

# Mild Cognitive Impairment Can Be Distinguished From Alzheimer Disease and Normal Aging for Clinical Trials

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**Background:** Mild cognitive impairment (MCI) represents a transitional state between the cognitive changes of normal aging and very early dementia and is becoming increasingly recognized as a risk factor for Alzheimer disease (AD). The Memory Impairment Study (MIS) is a multicenter clinical trial in patients with MCI designed to evaluate whether vitamin E or donepezil is effective at delaying the time to a clinical diagnosis of AD.

**Objective:** To describe the baseline characteristics of patients with MCI recruited for the MIS and compare them with those of elderly controls and patients with AD in another clinical trial.

**Design:** Descriptive and comparative study of patients with MCI participating in a multicenter clinical trial.

**Setting:** Memory disorder centers in the United States and Canada.

**Patients:** A total of 769 patients with MCI, 107 cognitively normal elderly controls, 122 patients with very mild AD (Clinical Dementia Rating [CDR] 0.5), and 183 patients with mild AD (CDR 1.0) were evaluated. Patients in the MIS met operational criteria for amnesic MCI. Controls were recruited in parallel with

the MCI group, underwent the same assessments, and had a CDR of 0.

**Main Outcome Measures:** Clinical, neuropsychological, functional, neuroimaging, and genetic measures.

**Results:** Mean  $\pm$  SD Alzheimer's Disease Assessment Scale-Cognitive Subscale scores were  $5.6 \pm 3.3$  for controls,  $11.3 \pm 4.4$  for patients with MCI,  $18.0 \pm 6.2$  for the AD CDR 0.5 group, and  $25.2 \pm 8.8$  for the AD CDR 1.0 group. Compared with controls, patients with MCI were most impaired on memory tasks, with less severe impairments in other cognitive domains. Patients with MCI were more likely than controls but less likely than patients with AD to carry the apolipoprotein E  $\epsilon 4$  allele. Patients with MCI had hippocampal volumes that were intermediate between those of controls and patients with AD.

**Conclusions:** Patients with MCI had a predominant memory impairment with relative sparing of other cognitive domains and were intermediate between clinically normal individuals and patients with AD on cognitive and functional ratings. These results demonstrate the successful implementation of operational criteria for this unique group of at-risk patients in a multicenter clinical trial.

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**M**ILD COGNITIVE IMPAIRMENT (MCI) represents a transitional state between healthy aging and very mild Alzheimer disease (AD) and has become the focal point of much research activity.<sup>1</sup> Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnesic MCI" and is frequently a prodromal state of AD.<sup>1,2</sup> In this study, MCI refers to amnesic MCI. Patients with MCI have a memory impairment that is out of proportion to that expected for their age, yet they do not meet commonly accepted

criteria for dementia or AD. Studies<sup>3-8</sup> suggest that these individuals tend to progress to clinically probable AD at a rate of approximately 10% to 15% per year. The American Academy of Neurology, in a recent evidence-based practice parameter on dementia,<sup>6</sup> recognized MCI as an important clinical condition to identify and monitor, since several potential treatments for the condition are under investigation.

There is no proven therapy for MCI. As MCI may represent a prodromal state to clinical AD, treatments proposed for AD, such as antioxidants and cholinesterase inhibitors, may be useful in MCI.<sup>9-11</sup>

The present study was designed to use the infrastructure of the Alzheimer's Disease Cooperative Study (ADCS), a National Institute on Aging consortium of AD research centers, to evaluate the potential treatment effects of vitamin E or donepezil on the rate at which patients with MCI progress to clinically probable AD during 3 years of follow-up. The diagnosis of MCI requires considerable clinical judgment; therefore, for this trial we developed operational criteria that could be implemented consistently across centers. We describe the cognitive and functional characteristics of the participants with MCI recruited to this trial. The primary question that this study addresses is whether these operational criteria successfully distinguish patients with MCI from controls and patients with mild AD on specific clinical, neuropsychologic, functional, neuroimaging, or genetic measures. This is the first study to compare performance on the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog),<sup>12</sup> a standard instrument used in AD trials, in large samples of patients with MCI, simultaneously recruited controls, and patients with AD. In addition, the neuropsychologic battery and functional assessments performed in this trial have not previously been reported in patients with MCI or compared with controls or patients with very mild AD.

