Predictors of Future Cognitive Decline in Persons with Mild Cognitive Impairment

Haiqun Xie^a Nancy Mayo^{a, b} Lisa Koski^{a, b}

^aDivision of Experimental Medicine, Department of Medicine, McGill University, and ^bDivisions of Geriatrics and Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, Que., Canada

Key Words

Group-based trajectory analysis • Dementia • Aging • Cognitive decline • Mini-Mental State Examination • Clinical prediction • Sensitivity • Mild cognitive impairment

Abstract

This study sought first to identify individual items of the Mini-Mental State Examination (MMSE) and demographic variables at baseline that predicted the trajectories of cognitive change among patients with mild cognitive impairment (MCI), and second to quantify the risk of cognitive decline in such patients based on their pattern of failure of MMSE items. 187 MCI patients were evaluated serially with the MMSE for up to 3.5 years. Patients who followed a declining cognitive trajectory differed from the stable reference group in their baseline profile of MMSE test performance. Patient age and performance on delayed recall, constructional praxis, attention, and orientation to time and floor predicted future cognitive decline with good accuracy (79.9%) and specificity (86.4%), and moderate sensitivity (67.2%). These results are presented in the form of a simple clinical tool for quantifying risk of future cognitive decline in MCI.

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Introduction

Mild cognitive impairment (MCI) has been defined as a transitional state between normal aging and dementia [1]. Given its high prevalence in the elderly and increased risk for the development of dementia [2–11], considerable attention has been given to investigating the possibility of predicting diagnostic outcome in individual patients with MCI. Combining information from neuropsychological assessment, neuroimaging, and genotyping with clinical and demographic variables yields high accuracy for predicting who will progress to dementia [12, 13]; however, these approaches are expensive, restricted in availability, and thus not recommended for routine use to predict cognitive decline [14]. More widespread utility could be obtained by developing approaches to the prediction of conversion to dementia that are based on available clinical data.

Several investigators have evaluated the predictive utility of individual questions or subtests from the Mini-Mental State Examination (MMSE), which is widely used and readily available in clinical and research settings [15, 16]. A study of 168 community-based elderly persons showed that the total MMSE score predicts the risk of conversion to dementia within 5 years among people with MCI, with a sensitivity of 82% but a specificity of only

62% [17]. In contrast, the MMSE suffers from low sensitivity to dementia conversion in studies conducted in clinical samples. Among 75 memory clinic patients with questionable dementia, the score on 3-word recall from the MMSE was the best predictor of conversion to dementia, with a sensitivity of 67% and a specificity of 71% [18]. In 165 nondemented patients referred for memory or other cognitive complaints, 3-word recall and orientation to time were specific (98%) but not sensitive (41%) predictors of conversion to dementia within 2 years [19]. Others demonstrated an association between performance on the attention item (serial 7s subtraction) of the MMSE and conversion from MCI to Alzheimer's disease (AD), although predictive accuracy was not reported in that study [20].

Interestingly, prediction based on the MMSE improves to a sensitivity of 90% and specificity of 94% when adding information from self-ratings and informant ratings [21]. Alternatively, combining clinician rating scales and patient-reported symptoms can predict conversion to dementia over 3 years with an accuracy of 89% in 123 community-dwelling elderly people who had questionable dementia at baseline [22]. Data from an informant questionnaire predicted conversion from MCI to dementia with 84% sensitivity and 75% specificity in a small group of 45 people from a neuropsychology outpatient clinic [23]. Unfortunately, 13% of volunteers for this study had to be excluded due to lack of an informant, suggesting that a more widely applicable approach might be to rely exclusively on patient-reported and/or performance-based predictors. One problem with this approach is that people with significant cognitive impairment may underreport cognitive symptoms [24]. The impact of discrepancies between patient and informant reports can be expected to weaken the utility of this index among patients with MCI whose cognitive profile is characterized by loss of insight, and who are the closest in time to reaching criteria for dementia. Indeed, a recent population-based study of the concept of MCI as a risk factor for progression to dementia found that the inclusion of subjective complaints actually *worsened* predictive accuracy [25].

