syndrome, as well as determination of the factors that play a significant role in predicting progression to AD.

PATIENTS AND METHODS

Study sample

The two study groups consisted of 170 subjects with MCI from MC and 133 from KI. The demographic details of the subjects of both study groups as well as their *APOE* ε4 genotypes are shown in table 1.

Mayo Clinic

The MC subjects were recruited through the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry (ADC/ADPR) using a standardised clinical protocol.[8][9] A more detailed description of the recruitment procedure has been reported elsewhere.[10] The commonest recruitment scheme involved screening of patients who were examined by primary care physicians for periodic general medical evaluation. On recruitment, patients were seen by a behavioural neurologist who obtained a medical history from the patients and corroborating sources, performed the Short Test of Mental Status,[10][11] Hachinski Ischemic Scale,[12] and a neurological examination. Subjects were diagnosed with MCI if they met the following criteria:

- memory complaint, preferably corroborated by an informant
- objective memory impairment for age and education
- essentially normal general cognitive functions
- largely normal activities of daily living
- not demented.

At the MC, the diagnosis of MCI was based on the clinical judgement of a consensus committee comprised of behavioural neurologists, neuropsychologists, geriatricians,

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Abbreviations: AD, Alzheimer's disease; AVLT, Auditory Verbal Learning Test; CDR, Clinical Dementia Rating (scale); KI, Karolinska Institute; MC, Mayo Clinic; MCFS, Mayo Cognitive Factor Scores; MCI, mild cognitive impairment; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised

Table 1 Demographic variables of the two study groups

	MC group (n = 170)	KI group (n = 133)	p value
Age (years)*	78.5 (8.4); 50–98	69.5 (5.8); 59–81	<0.0001
Education (years)*	13.2 (3.1); 4–20	9.3 (3.0); 5–18	<0.0001
Sex (M/F)	70/100	74/59	<0.06
MMSE*	26.0 (2.4); 18–30	25.2 (2.7); 17–30	<0.05
Follow up (months)*	37.50 (17.72); 9–128	27.55 (17.72); 8–84	<0.005
APOE ε4 genotype			
ε4/4	12 (7.1%)	9 (6.8%)	
ε4/3	50 (29.4%)	35 (26.3%)	
ε2/4	7 (4.1%)	4 (3%)	NS
ε3/3	60 (35.4%)	41 (30.8%)	
ε2/3	11 (6.5%)	11 (8.3%)	
Missing	30 (17.5%)	33 (24.8%)	

*Mean (SD); range.
KI, Karolinska Institutet; MC, Mayo Clinic; MMSE, Mini Mental State Examination; NS, not significant.

Table 2 Diagnostic criteria for mild cognitive impairment at the Mayo Clinic and the Karolinska Institutet

Mayo Clinic	Karolinska Institutet
Complaints about memory	Complaints about memory
Activities of daily living normal	No social interference with daily life as reported
General cognitive function normal	Decline in any cognitive domain (1.5 SD below age matched controls)
Memory for age abnormal	
Non-demented	Non-demented

psychiatrists, and nurses. There were no psychometric cut-off scores for the diagnosis; rather, the clinicians determined if the subject met the criteria outlined above. At each evaluation, the neuropsychological tests were administered by experienced psychometrists who were supervised by two clinical neuropsychologists. Patients were seen for follow up on an approximately annual basis.

Karolinska Institutet

The 133 patients with MCI were referred from the primary care centres in the community to the Geriatric Clinic, Huddinge University Hospital for investigation of suspected dementia. The objective impairment of the patients was 1.5 SD below the average for their age on neuropsychological tests, representing one or more domains of cognition as described by Wahlund et al.[13] All subjects were examined according to the same comprehensive procedure,[13] which included a physical examination, evaluation of neurological status, psychiatric status, review of previous case records, blood test, urine analysis, cerebrospinal fluid analysis, routine electrocardiogram, routine electroencephalogram, magnetic resonance imaging, single photon emission computed tomography, and the Mini Mental State Examination (MMSE).[14] The neuropsychological examination was performed by experienced neuropsychologists. All subjects lived independently in the community and in all cases a close informant was interviewed to gather information about the functional status of the patient.