## METHODS

### PATIENTS WITH MCI

The 769 participants in this study were recruited from 69 ADCS sites in the United States and Canada. The ADCS launched a nationwide advertisement campaign targeting the elderly population in cities with participating sites. In addition, individual sites also advertised locally and identified potential participants. To be eligible for study treatment, all participants had to meet the operational criteria for MCI, including (1) memory complaint, corroborated by an informant; (2) abnormal memory function, documented by delayed recall of one paragraph from the Logical Memory II subtest of the *Wechsler Memory Scale-Revised*<sup>13</sup> (cutoff scores:  $\leq 8$  for  $\geq 16$  years of education;  $\leq 4$  for 8 to 15 years of education; and  $\leq 2$  for 0 to 7 years of education [the maximum number of paragraph items possible to correctly recall is 25]); (3) normal general cognitive function, as determined by a clinician's judgment based on a structured interview with the patient and an informant (Clinical Dementia Rating [CDR]) and a Mini-Mental State Examination (MMSE) score greater than or equal to 24<sup>14</sup> (the clinician also had access to the ADAS-Cog, but no cutoff score on the ADAS-Cog was required for trial entry); (4) no or minimal impairment in activities of daily living (ADLs), as determined by a clinical interview with the patient and informant; and (5) not sufficiently impaired, cognitively and functionally, to meet National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD,<sup>15</sup> as judged by an experienced AD research clinician. In addition, patients had to be aged 55 to 90 years, be in good health with no significant cerebral vascular disease, have a modified Hachinski score less than or equal to 4,<sup>16</sup> have a Hamilton Depression Rating Scale score less than or equal to 12,<sup>17</sup> and undergo a computed tomographic or magnetic resonance imaging (MRI) brain scan within 12 months before screening without indication of infection, infarction, or focal lesions. Patients were required to have a global CDR of 0.5, with at least a 0.5 in the memory domain. All patients and

their representatives signed a written consent form that had been approved by the local institutional review board of each participating site.

At study entry, participants were assessed using the MMSE; the ADAS-Cog; the global CDR and CDR sum of boxes, the ADCS MCI-ADL Scale, a modification of the ADCS-ADL Scale<sup>18</sup> designed to increase sensitivity to impairments in instrumental activities that may occur in MCI; the Global Deterioration Scale<sup>19</sup>; and a neuropsychologic battery, which consisted of the New York University paragraph recall test,<sup>20</sup> the Symbol Digit Modalities test,<sup>21</sup> the category fluency test,<sup>22</sup> a number cancellation test,<sup>12</sup> the Boston Naming Test,<sup>23</sup> the digits backwards test,<sup>24</sup> the clock drawing test, and a maze tracing task.<sup>12</sup>

### CONTROL SUBJECTS

Simultaneously with the development of this trial, cognitively normal, healthy elderly control subjects were recruited in a parallel study. One objective in recruiting this control group was to assess for differences between MCI and normal aging on the clinical and neuropsychologic measures used in the MCI trial. The controls received the same instruments as the patients with MCI.

Cognitively normal subjects were drawn from cohorts followed at participating ADCS sites. The control subjects underwent a standard medical evaluation and were judged to be in good health. Enrolled controls were required to have a CDR of 0, an MMSE score greater than or equal to 26, and a delayed paragraph recall score greater than 10 for those with 16 or more years of education, greater than 6 for those with 8 to 15 years of education, and greater than 4 for those with 0 to 7 years of education. The ADCS recruited and assessed 107 controls at 20 sites. Twenty percent of the controls (1 of every 5 controls enrolled) were required to be minorities.

### PATIENTS WITH AD

To provide greater context for the cognitive and functional characteristics of patients with MCI, it was desirable to compare patients with MCI recruited for this trial with patients with AD recruited by the ADCS in a typical AD trial. We therefore included in these analyses patients recently recruited to an ADCS clinical trial.<sup>25</sup> We included patients with AD who had a global CDR of 0.5 (very mild AD) or 1.0 (mild AD). Patients with AD were required to meet the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD and to have an MMSE score between 13 and 26. Not all of the instruments used in the MCI trial could be compared with the AD group as only a subset of the instruments were included in the AD trial (ie, MMSE, ADAS-Cog, CDR, and Hachinski).

