

Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a Predictor of Conversion from Mild Cognitive Impairment to Alzheimer's Disease

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OBJECTIVES: To assess the usefulness of the Montreal Cognitive Assessment (MoCA) total score (MoCA-TS) and Memory Index Score (MoCA-MIS) in predicting conversion to Alzheimer's disease (AD) in individuals with mild cognitive impairment (MCI).

DESIGN: Retrospective chart review.

SETTING: Community-based memory clinic.

PARTICIPANTS: Individuals meeting Petersen's MCI criteria (N = 165).

MEASUREMENTS: Baseline MoCA scores at MCI diagnosis were collected from charts of eligible individuals with MCI, and MoCA-TS, MoCA-MIS, and a cognitive domain index score were calculated to assess their prognostic value in predicting conversion to AD.

RESULTS: One hundred fourteen participants progressed to AD (MCI-AD), and 51 did not (nonconverters; MCI-NC); 90.5% of participants with MCI with a MoCA-TS less than 20/30 and a MoCA-MIS less than 7/15 at baseline converted to AD within the average follow-up period of 18 months, compared with 52.7% of participants with MCI above the cutoffs on both scores. Individuals with multiple-domain amnesic MCI had the highest AD conversion rates (73.9%).

CONCLUSION: Identifying individuals with MCI at high risk of conversion to AD is important clinically and for selecting appropriate subjects for therapeutic trials.

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Key words: Montreal Cognitive Assessment; Memory Index Score; mild cognitive impairment; Alzheimer

Mild cognitive impairment (MCI)¹ is a transitional stage between normal aging and early dementia. Although MCI has been recognized as one of the major risk factors for Alzheimer's disease (AD) and other dementias, a significant proportion of individuals with MCI revert to normal cognition or remain cognitively stable on follow-up.^{2,3} Identifying individuals with MCI at high risk of conversion to AD is of great importance to clinicians, the individuals, and their families and for selecting appropriate subjects for therapeutic trials.

Many clinical and biological markers have been used to predict conversion from MCI to AD, including neuropsychological testing,^{4,5} neuroimaging,^{6–8} apolipoprotein E status,⁹ cerebrospinal fluid,^{10,11} and a biomarker combination.^{12–14} These biomarkers can be tested for only in tertiary care centers or are used mostly for research purposes. For clinical practice, it is important to provide simple and reliable tools to help clinicians assess dementia risk in individuals diagnosed with MCI who will need closer supervision and monitoring. A predictive tool would also be useful as a screening measure in therapeutic trials by selecting subjects more likely to decline cognitively and functionally and thus be more likely to benefit from treatment.

The Montreal Cognitive Assessment (MoCA) is a widely used 10-minute cognitive screening test for detection of MCI. It has high sensitivity (90%) and specificity (87%) for detecting individuals with MCI and distinguishing them from individuals with normal cognition.¹⁵

This study aimed to assess the usefulness of the MoCA total score (MoCA-TS) and MoCA newly devised Memory Index Score (MoCA-MIS) to predict conversion from MCI to AD.

Many studies using extensive neuropsychological batteries have shown that delayed recall is the first domain to be impaired in individuals with MCI who subsequently progress to AD.^{16–18} In early-stage MCI, preserved executive and frontal functions compensate for hippocampal dysfunction, which causes encoding memory deficit.¹⁹ Thus, subjects benefit from cueing that helps them retrieve newly learned materials and remain functional and autonomous. As the disease progresses, frontal executive networks are affected and are no longer able to compensate.^{19,20} At this stage, the retrieval memory deficit becomes an encoding memory deficit that does not improve with cueing and is more likely to progress to dementia.

This study examined the predictive nature of MoCA cognitive domains and devised a cognitive domain index score (CDIS) for memory executive function, visuospatial, language, attention, and orientation. The method used to calculate these CDIS is provided in the Methods section.

