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ORIGINAL PAPER

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Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status

Results from the Sao Paulo Ageing & Health Study

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Abstract *Background* The Mini-Mental State Examination (MMSE) is the most widely used instrument for the screening of cognitive impairment worldwide, but its ability to produce valid estimates of dementia in populations of low socioeconomic status and minimal literacy skills has not been adequately established. The authors investigated the psychometric properties of the MMSE in a community-based sample of older Brazilians. *Method* Cross-sectional one-phase population-based study of all residents of pre-defined areas of the city of Sao Paulo, aged 65 years or over. The Brazilian version of the MMSE was compared with DSM-IV diagnosis of dementia assessed with a harmonized one-phase procedure developed by the 10/66 Dementia Research Group. *Results* Analyses were performed with 1,933 participants of the SPAH study. Receiver operating characteristic analysis showed that the MMSE cut-point of 14/15 was associated with 78.7% sensitivity and 77.8% specificity for the diagnosis of dementia amongst participants with no formal education, and the cut-point 17/18 with 91.9% sensitivity and 89.5% specificity for those with at least 1 year of formal education (areas under the curves 0.87 and 0.94, respectively; *P* = 0.03). Even with these best fitting cut-points, the MMSE estimate of the prevalence of dementia was four times higher than determined by the DSM-IV criteria. Education, age, sex and income influenced MMSE scores, independently of dementia caseness. *Conclusion* The MMSE is an adequate tool for screening dementia in older adults with minimum literacy skills, but misclassification is unacceptably high for older adults who are illiterate, which has serious consequences for research and clinical practice in low and middle income countries, where the proportion of illiteracy among older adults is high.

Key words dementia · Alzheimer's disease · screening test · Mini-Mental State Examination · measurement · community studies · cognitive assessment

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Introduction

The World's population is ageing rapidly, and this demographic revolution has been particularly pronounced in low- and middle-income countries (LAMIC) [38]. Dementia, which is a mental health disorder characteristic of older age, is now a leading cause of disability worldwide, but reliable empirical data about its prevalence and consequences in LAMIC remains sparse [14]. Determining the prevalence of dementia in LAMIC is challenging because large epidemiological surveys require substantial financial and technical resources, and validity of the cognitive assessment of participants is often limited by poor literacy [16, 29].

The Mini Mental State Examination (MMSE) is one of the most commonly used instruments to assess cognitive impairment in clinical and epidemiological research [15, 28, 32]. It is brief, simple, is available in several languages, and has been adapted to suit populations from different cultural backgrounds [4, 17, 24, 27, 40]. However, MMSE scores are typically influenced by non-cognitive variables, such as age and poor literacy [6, 7, 11, 18, 36, 37]. Different cut-points that take into account the education of participants have been recommended to establish the likelihood of dementia caseness [1, 3, 24, 26, 38], but the validity of this approach remains uncertain. Results of a recent multicentre study in Latin America illustrate this point [8]. In Santiago (Chile), the participating center where the version of the MMSE used in all centers was validated, 35% of participants with no literacy scored below the threshold for probable dementia compared with only 5% of those with seven or more years of education. Results from the Framingham Study [3] and from a Brazilian survey [21] showed a similar pattern. Such ascertainment bias has substantial implications for health policy, planning and delivery of care for older adults in LAMIC. In Brazil, the largest country of South America, 63% of the heads of households aged 65 years or over have less than 4 years of formal education, and 38% are illiterate [22, 23]. To date, the psychometric properties of the MMSE have only been examined in clinical settings in Brazil [1, 4, 26], but the instrument may behave differently in community samples of older adults.

We designed the present study to determine the performance of the MMSE in a community representative sample of older Brazilians. We also aimed to clarify the role of socio-demographic and socioeconomic characteristics on misclassification of cognitive impairment associated with dementia according to the MMSE.

Methods

Study design and sample

Participants were those enrolled in the baseline assessment of the Sao Paulo Ageing and Health Study (SPAH) [34]. The investigation was carried out in the borough of Butantã, located on the west side of the city. In 2000, 6.5% of the population of the Butanta borough were aged 65 years or over and 13% lived in shanty towns. Between May 2003 and April 2005 all residents aged 65 years or older living in 66 census sectors of the Butanta borough, covering a population of approximately 63,000 residents, were invited to participate in the SPAH. A total of 2,072 persons (91.4% of those invited) were recruited through systematic door knocking. Interviews for the assessment of dementia took place at participants' residences approximately 1 week after recruitment. An independent research nurse completed the MMSE rating 2–15 days after the assessment interview. SPAH methods have been published previously in details [34, 35].