A commonality shared by the studies summarized above was the use of conversion to dementia as the primary outcome of interest. A potentially useful alternative is to examine baseline predictors of future decline in cognitive functioning as indicated by performance on the MMSE. A decline in MMSE performance is linked to the development of dementia but has the advantage of being an objective, measurable outcome. The concept of conversion to dementia over a specific time period may have

heuristic value, but it implies a defined transitional cut-point that holds little validity in the context of a progressive neuropathological process. Moreover, a person may decline in cognitive performance over time but still not meet criteria for dementia. The identification of such persons is arguably as important as identifying those who will convert to dementia over a specified period of time, to the extent that continued decline may be expected beyond the follow-up period of a study. Demographic variables such as older age have been associated with a greater rate of decline in MMSE score among people with MCI [26]; however, little is known about clinical predictors of change in cognitive ability. In a study of 505 elderly nursing home residents, orientation to time was found to predict subsequent decline in the total MMSE score [27]. Lower rates of decline were observed in people who scored high on delayed recall plus one of either attention or orientation to place. Of note, the sample for that study was not stratified by cognitive ability at baseline and included people with MMSE scores ranging from 10–25 of 30 points. Furthermore, the accuracy of prediction for identifying individuals at risk of greater decline was not reported.

Considering the limited evidence for clinical predictors of cognitive decline in people with MCI, the current study aimed to identify MMSE items and demographic variables that, alone or in combination, predicted future trajectories of cognitive decline. It is well established that MCI is a heterogeneous condition that may result in outcomes ranging from 'conversion to normal' to dementia [9, 10]. Therefore, longitudinal models of cognitive decline that are based on the concept of 'average' change may be misguided. In our previous work using a group-based trajectory modeling approach [28, 29], we provided empirical evidence for the existence of five distinct trajectories of cognitive change as measured by the MMSE total score, among a clinic sample of people with MCI who were followed for up to 3.5 years (fig. 1) [26]. In this cohort, some patients remained stable or even reverted to normal, and others declined with different initial MMSE total scores and rates of cognitive change.

The first objective of the present study was to identify items of the MMSE for which failure at the first clinic visit was significantly predictive of the probability of membership in each of these trajectory groups. The second objective was to develop a model based on these identified baseline variables that would optimize accuracy for predicting which patients with MCI will progress to a declining trajectory versus those who remain cognitively stable.

Fig. 1. Trajectories of cognitive change on the MMSE score.

Methods

Setting and Sample

This is a longitudinal study based on historic data collected for clinical purposes, with repeated measurements of the MMSE over 3.5 years, to identify baseline individual items of the MMSE and demographic variables that predict the trajectories of cognitive change. Data were obtained from a clinical database at the Geriatric Cognitive Disorders Clinic of the McGill University Health Centre (MUHC). Clinic patients had been referred for evaluation cognitive impairment and the MMSE was administered at their initial visits by geriatric nurses or physicians, using the serial 7s subtraction variant for the attention item. A geriatrician diagnosed MCI according to Petersen's criteria [1, 30] based on a clinical evaluation that included a full chart review, history, physical exam, assessment of basic and instrumental activities of daily living, blood tests, brain CT, as well as the results of the cognitive screening tests. Follow-up visits were scheduled at 3- to 12-month intervals with re-evaluation using the MMSE as clinically indicated.

The sample for this study was identical to that examined in our previous study for which trajectories of cognitive change were identified [26]. Of 311 MCI patients, a total of 187 patients who had been administered the MMSE at their initial visit to the clinic and at least once more over a period of up to 3.5 years were included. This subgroup did not differ by age, sex, education, language, or baseline MMSE score from the 124 who were not administered the MMSE at their initial visit or who had the MMSE only once [26]. The average number of MMSE administrations for included patients was 4 (± 1.7 ; range 2–9). The time elapsed between consecutive assessments was 1.8–42.8 months (average 23.6 months). The MUHC Research Ethics Board approved this use of de-identified clinical data for research purposes (BMB-06-002).