METHODS

Participants

Charts of consecutive individuals presenting with cognitive complaints to the Center for Diagnosis and Research on Alzheimer's disease, (CEDRA)/Neuro Rive-Sud memory clinic, Montreal, Canada, between November 2004 and May 2011 were reviewed. Individuals with MCI were selected from the reviewed charts. Selected individuals met MCI Petersen's criteria: subjective memory complaints, preserved general intellectual functioning, cognitive impairment detected using neuropsychological assessment (verbal and visual memory, executive function, language, visuospatial function, attention, concentration), intact activity of daily living (ADL) ability, and lack of criteria for dementia.¹ Individuals with evidence of moderate to severe white matter disease or other causes of cognitive impairment on computed tomography (CT) or magnetic resonance imaging (MRI) were excluded. One hundred sixty-five individuals meeting criteria for MCI were selected. Duration of follow-up was determined according to the number of months from MCI diagnosis to AD conversion for converters (MCI-AD) and to the end of the predetermined study observation date of May 2011 for nonconverters (MCI-NC). AD was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)/Alzheimer's Disease and Related Disorders Association criteria.²¹

Measurement

Trained cognitive technicians administered the MoCA as part of the routine cognitive screening assessment of all individuals presenting to the CEDRA/Neuro Rive-Sud Memory clinic. A cognitive technician assessed functional decline (autonomy) in a semistructured interview with the

family using a locally developed functional scale at baseline (0–16 points, 0 = not autonomous, 16 = fully autonomous) and at follow-up visits (0–8 points: 0 = not autonomous, 8 = fully autonomous). Each ADL or instrumental ADL (IADL) is scored 0 if impaired and 1 point if normal. Three basic ADLs are assessed: personal hygiene (bathing, toileting, grooming), dressing, and incontinence (urinary or fecal). Thirteen IADLs are assessed: driving, finances, planning activities, problem solving, using domestic appliances beside the oven, laundry, telephone, medication intake, cooking, grocery shopping, household chores, using the oven safely, getting lost walking or driving.

Scores on the scales were not used to determine conversion to dementia but were provided to the clinician as aids for determining autonomy and to further assess autonomy questions that the scales highlighted. While a technician was assessing functional decline with the family, another technician was administering the MoCA to the participant in another office, each blinded to the other's evaluations. A neurologist with extensive clinical expertise in the cognitive field (ZN) determined conversion to dementia according to the NINCDS and DSM-IV criteria based on an additional interview with the participant and family and the results of the functional and cognitive assessments that the cognitive technicians performed. The baseline MoCA at the time of MCI diagnosis was used to calculate the predictive value of the CDIS. Each CDIS was determined according to published neuropsychological and neuroimaging studies for each cognitive item used in the MoCA. Certain cognitive items can be part of different CDISs if several networks are implicated in the performance of the task. For example, serial 7 is part of the Executive Index score and Attention and Concentration Index score. The MoCA-MIS is calculated by adding the number of words remembered in free delayed recall, category-cued recall, and multiple choice-cued recall multiplied by 3, 2 and 1, respectively, with a score ranging from 0 to 15. This new scoring method was devised to better elicit and detect an encoding memory deficit. The Executive Index Score (EIS) is calculated by adding raw scores for the modified Trail-Making Test Part B, clock drawing, digit span forward and backward, letter A tapping, serial-7 subtraction, letter fluency, and abstraction, with a score ranging from 0 to 13. The Visuospatial Index Score (VIS) is determined by adding the raw scores of the cube copy, clock drawing, and naming, with a score ranging from 0 to 7. The Language Index Score (LIS) is obtained by adding the raw scores for naming, sentence repetition, and letter fluency, with a score ranging from 0 to 6. The Attention Index Score (AIS) is obtained by adding the raw scores for digit span forward and backward, letter A tapping, serial-7 subtraction, sentence repetition, and the words recalled in both immediate recall trials, with a score ranging from 0 to 18. The Orientation Index Score (OIS) is the sum of points for the orientation section of the MoCA, with a score ranging from 0 to 6.