Measurements

Gold standard

The diagnosis of dementia followed DSM-IV criteria [2], and was assessed with the harmonized one-phase dementia diagnostic procedure developed by the 10/66 Dementia Research Group and validated for use in population-based studies of developing countries [31]. The procedure includes assessment with the Community Screening Instrument for Dementia (CSI-D) [19, 20], an adapted version of the CERAD ten word list learning task with delayed recall and animal verbal fluency [39], the geriatric mental state (GMS; a clinical mental status assessment) [10, 30], and a structured neurological assessment of localizing signs, parkinsonism, ataxia, apraxia and primitive 'release' reflexes. We used the informant CSI-D to determine participants' daily functioning and general health and the History and Aetiology Schedule Dementia Diagnosis and Subtype (HAS-DDS) [13] to assess functional and cognitive decline. The protocol was applied by trained research assistants, who were all mental health professionals, and the final diagnosis of dementia was produced by the 10/66 algorithm that combines data from all assessments and classifies participants as cases of dementia according to DSM-IV criteria [31, 34].

MMSE

We used the Brazilian version of the MMSE [4, 15]. It includes items assessing orientation for time (five points) and place (five points), registration of information (three points), attention/calculation (five points), free recall (three points), naming of objects (two points), repetition of a sentence (one point), three-stage command (three points), following a written command (one point), writing a sentence (one point) and copying two intersecting pentagons (one point). The total MMSE score can range from 0 to 30; higher scores indicate better cognitive performance. For the present analysis, subjects' answers 'do not know' or 'no answer' were coded as an incorrect answer (score zero).

We included in our analysis 1,933 participants (93.3% of those assessed for the prevalence study). Among the 139 participants excluded, 48 were unable to answer 5 or more items of the questionnaire due to severe physical or mental impairment (18 cases of dementia, 20 subjects with sensory impairments—eye or hearing problems, 10 with other physical incapacities), 10 were approached but refused to answer the MMSE questions, and 81 were not approached by the research team for the battery of assessments that included the MMSE.

Ethical considerations

Participants provided written informed consent. Participants who lacked capacity for consent because of mental or physical incapacities were recruited on the basis of informants' signed agreement. When participants were illiterate the information sheet and consent form were read aloud, and verbal witnessed consent was obtained. The study received ethics approval from the Brazilian National Committee for Ethics and Research.

Statistical analysis

Participants were grouped into 4-year bands from 65 to 79 years, and one group aged 80 years or older. The number of years of formal school education was recorded for each subject. The sample

Table 1 Demographic and socio-economic characteristics of participants and mean MMSE scores, according to such characteristics and dementia status (n = 1,933)

Characteristics	All participants (n = 1,933)	MMSE score			
		Dementia (n = 84)		Non-dementia (n = 1849)	
	n (%)	Mean (SD)[a]	P value	Mean (SD)[a]	P value
Sex					
Female	1,172 (60.6)	11.1 (4.7)	0.96+	19.7 (4.5)	<0.001+
Male	761 (39.3)	11.2 (5.7)		21.5 (4.5)	
Age group (years)					
65–69	883 (43.1)	13.6 (6.0)	0.06 ≠	21.7 (4.1)	<0.001 ≠
70–74	528 (27.3)	12.5 (5.8)		20.5 (4.3)	
75–79	319 (16.5)	9.3 (5.0)		19.1 (4.8)	
80 or more	253 (13.1)	10.9 (4.1)		17.2 (4.6)	
Education					
None	744 (38.5)	10.8 (4.8)	0.50+	17.4 (4.0)	<0.001+
One or more years	1,189 (61.5)	11.6 (5.4)		22.2 (3.9)	
Personal income (American Dollars)					
None to US$127	970 (50.2)	10.7 (4.8)	0.19+	18.9 (4.5)	<0.001+
$128 or more	963 (49.8)	12.7 (5.8)		21.9 (4.2)	

MMSE Mini Mental State Examination

[a]SD standard deviation

+ $P_{\text{two-sided}}$ value for Student's t test

≠ P value for linear trend

was classified into two educational groups: (a) those who did not have any formal education or did not complete the first year or primary school; (b) those who completed one or more years of school education. Personal income was measured as the total monthly income subjects received from all sources (salary, government benefit or other sources, such as family donations), and was categorized into two categories according to the median of the population.