Data Analysis

The proportion of people who failed items on the MMSE according to trajectory group was calculated. The 5 trajectory groups identified in our previous study are depicted in figure 1 and named with reference to the initial MMSE score and the shape of the trajectory of cognitive changes, as follows: 29/stable ($n = 12$), 27/stable ($n = 108$), 25/slow decline ($n = 41$), 24/slow decline ($n = 20$), and 25/rapid decline ($n = 6$).

A two-stage analysis was performed to identify baseline variables that related to different trajectories of cognitive decline, using the 27/stable group as a reference. In the first stage, the univariate effect of individual baseline predictors on the probability of membership in each trajectory group (relative to the 27/stable group) was examined via conditional group-based trajectory analysis. This extension of the basic group-based trajectory analysis allows for introducing time-independent covariates into the model and examining their association with the probability of group membership [28, 29].

Variables evaluated for their predictive utility were baseline MMSE items/subtests, age, sex, years of education (low <13 years vs. high 13+ years), first language, and test language. The total MMSE score could not be included in the analyses because it was not independent of the outcome variable. Correlations between individual items and the total MMSE score were examined and only 3 exceeded 0.4 with a single item reaching a correlation of 0.56 (3-word recall). The degree to which a variable altered the probability of group membership is expressed as an odds ratio with 95% confidence intervals.

Variables that were predictive of group membership from this first phase were then evaluated in a second stage of analysis to develop a multivariate model. It would have been ideal to contrast the stable group to the three different decline groups, but the two slow decline groups were very similar and the rapid decline group comprised only 6 subjects. For all further analyses all the decline

Table 1. Number (and percentage) of patients who failed individual items/subtests of the MMSE at baseline within each trajectory group

	Group, n (%)				
	29/stable (n = 12)	27/stable (n = 108)	25/slow decline (n = 41)	24/slow decline (n = 20)	25/rapid decline (n = 6)
Year	0	0	1 (3)	8 (40)	0
Season	0	5 (5)	2 (5)	3 (15)	0
Month	1 (8)	4 (4)	2 (5)	3 (15)	0
Date	2 (17)	18 (17)	14 (35)	8 (40)	4 (67)
Day of the week	1 (8)	10 (9)	6 (15)	7 (35)	2 (33)
Country	0	0	0	1 (5)	0
Province	0	0	1 (3)	0	0
City	0	0	1 (3)	0	0
Hospital	0	2 (2)	1 (3)	1 (5)	0
Floor	0	7 (7)	8 (20)	3 (15)	1 (17)
Watch	0	0	0	0	0
Pencil	0	0	0	0	0
Repeating sentence	0	11 (10)	6 (15)	5 (26)	2 (33)
Eyes	0	0	0	0	0
Constructional praxis	2 (17)	34 (31)	19 (48)	10 (50)	3 (50)
Writing	1 (8)	4 (4)	5 (13)	0	0
Delayed recall = 0	0	16 (15)	13 (33)	9 (45)	1 (17)
Delayed recall ≤1	1 (8)	43 (40)	22 (53)	13 (65)	2 (33)
Delayed recall ≤2	7 (58)	84 (77)	35 (85)	18 (90)	4 (67)
Attention ≤3	0	9 (9)	10 (26)	5 (25)	0
Attention ≤4	0	18 (17)	21 (51)	8 (40)	1 (20)
Commands ≤ 2	0	22 (20)	7 (18)	2 (10)	3 (50)
Orientation to time ≤2	0	2 (12)	2 (5)	3 (15)	0
Orientation to time ≤3	1 (8)	5 (5)	6 (15)	11 (55)	2 (33)
Orientation to time ≤4	3 (25)	31 (28)	17 (43)	14 (70)	4 (67)

trajectories were combined into one decline group for contrast with the stable group using multivariate logistic regression. For this analysis individuals were assigned to trajectory groups deterministically based on highest posterior probability. The characteristics of these two groups were contrasted using χ^2 tests. Given 27% cases with missing value on the education level, multiple imputation was performed on the data to minimize the potential bias arising from missing data. Imputation was based on the baseline MMSE items/subtests, age, sex, first language, and test language. 10 imputed data sets were created. The pooled completed data set with imputed values for education level was then used for the multivariate model.