The original Delayed Recall Score, VIS, EIS, and LIS were also used to categorize the MCI subtype as defined previously.²² To determine MCI subtypes, the current MCI cohort was compared with a previously reported normal control cohort in terms of performance on different MoCA cognitive domain indexes from the original MoCA

validation study database.¹⁵ Participants who scored less than 1.0 standard deviation below the age- and education-adjusted mean value in free delayed recall score, VIS, EIS, and LIS were considered as being impaired in that cognitive domain. Institutional review board approval was not obtained because the study design was a retrospective analysis based on chart review.

Data Analysis

Analysis was conducted using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL). Independent *t*-tests were used (for large sample size, *n* = 165) to compare continuous variables of demographic data and MoCA items and CDIS for the MCI-NC and MCI-AD groups. Receiver operating characteristic (ROC) curves were created for the MoCA-TS and CDIS to identify subjects who had progressed to AD by the end of the study. Because the variance was not normally distributed, the Kruskal-Wallis H test was used to compare duration of AD conversion between diagnostic groups according to a recommended algorithm (Figure 1). Different cutoff scores of the identified variables were paired to identify the best combination of cutoff scores that provided the highest predictive values for conversion versus nonconversion to dementia.

RESULTS

One hundred sixty-five individuals meeting MCI criteria were selected.

AD Annual Conversion Rate, Average Follow-Up Period, and Rate of Cognitive Decline

In the 18.2 ± 1.0-month average follow-up period, the AD conversion rate was 69.1%, with an annualized rate of 46.1%. When 33 subjects who had only baseline MoCA scores were excluded, the rates of decline in MoCA-TS and MoCA-MIS were not significantly different between the MCI-AD (*n* = 82) and MCI-NC (*n* = 50) groups. The mean rate of MoCA-TS decline was 2.19 ± 0.39 points/yr in

MCI-AD and 1.72 ± 0.45 points/yr in MCI-NC (*P* = .45), and the mean rate of MoCA-MIS decline was 1.08 ± 0.37 points/yr in MCI-AD and 0.90 ± 0.57 points/yr in MCI-NC (*P* = .79).

Measured autonomy (expressed as a percentage of the total autonomy score on the ADL scale of 0–18 at baseline and 0–8 at follow-up) was available for MCI-AD (*n* = 64) and MCI-NC (*n* = 45). There was no statistically significant difference in ADL capacity at baseline between the groups (MCI-AD 87.1%, MCI-NC 87.2%; *P* = .96), which confirms the relatively preserved autonomy at the MCI stage. There was a significant decline in autonomy at follow-up for MCI-AD, from 87.1% to 60.3% (*P* < .001) and less decline for MCI-NC, from 87.2% to 80.4% (*P* = .04) which confirms the more-significant conversion to dementia in the MCI-AD group (Table S2).

Demographic Characteristics and Cognitive Performance in MCI-NC and MCI-AD

Baseline demographic data and MoCA item scores and CDIS are listed for both groups in Table S3. When considering the overall study period, there was no significant difference in age, education, or follow-up duration between the MCI-NC and MCI-AD groups. Risk of AD conversion was significantly greater in women than men (odds ratio = 1.45, 95% confidence interval (CI) = 1.12–1.88). MoCA-TS and MoCA item scores for naming, digit span forward, serial-7 subtraction, abstraction, and free delayed recall were significantly lower at baseline in MCI-AD than MCI-NC. Conversely, all CDISs were significantly higher in MCI-NC than MCI-AD (MoCA-MIS, *t*(163) = 3.41, *P* = .001; OIS, *t*(163) = 4.21, *P* < .001; EIS, *t*(163) = 2.76, *P* = .006; VIS, *t*(163) = 2.29, *P* = .02; AIS, *t*(163) = 2.92, *P* = .004), except LIS, which was not significantly different between groups (*t*(163) = 1.74, *P* = .08).