Diagnostic procedure

The diagnostic criteria for MCI at both institutions are shown in table 2. Follow up diagnoses of dementia and AD were made according to the DSM-III-R,[15] for dementia and the NINCDS-ADRDA[16] for AD at both institutions. For assessment of interference with activities of daily living (ADL), the Clinical Dementia Rating (CDR) scale was used at the MC and clinical judgement at KI.

Follow up procedure

Subjects were re-evaluated every 12–18 months at the MC and received an abbreviated clinical evaluation at that visit as described previously.[10] The initial and the follow up examinations included the same psychometric routine as well as an informant interview regarding behavioural and functional status. In these cases, a consensus diagnosis was again rendered as described above. At the KI, patients with MCI were re-evaluated every twelve months. The evaluation

included the same comprehensive clinical procedure applied at baseline as well as neuropsychological assessment. None of the patients from the two institutions was on acetylcholinesterase inhibitor treatment at initial evaluation.

Neuropsychological assessment

Neuropsychological assessment at both centres comprised a common set of measures, which facilitated the cross-comparison. The set included the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[17] (information, digit span, similarities, block design and digit symbol, and digit span subtests), immediate and delayed recall of the story from the Wechsler Memory Scale-Revised (WMS-R)[18] and Auditory Verbal Learning Test (AVLT).[19] We excluded tests that were not carried out in a similar way at both institutions.

Standardisation of the samples
Mayo Clinic

Mayo's Older Americans Normative Studies (MOANS) standard scores were calculated for the MC patients. MOANS scores provide norms for a number of cognitive tests (core battery) that are commonly used to evaluate individuals from age 55 to 97.[20 21] Smith et al[22–24] have previously demonstrated that five cognitive factors underlie the MOANS core battery in both a normative and a clinical sample. These factors, labelled the five Mayo Cognitive Factor Scores (MCFS), include verbal comprehension, perceptual organisation, attention/concentration, learning, and retention, as described elsewhere.[2] The tests included in each factor are further detailed in table 3.

Karolinska Institutet sample

The KI MCI neuropsychological scores were standardised by using a control group of subjects consisting of the patients' relatives, members of the Swedish Pensioner Society in the Huddinge community, and non-mutation carriers from AD families.

For comparisons between the MC and KI groups, we organised the neuropsychological measures according to the MCFS. We assumed that scores below 1.5 SD according to age and years of education was a sign of cognitive abnormality. We were thus able to calculate "the number of impaired cognitive domains", with scores ranging from 0 to 5. For the purpose of comparison, we restricted our analysis to those patients who had 1, 2, or 3 cognitive domains affected. These patients represented the major proportion overall in the cognitive spectrum.

Statistical procedure

Student's t test was used to analyse the differences between the groups with regard to the demographic and standardised z scores neuropsychological variables. APOE ε4 genotype distributions were compared with χ^2 test (see table 1). A Kaplan–Meier survival function with dementia diagnosis

Table 3 Neuropsychological standardised z scores of the two study groups with mild cognitive impairment

Cognitive function	Tests	Mayo Clinic (n = 170)	Karolinska Institutet (n = 133)
Verbal comprehension	WAIS-R: information	−0.36 (2.66)	−1.45 (1.04)*
	WAIS-R: similarities	−0.01 (0.97)	−2.15 (0.98)
Attention	WAIS-R: digit symbol	−0.04 (0.98)	−1.13 (0.96)*
	WAIS-R: digit span	−0.08 (2.33)	−4.01 (1.98)**
Perceptual organisation	WAIS-R: block design	−0.21 (1.03)	−0.24 (0.90)*
Learning and memory	WMS-R: logical memory (immediate story recall)	−0.39 (2.00)	−6.45 (1.25)**
	AVLT: learning over trials	−1.56 (1.65)	−1.25 (1.35)*
Retention	WMS-R: logical memory (delayed story recall)	−1.90 (2.70)	−2.3 (1.7)**
	AVLT: delayed recall	−1.03 (1.52)	−2.3 (1.9)**

All values are mean (SD).
*p<0.05.
**p<0.01.
AVLT, Auditory Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

used as "an event" was calculated. A global test for proportions was used to check the assumptions of the Cox proportional hazard model, which was then used to assess risk factors for incident AD among the patients with MCI. Potential risk factors in the hazards analysis included age, years of formal education, and the *APOE* ε4 genotype. The choice of these covariates was based on their associations with the outcome of AD in the literature.[9 25] We also examined the AD diagnosis as a discrete binary outcome. Logistic regression analyses were conducted with the same covariates after restricting the group with MCI to patients who had completed 50 months follow up or developed AD before that time.