To identify the best predictive model for cognitive decline, forward stepwise logistic regression was used including the predictors identified in stage 1. Sensitivity, specificity, and positive and negative predictive (PPV, NPV) of competing models were estimated as well as C-statistics representing the area-under-the-receiver operating characteristic curve (AUC) as a measure of predictive accuracy.

To illustrate a clinical application of the predictive model, an index was created based on the strength of the prediction of each item. For this, the beta coefficients for the MMSE items from the logistic model were used as weights with β 0.5–0.9 set to 1; 1.0–1.5

set at 2; 1.5–1.9 set at 3; 2.0–2.4 set at 4. A weight was derived for whether the person recalled none, 1, 2 or all of the words in word recall item. The maximum value of the index is 15. The predicted probability of belonging to a declining trajectory over the subsequent 3.5 years was calculated based on the index and age.

Results

Table 1 presents the proportion of failure in items/subtests of the MMSE at baseline according to the trajectory group membership. Delayed recall, constructional praxis and orientation to time were the most commonly failed items among all groups. The 25/slow decline group appears to show a slightly disproportionate tendency to make more errors in attention and writing a sentence when compared with the 24/slow decline group: 51% made one or more errors on the attention item versus 40% in the 24/slow decline group, and 13% failed writing a sentence versus none in the 24/slow decline group. The

Table 2. Univariate effect of MMSE items for which failure significantly predicted probability of trajectory group membership relative to the 27/stable reference group

MMSE item(s)	25/slow decline			24/slow decline			25/rapid decline		
	OR	β	SE	OR	β	SE	OR	β	SE
Date	4.57	1.52	0.63*	4.10	1.41	0.67*	11.1	2.41	0.94*
Day of the week	–	–	–	5.26	1.66	0.66*	–	–	–
Floor	10.5	2.35	1.10*	–	–	–	–	–	–
Repeating sentence	–	–	–	–	–	–	6.05	1.80	0.9*
Constructional praxis	2.94	1.08	0.54*	–	–	–	–	–	–
Delayed recall = 0	–	–	–	4.48	1.5	0.64*	–	–	–
Attention ≤ 3	7.17	1.97	0.75**	5.21	1.65	0.75*	–	–	–
Attention ≤ 4	8.94	2.19	0.64***	–	–	–	–	–	–
Orientation to time ≤ 2	–	–	–	11.9	2.48	1.13*	–	–	–
Orientation to time ≤ 3	–	–	–	25.3	3.23	0.76***	10.7	2.37	1.06*
Orientation to time ≤ 4	–	–	–	6.69	1.9	0.68**	–	–	–

OR = Odds ratio. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

None of the MMSE items significantly discriminated the 29/stable group from the 27/stable group.

proportion of patients in the 25/rapid decline group who failed at carrying out a complex command was higher than for the other groups.

The univariate effects of single MMSE items/subtests were examined with conditional group-based trajectory analysis and are shown in table 2. The 29/stable group could not be discriminated from the 27/stable reference group. Patients who failed orientation to date were 4 times more likely to be in a slowly declining group, and 11 times more likely to be in the 25/rapid decline group, than in the 27/stable reference group. Failing constructional praxis, attention, and orientation to floor was associated with higher risk of being in the 25/slow decline group than in the 27/stable reference group. Failing attention, delayed recall, and orientation to time, especially day of the week, was associated with higher risk of being in the 24-slow-decline group than in the 27/stable reference group. Failing to repeat a sentence and obtaining ≤ 3 points on the orientation to time subtest was associated with increased risk of being in the 25/rapid decline group rather than the 27/stable reference group. Age, educational level, test language and first language were not significantly associated with the probability of group assignment.