MCI Subtype and AD Conversion Rate

No association was found between age and the cognitive domain scores (free delayed recall score, VIS, EIS, LIS)

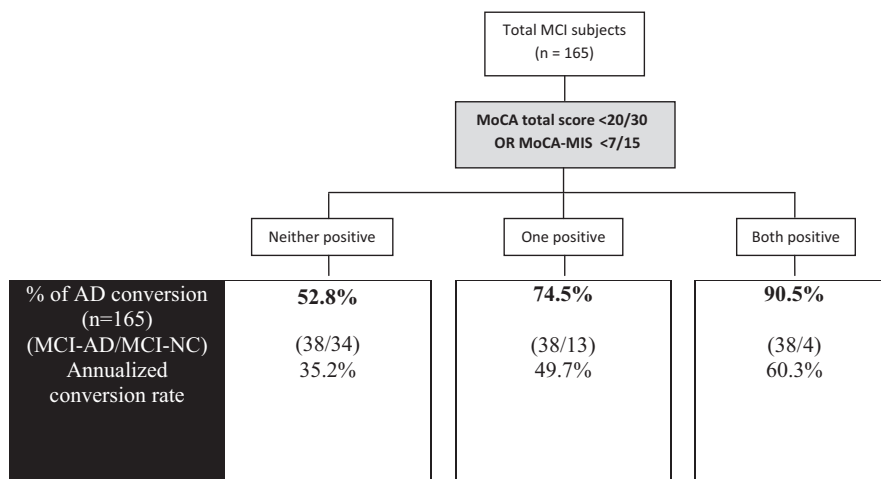


Figure 1. Recommended algorithm to predict conversion from mild cognitive impairment (MCI) to Alzheimer’s disease (AD) at an average follow-up of 18 months. MoCA = Montreal Cognitive Assessment.

Correction made after online publication March 17, 2014: Figure 1 has been updated.

after controlling for education level, although when age was controlled for, education was positively correlated with EIS, VIS, and LIS. Cutoff scores for each cognitive domain are presented in Table S1.

Multidomain amnestic (memory impairment plus one other impaired domain) MCI (multi-aMCI, 69.7%) was the most common group, followed by single-domain amnestic (only impaired memory) MCI (single-aMCI, 19.4%), multidomain nonamnestic MCI (multi-naMCI, 4.8%) and single-domain nonamnestic MCI (single-naMCI, 3.0%). Memory (89.1%) and executive function (63.0%) were the most frequently impaired cognitive domains. AD conversion rates were higher for the multi-aMCI group (73.9%), followed by the single-aMCI group (65.6%), multi-naMCI group (50.0%) and single-naMCI group (20.0%). In individuals with MCI-AD, 74.6% of the group had multi-aMCI, followed by single-aMCI (18.4%).

Mild cognitive impairment to AD conversion rates for each MCI subtype are shown in Table S4.

CDIS to Predict AD Conversion in Individuals with MCI

The education-corrected MoCA-TS and MoCA-MIS were good predictors of AD conversion in participants with MCI during the overall mean follow-up of 18.2 (standard error [SE] 1.04) months. Areas under the ROC curve (AUC) were 0.708 (95% CI = 0.623–0.793, $P < .001$) for the MoCA-TS and 0.662 (95% CI = 0.571–0.753, $P = .001$) for the MoCA-MIS. The AUCs for the EIS, OIS, AIS, and VIS were also good predictors of conversion from MCI to AD (Table S5). The AUCs of LIS did not reach significance in predicting AD conversion. ROC curves for MoCA score and CDIS for AD conversion prediction are illustrated in Figure S1.

Recommended Algorithm in Prediction of AD Conversion

An algorithm using the education-adjusted MoCA-TS and the MoCA-MIS is proposed to improve prediction of conversion from MCI to AD (Figure 1). Using a cutoff of 20 out of 30 for MoCA-TS and seven out of 15 for MoCA-MIS, the AD conversion rate was 90.5% for participants with MCI who were below the cutoff on both measures and was 52.8% for those who were above the cutoff on both measures (mean follow-up duration 18.2 months [SE 1.0]). This yields an annualized conversion rate of 60.3% for the high-risk group and 35.2% for the low-risk group. Mean time for AD conversion in the MCI-AD group ($n = 114$) was 17.5 months (95% CI = 15.15–19.87).