### MAGNETIC RESONANCE IMAGING

The hippocampus is one of the first brain regions affected in patients with AD. Previous studies<sup>26</sup> suggest that hippocampal atrophy, as measured using MRI, may be a marker for early AD in patients with MCI and may predict a more rapid deterioration to clinically defined AD. In this MCI trial, MRIs were obtained before baseline at a subset of sites with the ability to perform MRIs conforming to a specified protocol. Volume measurements of the hippocampi were performed by research associates who were masked to clinical information to ensure that the volumetric data were unbiased.<sup>27</sup> The borders of the hippocampi were manually traced on the workstation screen for each image slice sequentially from posterior to anterior using previously described methods.<sup>28</sup>

We compared the baseline hippocampal volumes of patients with MCI participating in the Memory Impairment Study

**Table 1. Demographic Characteristics of the Participant Groups**

Characteristic	Controls (n = 107)	MCI Group (n = 769)	AD (CDR 0.5) Group (n = 122)	AD (CDR 1.0) Group (n = 183)	P Value	P < .05*
Age, mean ± SD, y	70.0 ± 8.3	72.9 ± 7.3	73.1 ± 7.1	74.0 ± 8.0	.001	a,d,e
Education, mean ± SD, y	14.8 ± 3.3	14.7 ± 3.1	14.5 ± 3.2	13.8 ± 3.2	.01	c
Years from onset of first symptoms, mean ± SD	NA	3.1 ± 2.6	3.7 ± 2.4	4.3 ± 2.9	<.001	b,c
Sex, %					.01	a
M	40.4	54.2	54.9	45.4		
F	59.6	45.8	45.1	54.6		
Marital status, %					.31	NA
Married	69.2	77.6	82.0	78.7		
Widowed	20.2	12.6	10.7	16.9		
Divorced	7.7	6.9	4.9	3.8		
Never married	2.9	2.7	2.5	0.5		
Unknown	0	0	0	0		
Apolipoprotein E ε4, %					<.001	a,b,c,d,e
Positive	29.5	55.1	68.6	68.2		
Negative	70.5	44.9	31.4	31.8		
Ethnicity, %					<.001	a,d,e
American Indian	1.0	0.4	1.6	0.5		
Asian American	2.9	0.9	0	0		
African American	14.4	2.3	3.3	2.2		
Hispanic	9.6	3.9	2.5	7.1		
White	71.2	92.1	92.6	90.2		
Other	1.0	0.4	0	0		

Abbreviations: AD, Alzheimer disease; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment; NA, not applicable.

\*Indicates significance at  $P < .05$  after Bonferroni adjustment for multiple comparisons: a, MCI to control comparison; b, MCI to AD (CDR 0.5) comparison; c, MCI to AD (CDR 1.0) comparison; d, control to AD (CDR 0.5) comparison; and e, control to AD (CDR 1.0) comparison.

with hippocampal volumes of controls, patients with MCI, and patients with AD evaluated separately at the Mayo Clinic. To control for variation in head size, the hippocampal volumes for each individual were summed and divided by the total intracranial volume of that particular patient. Age- and sex-specific normal percentiles were determined for normalized hippocampal volume in a group of cognitively normal older controls. The control subjects used for this purpose were recruited from the community through primary care practices.<sup>28</sup> Age- and sex-specific normal percentiles for the hippocampal volume measure for each patient with MCI were determined using this normal-value database. Each percentile was then converted to a W score. The W score is the value from a standard normal distribution corresponding to the observed percentile in control subjects. For example, for a standard normal distribution, the 50th, 5th, and 2.5th percentiles are given by W scores of 0, -1.64, and -1.96, respectively.