Group differences in demographic and clinical variables were examined after assigning patients to groups based on posterior probabilities and then combining the two stable groups (29/stable, 27/stable) and the three declining groups (25/slow decline, 24/slow decline, 25/rapid decline). We contrasted age, educational level, sex, test

Table 3. Best-fitting model for predicting increased risk for membership in a declining cognitive trajectory as identified with multivariate logistic regression

Variables	Estimated β	Odds ratio	95% Wald confidence limits		$\Pr > \chi^2$
Attention ≤ 4	2.0	7.7	3.2	18.3	<0.0001
Orientation to time ≤ 3	2.1	8.3	2.6	27.1	0.0004
Delayed recall = 0	1.6	5.0	1.5	16.7	0.0089
Orientation to floor = 0	1.3	3.6	1.1	11.3	0.0304
Constructional praxis	1.0	2.7	1.2	5.9	0.0128
Age	0.1	1.1	1.0	1.2	0.0025

Probability modeled is membership in any declining group ($c = 0.830$; $R^2 0.3102$; max-rescaled $R^2 0.4269$).

language, and first language for the groups characterized as stable and declining. Patients in a declining trajectory were older (81.3 years, SD 5.4 vs. 78.8 years, SD 6.1; $p < 0.05$ by t test) and less educated (70.4 vs. 48.2% for patients with education level ≤ 12 years; $p < 0.05$, χ^2 test), but did not differ by sex, test language or first language.

In the next step, combinations of different baseline characteristics and MMSE items were used to build a model with the best accuracy for predicting cognitive decline. Table 3 shows the best fitting model for predicting cognitive decline versus stable cognition identified with stepwise regression. Each additional year of age increased by

Table 4. Comparison of the accuracy (AUC values) of different models for predicting cognitive decline

Variables in the base model	Base model	Variables added to the base model				
		+ attention	+ orientation to time	+ delayed recall	+ attention + orientation to time	+ attention + orientation to time + delayed recall
Age	0.605	0.710	0.691	0.668	0.782	0.807
Age + orientation to floor	0.647	0.741	0.710	0.701	0.792	0.815
Age + constructional praxis	0.653	0.736	0.730	0.710	0.799	0.823

Columns 1 and 2 refer to the variables included in the base model, and their AUC values, respectively. Columns 3–7 present the AUC values obtained when adding different predictor variables to the base model.

Table 5. Individual risk of cognitive decline over 3.5 years as predicted by baseline characteristics and MMSE item failure

MMSE items	Yes No		Total score	Age ranges, years							
				60–63	64–67	68–71	72–75	76–79	80–83	84–87	88+
Orientation to time ≤3	4	0	4	<50	<50	<50	<50	<50	<50	30–57	40–65
Orientation to floor = 0	2	0	5	<50	<50	<50	<50	<50	<50	55–71	66–78
Attention ≤4	4	0	6	<50	<50	<50	<50	34–61	45–72	56–78	71–85
Delayed recall = 0	3	0	7	<50	<50	<50	47–62	56–72	67–81	76–87	84–90
Delayed recall = 1	2	0	8	<50	<50	41–63	46–73	58–81	69–87	82–92	88–94
Delayed recall = 2	1	0	9	37–55	49–66	60–76	71–83	80–89	86–93	90+	90+
Delayed recall = 3	0	0	10	46–65	55–75	69–83	75–88	83–92	90+	90+	90+
Constructional praxis = 0	2	0	11	65–77	72–84	82–89	87–93	90+	90+	90+	90+
TOTAL SCORE (sum)			12	70–83	79–89	86–93	90+	90+	90+	90+	90+
			13	83–90	90+	90+	90+	90+	90+	90+	90+
			14	90+	90+	90+	90+	90+	90+	90+	90+
			14+	90+	90+	90+	90+	90+	90+	90+	90+

The risk score (total score) is calculated based on performance on specific MMSE items using the legend on the left. The % risk of cognitive decline is determined by the cell corresponding to the patient's age range and risk score: first, look in the column total score to find the row containing the number corresponding to the patient's total score as calculated in the legend on the left. Next, move across that row to find the cell underlying the patient's age range as indicated in the first row. The range of values in that cell corresponds to the probability of cognitive decline. The total score is a numeric simplification of risk based on rounding of β -coefficients. Thus, the probability reported for each cell is presented as a range to reflect variation in the sum of β -coefficients derived from different combinations of items failed.