We calculated the mean MMSE score according to dementia status and demographic and socioeconomic categories. Statistical associations with MMSE scores were examined with Student's t tests or tests for trend in the case of ordered groups. We also determined the overall mean MMSE score, and the overall MMSE score according to dementia status. The influence of sex, age, education, and personal income on MMSE scores was examined with multiple regression. The association between these variables and MMSE mean scores was estimated by calculating the regression coefficient for each variable of interest, and its 95% confidence intervals (CI), adjusted by dementia caseness. If there were no systematic misclassification according to each characteristic of participants, a regression coefficient of zero would be expected for such variables, after controlling for dementia caseness. A regression model was then constructed, with dementia caseness and all variables that showed statistically significant association with MMSE misclassification in the previous models, to examine which associations were independent or if some of these associations were confounded by any another of the variables considered. Diagnostic plots were used to check if there was any pattern in the data that indicated non-linearity, whether there were outliers and influence points, and how much influence any particular observation had on the model.

Analyses on the diagnostic accuracy of the MMSE were then performed separately for the group of participants without any formal education and for those with one or more years of formal education. The diagnostic accuracy of the MMSE was assessed by estimating the sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), the positive predictive value (PPV), and the overall misclassification rate (OMR) for various cut-off points of the MMSE. Receiver operating characteristic (ROC) curve analysis was used to estimate the optimal threshold score and to compare the ability of the MMSE to discriminate between 'cases' and 'non-cases' for various cut-points using the DSM-IV diagnosis of dementia as the reference criterion. A ROC curve was obtained by plotting the sensitivity against the false-positive rate (one-specificity) for several cut-points of the MMSE. The area under the ROC curve and its 95% CI were used as the index of the discriminating ability of the MMSE [5]. The ROC curve was also used to determine the ideal cut-point, that we considered the one that gave the best trade-off between sensitivity and specificity.

The influence of education on misclassification of cognitive impairment associated with dementia was examined with logistic regression. The outcome MMSE dementia caseness was constructed using the best cut-off points we found for each educational group. The association between educational attainment and a false positive MMSE result was estimated via odds ratio adjusted for a DSM-IV diagnosis of dementia, sex and age group. If there was no systematic misclassification according to educational level, an odds ratio of one would be expected for education. We used STATA (version 9) software for all analyses.

Results

A total of 1,933 subjects provided valid MMSE ratings and were included in the present study (Table 1). Ages ranged from 65 to 102 years (mean = 72.2, SD = 6.2) and approximately 2/3 were women. Only 182 participants (9%) had received four or more years of formal education. Eight four (4.4%) participants received a diagnosis of dementia.

Considering all MMSE items, the frequency of MMSE incorrect answers (score zero) was higher for participants with dementia, followed by those without dementia but with no formal education (Table 2). Among participants without dementia, those with one or more years of formal education had consistently higher frequency of correct answers (higher scores) than those with no formal education across all MMSE items.

Most participants answered correctly the registration, naming objects and the three-stage command items, independent of their dementia or educational

Table 2 Frequency (%) of answers for each MMSE item, according to dementia status and educational level (n = 1,933)

MMSE items	Frequency (%) of positive answers		
	Non-dementia		Dementia (n = 84), %
	Level of education		
	None (n = 744), %	One or more years (n = 1,189), %	
Orientation—time			
0	4.3	1.1	51.2
1	8.5	1.6	23.8
2	15.2	3.0	9.5
3	29.1	10.5	8.3
4	29.3	30.8	2.4
5	13.6	53.0	4.8
Orientation—place			
0	1.2	0.4	20.2
1	1.9	0.2	9.5
2	7.3	1.1	23.8
3	14.5	3.1	8.3
4	30.9	16.3	23.8
5	44.3	78.9	14.8
Regsitration—three objects			
0	0.7	0.3	1.2
1	0.4	–	6.0
2	1.2	0.3	8.3
3	97.7	99.5	84.5
Attention and calculation—serial 7's or spelling			
0	64.7	21.6	85.7
1	24.7	41.4	9.5
2	3.4	8.2	–
3	1.9	4.2	3.6
4	0.7	4.2	–
5	4.6	20.5	1.2
Recall—three objects			
0	28.4	15.6	66.7
1	20.7	21.1	14.3
2	31.9	32.8	13.1
3	19.1	30.5	6.0
Language—name objects			
0	1.9	0.9	15.5
1	6.9	3.7	16.7
2	91.3	95.5	67.9
Language—repeat sentence			
0	13.9	5.7	31.0
1	86.1	94.3	69.0
Language—three stage command			
0	2.4	1.1	17.9
1	12.3	5.3	17.9
2	40.3	24.8	46.4
3	44.9	68.7	17.9
Language—read and follow command			
0	88.9	36.9	89.3
1	11.1	66.1	10.7
Language—write sentence			
0	91.7	42.3	92.9
1	8.3	57.7	7.1
Visual construction—copying a drawing			
0	89.4	57.6	94.0
1	10.6	42.4	6.0