Imaging

Mild white matter hypodensities were reported in 38.3% and mild to moderate cerebral atrophy in 68.0% of all subjects who underwent a brain CT scan. The presence of white matter changes (odds ratio [OR] = 1.60, 95% CI = 0.70–3.64) or brain atrophy (OR = 1.29, 95% CI = 0.57–2.91) on CT scan was not predictive of risk of conversion to AD.

DISCUSSION

This study found that individuals with MCI with a low MoCA-TS and a low MoCA-MIS at the time of diagnosis were at risk of conversion to AD in a short follow-up period (mean 18 months), with a conversion rate of 90% and an annualized (12 month) conversion rate of 60%. Individuals with MCI and higher MoCA-MIS and MoCA-TS had a 35% annualized conversion rate. No effects of education and age were found on the conversion rate from MCI to AD. Using the MoCA CDIS to classify MCI subtypes, it was found that the multi-aMCI group had the highest AD conversion rates, followed by single-aMCI, multi-naMCI, and single-naMCI. This finding confirmed previous studies that have shown that delayed verbal recall is highly predictive of AD progression in individuals with MCI.^{23–26} Memory has been consistently reported to be the first domain to be impaired in individuals with MCI at risk of conversion to AD and in subjects with early AD.^{16–18} The MoCA-TS represents global cognitive function and provided the highest discriminative ability in predicting conversion from MCI to AD. This has already been shown with other measures of global cognitive dysfunction such as the Mini-Mental State Examination and Alzheimer's Disease Assessment Scale—Cognitive Subscale.^{3,24,25,27,28}

The AD annualized conversion rate for all participants with MCI in this study (46.1%) is higher than in previous reports (1-year follow-up rate 23.8%,³ 18.2%²⁵). The differences in the conversion rate in the current study sample may be because subjects were selected from a memory clinic population and were thus already more likely to have memory impairment. The MoCA was also used for cognitive screening, thus further selecting subjects with objective cognitive impairment and increasing the likelihood of further cognitive decline. (Individuals with MCI had an average MoCA score of 20.1 ± 0.3 .) In addition, conversion rates in memory clinics are higher than in community-based studies.²⁹ The majority of participants with MCI in the current study also had impairment in other cognitive domains, which also increases the likelihood of faster conversion, as has been shown.^{25,26} This could imply more-widespread brain pathology in individuals with MCI and greater risk of conversion to dementia. In the current study sample, executive and memory function were the most significantly affected domains that best predicted conversion to AD. Executive function has frequently been reported to be impaired in MCI.³⁰ Executive function may help compensate for memory impairment and thus preserve autonomy, and executive dysfunction would more likely lead to loss of autonomy and to meeting AD criteria.

Fluctuations back to normal in this memory clinic-based MCI population were not observed, maybe because of small sample size or because subjects were more cognitively impaired than in population-based studies or other memory clinic studies and were thus less likely to be confused with subjects with benign forgetfulness. The current study may also have had higher proportion of APOE4-positive individuals with MCI. (Ninety percent of a sample of 20 consecutive individuals with meeting MCI meeting criteria in the memory clinic were carriers of at least one allele (Z. S. Nasreddine, unpublished data), which would increase the risk of progression rather than regression back

to normal.) The predictive power of the MoCA-MIS, which assesses delayed verbal recall, may be related to pathological involvement of the hippocampal and entorhinal cortex, which occurs first in the AD pathophysiological cascade and is followed by the frontal- and parietal-mediated cognitive function impairment,^{28,31–33} which the other MoCA CDISs (EIS, VIS, LIS, AIS) assess, and probably reflect more widespread disease.