10% the odds of cognitive decline within the next 3.5 years. Increased risk of cognitive decline was also predicted among those who failed constructional praxis or orientation to floor, and among those who lost at least 2 points on orientation to time, 1 point on attention, or 3 points on delayed recall. For example, in an MCI patient who obtains ≤3 points on the attention item, the odds of cognitive decline within the next 3.5 years are 8.3 times greater than that of a patient who obtains >3 points on attention.

Sex and education level were not significantly associated with cognitive decline. When they were forced in the model, they did not improve model fitting and resulted

in reduced predictive ability of the model, so that sex and education level were not included in the final model.

Table 4 compares the AUC values for predicting cognitive decline based on the different models tested. The best-fitting model had an AUC value of 0.83. The model showed 67.2% sensitivity and 86.4% specificity for cognitive decline. The accuracy of classification into declining versus stable groups was 79.7%. The positive and negative predictive values of the model were 72.9 and 82.9%, respectively.

To facilitate the use of these findings in clinical practice, table 5 shows the age-specific probability of cognitive decline over 3.5 years as a function of failing particu-

lar MMSE items at first interview. The weights for each item are shown on the left side of the table. The total score derived from summing these weights is represented by the rows with the columns indicating the age group of the patient.

Discussion

The first objective of this study was to identify individual items/subtests of the MMSE that were significantly predictive of future cognitive trajectories amongst people with mild cognitive impairment. In our previous work, we identified 5 cognitive trajectories that could be characterized by different starting points in terms of their baseline MMSE score and by different patterns of longitudinal cognitive change [26]. Here, we demonstrate that each group that followed a declining cognitive trajectory could be distinguished from the 27/stable reference group by a slightly different baseline profile of MMSE test performance. The 24/slow decline group failed orientation to time, delayed recall, and attention subtests; the 25/slow decline group failed orientation to date and floor, constructional praxis, and attention subtests, and the 25/rapid decline group failed orientation to time and repeating a sentence.

MMSE items that emerged as significant predictors of membership in a declining trajectory were similar to those identified in previous studies on predictors of risk for cognitive decline [20, 27, 31]. However, previous studies analyzed all participants with MCI as if they constituted a homogeneous group, despite ample evidence that they are not [9, 10]. Potentially informative predictors of future cognitive status may fail to be identified by analysis of the correlation with 'average' cognitive decline. The present study is unique in that it sought to identify predictors of membership in specific cognitive trajectory groups, identified through group-based trajectory modeling as being comprised of patients who follow a similar cognitive course.

In the current approach, we conducted separate analyses of the distinct longitudinal relationship between baseline predictors and each cognitive trajectory group. A consequence is that we were able to discover differences in baseline cognitive profiles, as determined by failure of specific MMSE items, amongst people with a similar MMSE total score, and to associate these failure profiles with a particular cognitive outcome. Items predictive of membership in the 24/slow decline group, orientation to time and delayed recall, have been associated with epi-

sodic memory ability [32], hippocampal dysfunction caused by beta-amyloid deposition [33], and possession of the APOE-4 genetic variant [34, 35]. In contrast, items failed by the 25/slow decline group, namely attention and constructional praxis, are known to correlate with performance on neuropsychological tests of working memory [16, 36]. Deficits in working memory have been associated with small vessel cerebrovascular disease, visualized as white matter hyperintensities on neuroimaging [37], and commonly seen in the frontal lobe [38]. Thus, heterogeneous pathological processes may exist in MCI patients, who then experience different cognitive dysfunction patterns. Different cognitive profiles are also associated with different prognoses, with episodic memory impairment regarded as a predictor of development of AD [35, 39, 40], whilst working memory impairment is more strongly associated with the onset of other types of dementia, such as vascular dementia and Lewy body dementia [41–45].