RESULTS
Baseline clinical features
There were differences between the KI and MC groups in terms of age, education, and MMSE as shown in table 1. The *APOE* ε4 genotype was evaluated in a total of 240 patients from MC and KI (see table 1). The distribution of the *APOE* ε4 genotype frequencies for the two institutions was not different ($\chi^2 = 1.66$; df = 3; p>0.05). On the other hand, there was no association between the ε4 allele and the outcome of AD.

Prediction of AD
Figure 1A shows the survival function when all the patients from the two institutions are considered together, without taking into account "the number of impaired cognitive functions" at baseline. The two curves differed significantly (log rank = 11.8; df = 1; p<0.0001). Since the major proportion of patients had two impaired cognitive domains, we calculated Kaplan–Meier survival curves for patients from MC and KI (fig 1B). The difference between the two curves was significant (log rank = 3.61; df = 2; p<0.05). When the two institutions were considered together in a Cox proportional hazard model, "the number of affected cognitive factors" was a significant predictor of time to AD diagnosis with age (not significant (NS)), number years of formal education (NS), and *APOE* ε4 genotype (NS) entered into the same model as covariates. The only significant covariate in the model was "institution" (MC *v* KI). Additional Cox analyses were conducted for the two institutions separately. When the model was adjusted for each institution independently for age, years of formal education, and *APOE* ε4 genotype, the number of impaired cognitive domains remained a significant predictor. In addition, the *APOE* ε4

genotype was a significant predictor for the KI group when investigated in isolation.

For the two groups followed up at two years, the number of impaired cognitive factors (−1.5 SD) at baseline led to sensitivity of 80% and specificity of 75% for the diagnosis of AD, including a progressive increase in sensitivity and a decrease in specificity with two or three "cognitive factors below 1.5 SD".
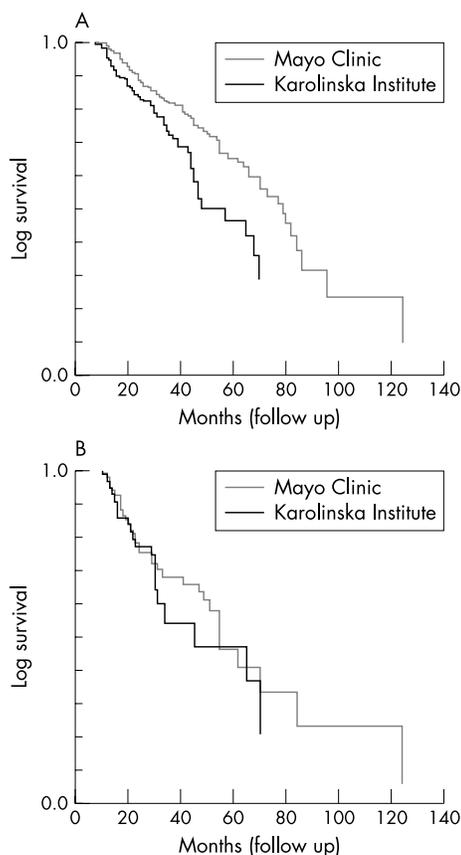

Figure 1 (A) Kaplan–Meier survival curve of probability of developing Alzheimer's disease (AD) over 140 months (Mayo Clinic and Karolinska Institutet patients with mild cognitive impairment (MCI) combined). (B) Kaplan–Meier survival curves of probability of developing AD over 50 months (Karolinska Institutet) and over 140 months (Mayo Clinic) in subjects with MCI with two cognitive functions below 1.5 SD at baseline.

Neuropsychological measures were also entered into a logistic model of AD outcome (table 4). The results revealed that WMS: delayed recall was the only significant predictor of AD, when the two samples were added together. When the KI MCI sample was considered in isolation, the predictive values were AVLT: delayed recall, WMS: delayed recall, WAIS-R: information, and WAIS-R: digit span. Similarly, when the MC sample was analysed independently, the best two predictors were WMS: delayed recall and WMS: immediate recall. Neither age or education nor *APOE* ε4 genotype was significant in any of the three models.