#### DATA ANALYSIS

Statistical analyses were conducted using a statistical software package (SPSS 11.0; SPSS Inc, Chicago, Ill). Demographic data that were continuous in nature were analyzed using analysis of variance, and categorical data were analyzed using  $\chi^2$  statistics. Pairwise group comparisons were considered statistically significant if  $P < .05$  after Bonferroni adjustment for multiple comparisons. Cognitive and functional measures were analyzed using general linear models in which the diagnostic group was entered as a fixed effect, with age, sex, education, ethnicity, and apolipoprotein E ε4 status included as covariates. Pairwise group comparisons in these analyses were considered significant if  $P < .05$  after Bonferroni adjustment for multiple comparisons. To estimate the degree of impairment in patients with MCI, standardized z scores were calculated based on the mean and SD scores of the ADAS-Cog and other instruments from the neuropsychologic test battery administered to

the control group. The z score indicates the relative degree of impairment from normal in SD units, thereby allowing comparison with other instruments.

## RESULTS

A total of 769 patients were recruited in the MCI study, and baseline data were collected. One hundred seven cognitively normal elderly controls and 305 patients with mild AD were recruited for comparison purposes on the assessment measures. The demographic characteristics of the participants are given in **Table 1**. Patients with MCI were similar in age (mean age, 73 years) to patients with AD but were on average approximately 3 years older than controls. The educational level was similar among the MCI, control, and AD CDR 0.5 groups but slightly lower in the AD CDR 1.0 group. Patients with MCI reported an average duration of symptoms of approximately 3.1 years, which was about 0.6 years less than AD CDR 0.5 patients and approximately 1.2 years less than AD CDR 1.0 patients. Men were equally represented among the MCI and AD groups but were relatively less represented among controls. Patients with MCI were much more likely to carry the apolipoprotein E ε4 allele than controls but were less likely to carry it than patients with AD. Patients with MCI were 92% white, a frequency similar to that observed in the AD groups but greater than that observed in the control group, which had a greater representation of minorities.

Mean scores on the screening measures (MMSE, paragraph recall, CDR, Hamilton scale, and Hachinski scale), the Global Deterioration Scale, and the MCI-ADL are given in **Table 2**. Patients with MCI had a mean

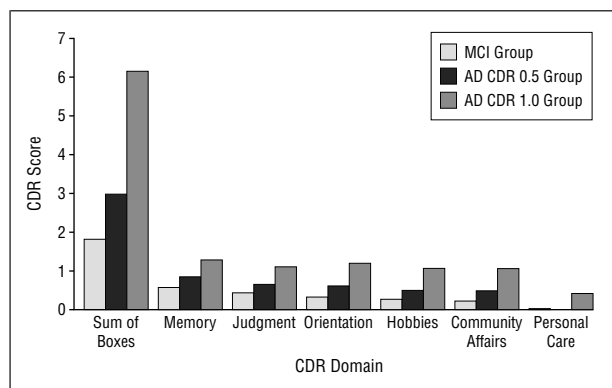
**Table 2. Baseline Assessments: MMSE, Logical Memory, CDR, Hamilton, Hachinski, GDS, and ADCS MCI-ADL\***

Assessment Variable	Controls (n = 107)	MCI Group (n = 769)	AD (CDR 0.5) Group (n = 122)	AD (CDR 1.0) Group (n = 183)	P Value	P<.05†
MMSE score	29.1 ± 1.3	27.3 ± 1.9	23.3 ± 2.4	19.9 ± 3.5	<.001	a,b,c,d,e,f
Immediate paragraph recall score	13.1 ± 3.5	6.3 ± 3.1	NA	NA	<.001	NA
Delayed paragraph recall score	12.3 ± 3.3	3.3 ± 2.5	NA	NA	<.001	NA
CDR (global) score	0 ± 0	0.5 ± 0	0.5 ± 0	1.0 ± 0	NA	NA
CDR sum of boxes score	0.1 ± 0.2	1.8 ± 0.8	3.0 ± 0.8	6.2 ± 1.3	<.001	a,b,c,d,e,f
Memory score	0 ± 0	0.6 ± 0.2	0.9 ± 0.3	1.3 ± 0.5	<.001	a,b,c,d,e,f
Orientation score	0 ± 0.1	0.3 ± 0.3	0.6 ± 0.3	1.2 ± 0.5	<.001	a,b,c,d,e,f
Judgment score	0.1 ± 0.2	0.4 ± 0.2	0.7 ± 0.3	1.1 ± 0.4	<.001	a,b,c,d,e,f
Community affairs score	0 ± 0.1	0.2 ± 0.3	0.5 ± 0.3	1.1 ± 0.4	<.001	a,b,c,d,e,f
Hobbies score	0 ± 0	0.3 ± 0.3	0.5 ± 0.3	1.1 ± 0.4	<.001	a,b,c,d,e,f
Personal care score	0 ± 0	0 ± 0.1	0 ± 0.2	0.4 ± 0.5	<.001	c,e,f
Hamilton score	1.1 ± 1.8	2.7 ± 2.8	NA	NA	<.001	NA
Hachinski score	0.3 ± 0.5	0.5 ± 0.7	0.4 ± 0.7	0.4 ± 0.7	.02	NA
GDS score	1.2 ± 0.4	2.7 ± 0.6	NA	NA	<.001	NA
ADCS MCI-ADL score	50.7 ± 2.6	45.9 ± 5.1	NA	NA	<.001	NA