Identifying individuals with MCI at high risk of conversion to AD is important to provide appropriate interventions and monitoring.^{34–36} Individuals at high risk of dementia will be followed more closely to anticipate any functional dysfunction that could place them or others at risk, such as driving and capacity to manage their finances. Their legal documents could be put in order (e.g., mandate in case of incapacity, will). More-aggressive management of vascular risk factors could be encouraged because they may hasten cognitive decline. Participating in cognitively stimulating activities could be recommended. Early treatment with cholinesterase inhibitors could be instituted once they reach the dementia stage. Early treatment is also economically crucial because it may reduce the cost of care.³⁷

Mild cognitive impairment therapeutic trials would benefit from MoCA's predictive ability. Better selection criteria, by recruiting appropriate subjects at higher risk of conversion to AD, could help avoid false-negative results, particularly when placebo and actively treated groups remain stable over the study period. Using the MoCA could mean shorter trial duration and lower costs.

Study limitations include retrospective design with no preset follow-up period, which could bias time to conversion. Despite this limitation, time to conversion was not significantly different in converters from the average follow-up period for nonconverters. Most individuals with MCI underwent CT but not MRI. MRI might have better classified subjects and possibly excluded subjects with vascular cognitive impairment that might have been missed on CT. Nonetheless, imaging findings did not influence rate of conversion. The use of the MoCA as a screening cognitive tool in the memory clinic might have biased the selection toward more-impaired subjects who were classified as having MCI when their MoCA score was below the cutoff score of 26 out of 30. There was no normal control group. Participants with normal MoCA scores were not systematically followed up, and neuropsychological testing was not administered to subjects with normal MoCA scores except for highly educated subjects (>15 years of education). These findings cannot be generalized to individuals scoring in the normal range on the MoCA because they were not automatically included or followed up. Sensitivity and specificity for the MoCA-TS and MoCA-MIS for predicting conversion to AD can therefore not be provided. This is particularly true given that the duration of follow-up was short; nonconverters might still convert to dementia over longer follow-up. The assessment of functional decline was determined in a semistructured interview by a cognitive technician with the family and not using a specific functional scale. This could have caused variation in determination of functional impairment and dementia. Clinicians were not blinded to the original MoCA score or the follow-up score, which could have biased them toward detecting more functional impairment

in subjects with low MoCA baseline scores or in subjects with declining scores, thus exaggerating the conversion rates in subjects with low MoCA scores. This is less likely because the rate of cognitive decline on the MoCA was similar in converters and nonconverters. Clinicians most likely based the conversion to AD decision on functional status, which was assessed independently of cognition. These findings may not be applicable in unselected populations, and it may not be possible to predict the conversion rate in less-impaired subjects as well.

Despite the study's limitations, subjects presenting with cognitive complaints to a memory clinic, meeting criteria for MCI, and having low MoCA-TS and MoCA-MIS at baseline are most probably at high risk of short-term conversion to AD. Well-designed prospective studies that include a control group and independent functional raters would be useful to confirm these findings and the usefulness of the MoCA to predict conversion from MCI to AD in memory clinic and community settings.

In conclusion, identifying subjects with MCI at high risk of conversion to AD is important for clinicians, individuals, and their families and is crucial for selecting appropriate subjects for MCI therapeutic trials.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Receiver operating characteristic curves of the Memory Index Score and the education-corrected Montreal Cognitive Assessment (MoCA) total score in prediction of conversion to Alzheimer's disease in individuals with mild cognitive impairment.

Table S1. Age- and education-adjusted cutoff scores for each cognitive domain.

Table S2. Baseline and follow-up activity of daily living (ADL) scores according to mild cognitive impairment (MCI) Group.

Table S3. Demographic features and Montreal Cognitive Assessment (MoCA) items and cognitive domain index scores according to mild cognitive impairment (MCI) Group (N = 165).

Table S4. Mild cognitive impairment (MCI) subtypes and conversion rates.

Table S5. Area under the receiver operating characteristic curve (AUC) for the cognitive domain index scores to predict conversion from mild cognitive impairment to Alzheimer's disease (N = 165).

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