level status. Items on attention and calculation, copying a drawing, and those that required reading skills (read/follow command and write sentence) were scored very poorly by those with dementia and those without dementia and no formal education, with approximately 90% of incorrect answers on items that required reading and/or writing skills.

Association of MMSE scores with demographic and socioeconomic characteristics

The overall mean MMSE score was 10.0 (SD = 5.0). Participants without dementia had a MMSE mean score of 20.4 (SD = 4.6), whereas those with dementia had a mean score of 11.1 (SD = 4.6), statistically significant difference ($P < 0.001$). The associations of mean MMSE scores with gender, education and personal income were evident only in the group of participants without dementia, with better performance among women, younger participants and participants with higher levels of education and income (Table 1). The associations between these variables and MMSE scores remained statistically significant after the regression models were adjusted for DSM-IV dementia diagnosis, and for all variables (Table 3). Men, younger participants, and those with higher education or personal income had higher MMSE scores (better performance), regardless of whether dementia was present or not. The adjusted β coefficients of sex and income showed greater relative reductions than the adjusted β coefficients of education and age. Participants with one or more years of formal education had MMSE scores 3.7 points higher than those with no formal education, whereas men and participants with higher income had mean MMSE scores approximately one point higher than women and participants with lower incomes, respectively. MMSE scores decreased with age, with participants aged 80 years or older having a mean MMSE scores approximately three points lower than subjects aged between 65 and 69 years. Diagnostic plots for the regression model did not show any evidence of problems regarding the plausibility of key assumptions.

Performance of the MMSE in the identification of cases of dementia

Using the DSM-IV dementia diagnosis as the reference criterion, we obtained estimates of sensitivity, specificity, LR+, LR−, OMR and proportion of the sample below several cut-off points of the MMSE for those with/without formal education (Table 4). According to the ROC curve, the optimal MMSE thresholds for case definition were 14/15 for participants with no formal education and 17/18 for those with one or more years of formal education, yielding estimates of sensitivity and specificity of 78.7 and 77.8% for those with no formal education, and 91.9 and 89.5% for those with at least 1 year of formal education. The areas under the ROC curve for the groups with no formal education and the group of one or more years of education were 0.87 (95% CI: 0.81,

Table 3 Multivariate linear regression models for MMSE mean scores according to sex, age, education and personal income, adjusted for the diagnosis of dementia ($n = 1{,}993$)

Characteristic	Model 1 adjusted for DSM-IV diagnosis of dementia				Model 2 adjusted for DSM-IV diagnosis of dementia and all other variables in the table			
	Multivariable adjusted β coefficient	95% CI[a]	Standard error	*P* value+	Multivariable adjusted β coefficient	95% CI[a]	Standard error	*P* value+
Sex	1.73	1.32, 2.15	0.21	<0.001	0.91[b]	0.56, 1.27	0.18	<0.001
Age	−1.40	−1.59, −1.21	0.10	<0.001	−0.94[c]	−1.12, −0.78	0.08	<0.001
Education	4.64	4.27, 5.00	0.19	<0.001	3.76[d]	3.40, 4.19	0.19	<0.001
Income	2.94	2.54, 3.33	0.20	<0.001	1.52[e]	1.15, 1.88	0.19	<0.001

+ *P* value for the likelihood ratio test
[a]CI confidence interval
[b]β coefficient adjusted for age, education, income and DSM-IV diagnosis of dementia
[c]β coefficient adjusted for sex, education, income and DSM-IV diagnosis of dementia
[d]β coefficient adjusted for sex, age, income and DSM-IV diagnosis of dementia
[e]β coefficient adjusted for sex, age, education, and DSM-IV diagnosis of deme

Table 4 Estimates of performance of the MMSE based on receiver operating characteristic (ROC) analysis for different cut-points by level of formal education ($n = 1{,}993$)