Abbreviations: AD, Alzheimer disease; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for patients with MCI; CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NA, not applicable.

\*Scores are given as mean ± SD.

†Indicates significance at  $P < .05$  after Bonferroni adjustment for multiple comparisons: a, MCI to control comparison; b, MCI to AD (CDR 0.5) comparison; c, MCI to AD (CDR 1.0) comparison; d, control to AD (CDR 0.5) comparison; e, control to AD (CDR 1.0) comparison; and f, AD (CDR 0.5) to AD (CDR 1.0) comparison.



**Figure 1.** Mean Clinical Dementia Rating (CDR) domain scores in patients with mild cognitive impairment (MCI), patients with Alzheimer disease (AD) and global CDR 0.5, and patients with AD and global CDR 1.0.

MMSE score of 27.3 and a delayed paragraph recall score of 3.3. The MMSE score was intermediate between that of controls and patients with AD CDR 0.5 and significantly different from both groups. The immediate and delayed paragraph recall scores were significantly lower than those in controls (the paragraph recall test was not performed in patients with AD). The mean CDR sum of boxes score was 1.8 for patients with MCI, a value significantly lower than that observed in AD CDR 0.5 patients (3.0) and AD CDR 1.0 patients (6.2). Similarly, patients with MCI were significantly less impaired than patients with AD CDR 0.5 in all individual box scores on the CDR except personal care, which was not impaired in either group. As might be expected, the MCI group had its greatest impairment in the memory domain (mean=0.6) compared with the other CDR domains. Scores on the CDR sum of boxes and the CDR domains are shown graphically in **Figure 1**. The MCI group had a significantly higher mean Hamilton score than controls. Patients with MCI had a significantly lower

score on the MCI-ADL scale (designed to be sensitive to very mild impairments in instrumental ADLs) than controls (Table 2).

Patients with MCI had mean ADAS-Cog scores intermediate between those of controls and AD CDR 0.5 patients (**Table 3** and **Figure 2**). Subscores on the ADAS-Cog are shown graphically in **Figure 3** for controls, patients with MCI, and patients with AD. As can be seen in Table 3 and Figure 3, controls gained 0.9 error points on non-word list items on the ADAS-Cog compared with a gain of 2.1 points for patients with MCI, 5.7 points for patients with AD CDR 0.5, and 10.7 points for patients with AD CDR 1.0. In terms of z scores (SD units), patients with MCI performed on average 1.8 SD higher on the immediate word list recall test and 2.1 SD higher on the delayed word list recall test from the ADAS-Cog compared with 1.0 SD higher on the non-word list items (Table 3). Examination of the subitems from the ADAS-Cog revealed that, similar to controls, patients with MCI gained most of their error points (81%) on the word list recall and recognition items.

The neuropsychologic battery was performed only in controls and patients with MCI (**Table 4** and **Figure 4**). Compared with the control group, the results indicate that the largest decline from normal was observed on the New York University paragraph delayed recall (1.5 SD) and the New York University paragraph immediate recall test (1.2 SD) (Table 4). Beyond these memory tasks, the greatest impairment was seen on the Symbol Digit Modalities test and the category fluency tasks, although these deviated from normal by 1 SD or less.