DISCUSSION

This study addressed two issues concerning the variability of results in the literature concerning MCI: (*a*) the sources of subject recruitment, and (*b*) the diagnostic criteria.

The MC recruited its patients from a primary care setting by proactively reviewing medical records to detect any suspicion of the subjects having a cognitive concern—if there was a suggestion that the subject might be impaired, permission was sought to approach the individual for participation in the research study. This design allowed for detecting cognitive impairment prior to the point at which subjects would be referred either by themselves, their family, or physicians. The KI is an academic medical centre where subjects were recruited from consecutive clinical patients referred to the geriatric department by primary care physicians. Therefore, it is possible that these subjects may have had more advanced cognitive symptoms. When common sets of neuropsychological measures were used to compare the samples, it became apparent that the KI subjects with MCI were slightly more impaired than the MC subjects. The indices of general cognition and individual neuropsychological test performance revealed more impairment in the KI subjects, yet the experienced clinicians in this institute did not feel that the subjects were demented. These data document that individual subjects may have various types of MCI and their clinical profiles may vary as a function of the recruitment strategy used to enrol them in the study. Slightly different populations of subjects can have a significant impact on the clinical profile of the subjects recruited.

In addition to the differences in the recruitment procedures, the subjects were ascertained with slightly different criteria. The MC subjects with MCI were impaired primarily in the memory domain (amnestic MCI), while other cognitive domains were relatively intact.[1] The other non-memory cognitive domains were not statistically normal, but the impairments in these other areas were not believed to be clinically significant. However, the KI subjects were impaired slightly in multiple cognitive domains but these were not of sufficient magnitude to constitute the diagnosis of dementia.

Consequently, these subjects would be more characteristic of the subjects with multiple domain MCI described previously.[1] This type of variability has been seen in other studies.[7 26] In addition, the assessment of interference with daily living was different, at the MC the CDR scale was used and at KI clinical judgement was used. The latter procedure may be more conservative in terms of degree of change required than a procedure that make use of a specified scale such as the CDR scale. This might have also resulted in the sample of patients at KI being slightly more impaired compared with those from MC.

Using the number of impaired cognitive domains at baseline, the Kaplan–Meier curves demonstrated that it was possible to predict the progression from MCI to AD in both groups. The survival curves for the two institutions were slightly different indicating that conversion from MCI to AD depended on the particular institution, and that the severity of impairment in the various domains was also different between the two institutions.

It is interesting to note that clinical heterogeneity was also observed when the two institutions were considered separately. While some controversy exists as to the precise characterisation of subjects with MCI, these data suggest that detailed neuropsychological testing can accurately identify individuals experiencing mild or even unrecognised cognitive impairment in the primary care setting who are at a greater risk of developing AD.[27–29] However, excessive reliance on neuropsychological data in the absence of the judgement of clinicians can lead to exaggerated inclusion of patients into the MCI cohort.[5] It is important to note that the diagnosis of MCI was made on a clinical basis at both institutions. While the neuropsychological tests were supportive of the clinician's judgement, the final diagnosis of MCI was rendered by clinicians at both institutions. This likely led to the stability of the diagnosis and the reliability of the progression of the subjects over time.

To highlight this point, a recent study by Ritchie *et al*[6] documented the finding that when neuropsychological criteria are applied retrospectively, this type of MCI diagnosis can be unreliable. In this study, the authors set the memory criteria at 1 SD below the mean and required other non-memory cognitive domains to be at the mean or above. In so doing, they demonstrated that subjects who fit this profile were uncommon and generally did not progress to dementia. Petersen *et al*[9] showed that when clinical judgement was invoked in characterising patients with a primary memory impairment and only slight impairments in other cognitive domains, subjects progressed at a regular rate to AD. These individuals did not have statistically normal performance in other non-memory domains; however, the clinicians did not feel these other impairments were of sufficient magnitude to constitute dementia. The present study corroborated these

Table 4 Regression estimates and predictive values for the baseline neuropsychological variables for the two institutions

Mayo Clinic			Karolinska Institutet			Mayo and Karolinska		
Tests	β	p	Test	β	p	Tests	β	p
WMS			AVLT			WMS		
Delayed recall	−0.17	<0.01	Delayed recall	0.14	<0.05	Delayed recall	−0.20	<0.01
WMS			WMS					
Immediate recall	−0.22	<0.005	Delayed recall	−0.23	<0.05			
			WAIS-R					
Constant	4.77	=0.05	Information	−1.12	<0.05	Constant	3.55	=0.05
			Digit span	0.12	<0.05			
			Constant	2.23	=0.03			

findings by using clinical judgement to augment the neuropsychological data.