The small size of the 25/rapid decline group limited the statistical power to detect baseline variables that distinguished patients in this group from those in other trajectory groups. Regardless of this limitation, orientation to time and repeating a sentence were found to have predictive value in this group when compared with the 27/stable group. Although orientation to time was failed by a majority of MCI patients who followed a declining trajectory, language impairment appeared to be of greater importance in patients in the 25/rapid decline group. This suggests that language impairment, which is usually a late symptom in patients with dementia, occurred relatively early in the course of disease for patients in this group.

The second objective of this study was to develop a model for specifying the risk of following a declining trajectory over the next 3.5 years in a person with a new diagnosis of MCI. The final model was selected to maximize accuracy of prediction in the clinic (80%). The best-fitting prediction model included the variables age, failure of constructional praxis, failure of orientation to floor, losing 2 or more points on orientation to time, losing 1 or more points on the attention item, and losing all 3 points for delayed recall. The specificity of the model was 86%, which is slightly lower than the value obtained when using delayed recall and orientation to time to predict conversion to dementia (98%) [19], but the sensitivity is better (67 vs. 41%).

We note that the best-fitting model for predicting cognitive decline among people with MCI included items assessing a range of domains of cognitive performance.

Previous work in which patients with amnesic MCI revealed that those whose neuropsychological test results indicated impairment in multiple domains progressed more rapidly toward dementia than those with single-domain amnesic MCI [46]. A prediction method based on a risk score that is derived from performance on individual MMSE items may be an attractive alternative when detailed neuropsychological testing is not available.

Age has been identified previously as a significant predictor of cognitive decline or of conversion to dementia [25, 47–50]. In the present study, the odds ratio was 1.1 per year of age and the predictive accuracy of age alone was 0.61. In our study, education was not associated with cognitive decline in the subsample of 136 patients with complete data after controlling covariates. The same result obtained when analyzing the complete set of data from 187 patients with multiple imputation for education. Others have also reported that level of educational achievement, although associated with cognitive performance [51, 52], was not associated with cognitive change over time in people with MCI [21, 23, 53–56].

A limitation of this study is the small sample size in some of the cognitive trajectory groups. This had an impact on the choice of statistics used to analyze multiple covariates simultaneously. The conditional group-based trajectory approach allows for introducing multiple covariates into the model, a process through which the joint effect of multiple variables is linked to the probability of trajectory of group membership. Due to limited sample size in some trajectory groups, a convergence problem occurred when we attempted to fit the model with more than three covariates. Thus, although group membership is not definitely determined for individuals, we chose to classify patients into trajectory groups based on the maximum posterior probability and then to collapse some of the groups before modeling multiple predictors using conventional multiple logistic regression techniques. As Roeder and Nagin [57] indicated, this approach may overestimate the effect of covariates.

In conclusion, our results suggest that a simple screening test can provide indications of domain-specific cognitive impairment that are early clues as to the risk and etiology of later cognitive decline. Furthermore, performance on specific items of the MMSE provided showed good accuracy in predicting those patients with MCI who went on to show cognitive decline. Our results were obtained in a clinic setting, so the results may not generalize to community-based populations. Recent work by others has sought to use information obtained from the MMSE or from the Clock Drawing Test to predict conversion to

dementia in population-based samples, with modest success to date in terms of diagnostic accuracy (~70%) [58, 59]. In a community-based study of incident dementia cases, predictors of cognitive decline were found to differ from those identified in similarly-aged control cases [60]. This suggests that results of the present study may only be valid for those persons already identified as having mild cognitive impairment that does not reach criteria for dementia. However, the model derived in the present study can be applied easily for prognostic purposes in MCI patients in a geriatric clinic setting. For example, the baseline risk of belonging to a declining cognitive trajectory is 40% in our sample [26]. Table 5 shows how this estimate must be revised upward or downward depending on failure of specific MMSE items and on a patient's age. The risk index presented here was developed using the same methods as the widely used Charlson Index of prognostic comorbidity [61]. In clinical settings without access to sophisticated neuroimaging, neuropsychological, or biochemical techniques, a simple screening test may serve as a useful tool for identifying MCI patients at higher risk of cognitive decline, and may help target at-risk groups for early interventions aimed at delaying the onset of dementia.

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Disclosure Statement

None.

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