A subset of patients with MCI (n=193) had MRIs performed and hippocampal volume measured at baseline. Patients with MCI in the Memory Impairment Study had hippocampal volumes that were virtually identical to those of patients with MCI from the Mayo Clinic described in a previous study by Jack et al,<sup>29</sup> with mean ± SD

**Table 3. ADAS-Cog Scores by Participant Groups\***

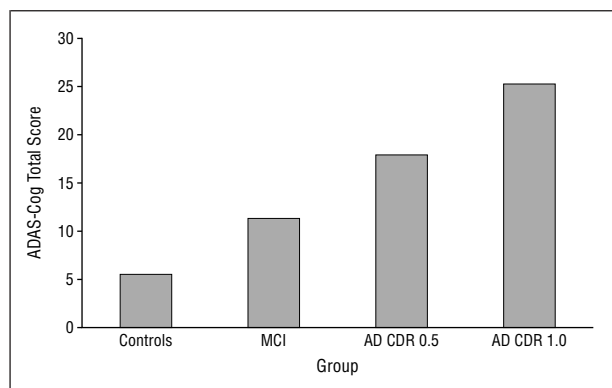
Variable	Controls (n = 107), Score, Mean ± SD	MCI Group (n = 769)		AD (CDR 0.5) Group (n = 122)		AD (CDR 1.0) Group (n = 183)		P Value	P<.05†
		Score, Mean ± SD	z Score	Score, Mean ± SD	z Score	Score, Mean ± SD	z Score		
ADAS-Cog total	5.6 ± 3.3	11.3 ± 4.4	1.7	18.0 ± 6.2	3.7	25.2 ± 8.8	5.9	<.001	a,b,c,d,e,f
ADAS word list immediate recall	2.7 ± 1.2	4.9 ± 1.4	1.8	6.0 ± 1.3	2.8	6.9 ± 1.4	3.6	<.001	a,b,c,d,e,f
ADAS word list recognition	2.0 ± 2.2	4.3 ± 2.8	1.1	6.2 ± 3.1	2.0	7.7 ± 3.0	2.6	<.001	a,b,c,d,e,f
ADAS-Cog without word list items	0.9 ± 1.2	2.1 ± 1.8	1.0	5.7 ± 3.5	4.1	10.7 ± 6.5	8.2	<.001	a,b,c,d,e,f
ADAS word list delayed recall‡	2.6 ± 1.7	6.3 ± 2.2	2.1	8.3 ± 1.7	3.3	8.9 ± 1.5	3.7	<.001	a,b,c,d,e
ADAS score from word list/non-word list items, %	84/16	81/19		68/32		58/42		<.001	b,c,d,e,f

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment.

\*Higher ADAS-Cog total scores and subscores indicate a greater number of errors.

†Indicates significance at  $P < .05$  after Bonferroni adjustment for multiple comparisons: a, MCI to control comparison; b, MCI to AD (CDR 0.5) comparison; c, MCI to AD (CDR 1.0) comparison; d, control to AD (CDR 0.5) comparison; e, control to AD (CDR 1.0) comparison; f, AD (CDR 0.5) to AD (CDR 1.0) comparison.

‡ADAS word list delayed recall is not included in the classic 70-point ADAS-Cog total score.



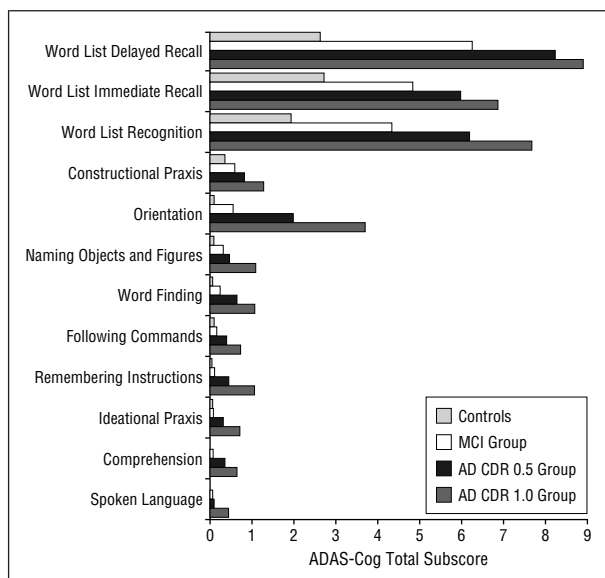
**Figure 2.** Mean Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) total scores for controls, patients with mild cognitive impairment (MCI), patients with Alzheimer disease (AD) and global Clinical Dementia Rating (CDR) 0.5, and patients with AD and global CDR 1.0.