There were also a few other methodological differences between the two institutions. For example, the use of five MCFS allowed the MC investigators to assess quantitatively the MC cognitive profile, whereas the KI neuropsychological assessment battery was based on clinical evaluation of abnormal test results depending upon the age and education of the subject.

The regression model demonstrated that tests assessing learning and retention were the best predictors for progression to AD when the two samples were considered together. This finding has been reported in previous research.[28] [30–32] In fact, Bozoki *et al*[32] and Albert *et al*[33] have demonstrated that when other cognitive functions beyond memory become significantly impaired, the likelihood of more rapid progression to dementia or AD increases.

The finding that *APOE* ε4 was a significant predictor in the KI but not in the MC group may reflect the influence of the ε4 allele in the early stages of the disease since the KI patients were younger than the MC subjects. Other work has indicated that the *APOE* ε4 allele is not only a risk factor for developing AD but may also influence the age of expression.[34] Therefore, the age differences in these two samples might have been significant.

In summary, this study demonstrated that MCI populations can be compared cross-nationally. The two research groups are experienced in evaluating cognitive impairment and dementia and characterised two groups of subjects who were felt to be impaired but did not fulfil the criteria for dementia. One research group used a memory predominant set of criteria (amnestic MCI) and their results demonstrated a regular progression to dementia. The other research group used a definition of MCI which included mild impairments in multiple cognitive domains (multiple domain MCI).[4] While both sets of criteria are valid, they led to slightly different populations of subjects. In addition, the degree of impairment of the two samples also had an impact on the characterisation of the two groups and their progression to dementia. The results of the present study lend support to the idea that although the MCI concept covers a heterogeneous group of patients, it still has predictive value for future development. However, at the same time it is an unanswered question whether subgroups of MCI could be separated as suggested recently by an international working group[1] and whether these subgroups differ with regard to future outcome.

To conclude, our study indicates that MCI is a viable concept in different clinical settings and also emphasises the importance of recognising the various factors that can have an impact on the characterisation of the clinical groups being studied and on their outcome. As greater attention is paid to these sources of variability, the concept of MCI can be refined and the appropriate selection of subjects for clinical trials enhanced.

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ECHO ....

Sydenham's chorea may be relevant to common childhood idiopathic conditions

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Doctors studying neurological disorders arising in children after streptococcal infections have suggested that understanding how these are expressed could greatly improve our knowledge of common but unexplained childhood movement and psychiatric conditions.

The disorders in question are dyskinesias which routinely occur with disabling psychiatric conditions—the legacy of infection with β haemolytic streptococci. Doctors at a tertiary referral centre found a wide range of psychiatric conditions among 40 children seen between 1999 and 2002 with neurological complications after such infection. Sex differences and a genetic component were also evident.

Chorea—including Sydenham's chorea, the classic dyskinesia after streptococcal infection (20 patients)—and motor tics (16, 40%) were the most common neurological complications. Chorea occurred mostly in girls (65%) and tics in boys (69%).Only children with chorea had systemic complications of infection—carditis and arthritis—which always preceded neurological complications. Acute emotional or behavioural changes became evident in 33 (83%) children after their streptococcal infection, with emotional lability, anxiety, obsessive compulsive disorder, and depression occurring most commonly.

All 40 children were positive for β haemolytic streptococcal antibody, but 34 (85%) had clinical evidence of such infection before the neurological disorder appeared, after a mean interval of 18.9 (range 1–67) days. Almost three quarters have continuing symptoms of movement disorders after an average of two and a half years, some for as long as 13 years. Forty per cent had a family history of psychiatric or movement disorders in first degree relatives and a similar proportion autoimmune complications in first or second degree relatives.

▲ Dale RC, et al. *Archives of Disease in Childhood* 2004;**89**:604–610.