hippocampal volumes ( $W = -1.2 \pm 1.0$ ) approximately 1.0 SD smaller than those of controls ( $W = -0.2 \pm 1.2$ ;  $P < .001$ ) and 0.9 SD larger than those of patients with AD ( $W = -2.1 \pm 1.2$ ;  $P < .001$ ).

**COMMENT**

The Memory Impairment Study represents one of the first attempts to perform a multicenter trial in individuals with MCI. Several studies on MCI have been conducted at single sites, but the ability to operationalize MCI criteria across sites has not been previously demonstrated, to our knowledge. Operationalizing these criteria, and determining whether they identify patients with characteristics different from those with mild AD, is an essential step if MCI is to become a valid treatment target.

In keeping with the recruitment criteria, the characteristics of this cohort indicated that they had primarily a prominent memory impairment but were also very mildly impaired in other cognitive domains. This is similar to the recruitment characteristics of other MCI studies in the literature.<sup>4,6,30-32</sup> There is some debate as to whether individuals with this degree of impairment might be considered to have dementia<sup>33</sup>; however, the experienced



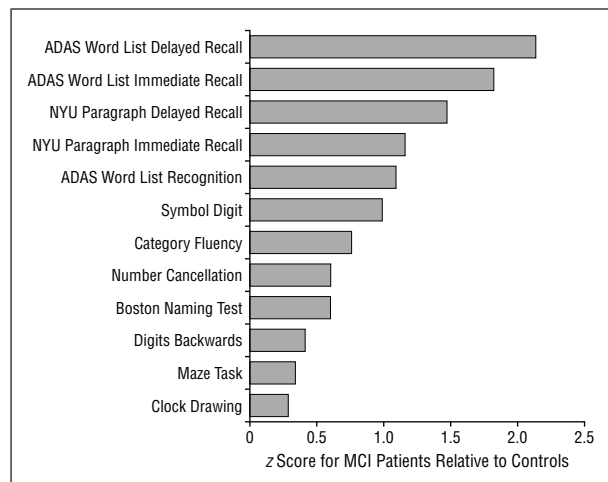
**Figure 3.** Mean Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) subscores for controls, patients with mild cognitive impairment (MCI), patients with Alzheimer disease (AD) and global Clinical Dementia Rating (CDR) 0.5, and patients with AD and global CDR 1.0.

investigators in this study, after reviewing the available clinical and psychometric data, judged the participants in this MCI trial to be insufficiently impaired to warrant a clinical diagnosis of AD at the time they entered the study. Patients with MCI had higher ADAS-Cog total scores than controls, but the proportion of the points contributing to the ADAS-Cog total score derived from the word list memory tasks (81%) was similar to that of controls (84%). In contrast, only 68% and 58% of the points of the ADAS-Cog total were derived from the word list tasks for AD CDR 0.5 patients and AD CDR 1.0 patients, respectively. Patients with AD thus show a pattern of increasing involvement of nonmemory domains. Whereas patients with MCI performed about 1 SD below normal on the ADAS-Cog non-word list items, those with AD CDR 0.5 performed approximately 4 SD below normal (Table 3). Patients with MCI performed better than AD CDR 0.5 patients on all

**Table 4. Neuropsychologic Measures in the Control and MCI Groups\***

Measure	Controls (n = 107)	MCI Group (n = 769)	z Score	P Value
<b>Memory tasks</b>				
NYU paragraph delayed recall	8.1 ± 3.1	3.5 ± 2.8	-1.5	<.001
NYU paragraph immediate recall	7.4 ± 2.8	4.1 ± 2.3	-1.2	<.001
<b>Nonmemory tasks</b>				
Symbol digit	42.4 ± 11.0	31.6 ± 10.8	-1.0	<.001
Category fluency	20.5 ± 6.0	15.8 ± 5.3	-0.8	<.001
Number cancellation	26.2 ± 6.4	22.2 ± 6.3	-0.6	<.001
Boston Naming Test	8.1 ± 2.1	6.9 ± 2.4	-0.6	<.001
Digits backwards	7.1 ± 2.3	6.3 ± 1.9	-0.4	<.001
Maze task	30.0 ± 27.9	39.9 ± 30.5	0.3	.002
Clock drawing	4.6 ± 0.8	4.3 ± 1.0	-0.3	.005

Abbreviations: MCI, mild cognitive impairment; NYU, New York University.  
\*A lower z score indicates reduced performance on all measures except the maze task. Scores are given as mean ± SD.



**Figure 4.** Performance on the Alzheimer's Disease Assessment Scale (ADAS)-Cognitive Subscale and the neuropsychologic test battery in patients with mild cognitive impairment (MCI) compared with controls. Mean z scores are shown with absolute values to illustrate relative worsening on each measure. NYU indicates New York University.

ADAS subscores except spoken language (Figure 3). Compared with AD CDR 0.5 patients, patients with MCI had generally preserved orientation. Patients with MCI gained only 0.5 error points on orientation compared with approximately 2 points gained for AD CDR 0.5 patients (Figure 3). Although orientation involves memory abilities, performance usually declines after more rigorous memory tests, for example, list learning procedures, have become impaired.

Performance by patients with MCI on the neuropsychologic battery further indicated that patients could be consistently recruited with the profile of a clearly defined memory impairment but only mild impairments in other cognitive domains. Patients with MCI performed, on average, less than 1 SD below normal on non-memory cognitive measures included in the battery. As noted by other investigators,<sup>34</sup> tests of learning, attention, perceptual speed, category fluency, and executive

function may be impaired in patients with MCI, but these are far less prominent than the memory deficit.

In patients with clear memory impairment, one would expect to see a degree of functional impairment. This was relatively mild on the CDR and ADCS-ADL scales. The fact that patients with MCI were rated significantly better than those with AD CDR 0.5 on the CDR sum of boxes and CDR domains, including orientation, judgment, hobbies, and community affairs (Table 2), suggests that the extent of decline in these domains is inconsistent with the diagnosis of AD to a clinician.

The hippocampal volumes for a subset of patients with MCI in this study were similar to those reported by Jack et al,<sup>26,29</sup> that is, approximately 1 SD below normal. As previously reported,<sup>26,35</sup> patients with MCI and hippocampal atrophy have an increased likelihood of developing AD. The consistency of these data suggests that the patients with MCI recruited in this study are likely to have a pathological basis for their memory impairment and an increased likelihood of developing AD.<sup>36</sup>

The diagnosis of MCI was established with clinical efficiency using a simple memory test (paragraph recall) to establish an objective memory deficit, a measure of general cognition (MMSE) to exclude a broader cognitive decline beyond memory, and a structured clinical interview (CDR) with patients and caregivers to verify the patient's memory complaint and memory loss and to ensure that the patient was not demented. Diagnosis was made on clinical grounds and not algorithmically determined by neuropsychologic tests or other rating instruments. Results of recent studies<sup>37</sup> have indicated that the concept of MCI can be unstable if only neuropsychologic criteria are arbitrarily retrofitted to data without clinical judgment being used.

In summary, our operational criteria for MCI were successful in identifying patients with MCI who had characteristics distinguishable from cognitively normal elderly controls and very mildly impaired AD patients. The clinical, neuropsychologic, functional, neuroimaging, and genetic profiles of patients with MCI are all consistent with a transitional stage between the cognitive changes of normal aging and very mild AD. Based on the data presented in this article, AD prevention trials with patients with MCI seem to be a promising tool for detecting, intervening, and delaying clinical AD while the disease is still in a transitional clinical stage.

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