Level of education	Cut-off point[b]	Sensitivity	Specificity	LR+[a]	LR−[a]	OMR[a]	PPV[a]	%+[a]
None	13/14	72.3	84.9	4.8	0.3	15.9	24.5	18.7
	(14/15)	**78.7**	**77.8**	**3.5**	**0.3**	**22.2**	**19.3**	**25.8**
	15/16	87.2	70.4	3.0	0.2	28.5	16.6	33.2
	16/17	93.6	61.3	2.4	0.1	36.7	14.1	42.2
	17/18	93.6	49.1	1.8	0.1	48.1	11.3	53.6
	18/19	95.7	40.2	1.6	0.1	56.3	9.7	62.1
	19/20	97.9	29.7	1.4	0.1	66.0	8.6	72.0
One or more years	**(17/18)**	**91.9**	**89.5**	**8.7**	**0.1**	**10.4**	**21.9**	**13.0**
	18/19	91.9	85.4	6.3	0.1	14.4	16.8	17.0
	19/20	94.6	78.8	4.5	0.1	20.7	12.5	23.5
	20/21	94.6	69.9	3.1	0.1	29.4	9.2	32.1
	21/22	94.6	59.9	2.4	0.1	39.0	7.0	41.8
	22/23	94.6	50.6	1.9	0.1	48.0	5.8	50.8
	23/24	100.0	37.6	1.6	0.0	60.5	4.9	63.6
	24/25	100.0	27.8	1.4	0.0	70.0	4.3	77.1

[a]*LR+* positive likelihood ratio, *LR−* negative likelihood ratio, *OMR* overall misclassification ratio, *PPV* positive predictive value, %+ Proportion below cut-off point
[b]MMSE cut-points to differentiate between likely non-dementia and dementia case

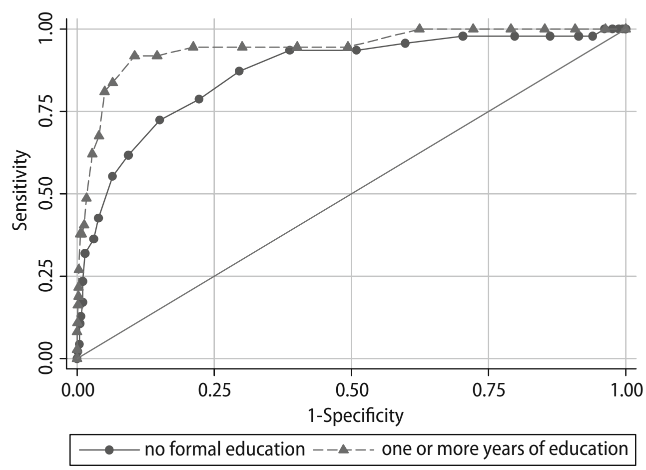

Fig. 1 Receiver operating characteristic (*ROC*) curves for participants with no formal education and for participants with one or more years of formal education

0.92) and 0.94 (95% CI: 0.90, 0.98), respectively (Fig. 1). The difference between the areas under the ROC curve was statistically significant ($\chi^2 = 4.49$; 1 degree of freedom; $P = 0.03$). The sensitivity and LR+ of the test improved with the increase of the cut-off point, with concurrent decreases in specificity, LR+, PPV, and the percentage of cases identified as positive by the instrument.

Using the optimal cut-off points 14/15 for subjects without formal education and 17/18 for subjects with one or more years of formal education, the proportion of positive MMSE cases in the sample was approximately four times higher than the proportion of cases of dementia according to the reference criterion (18.0 vs. 4.4%), regardless of their educational status. This same pattern was observed among the sub-group of participants with no formal education (25.8 vs. 6.3%), and among the sub-group of participants with one or more years of formal education (13.4 vs. 3.1%).

The use of differential MMSE threshold scores according to education did not avoid misclassification by education. Participants with at least 1 year of formal education were approximately 42% less likely to be incorrectly identified as cases by the MMSE than participants with no formal education (OR = 0.58; $\chi^2 = 18.3$; 1 degree of freedom; $P < 0.001$; 95% CI: 0.45, 0.74), independent of their sex and age.

Discussion

To the best of our knowledge, this is the first population-based study to examine the performance of the MMSE for the screening of cognitive impairment associated with dementia in a large community-representative sample of older adults from low socioeconomic backgrounds and limited education. We found that a large proportion of participants with no formal education rated several MMSE items incorrectly and that even when using optimal cut-points according to educational level, estimates of sensitivity and specificity were more robust for participants with one or more years of education than for those with no formal education. MMSE scores were strongly influenced by age, and less markedly by gender and personal income, independent of dementia caseness.

A unique and major strength of the present study is its population-based sample with socio-demographic and educational characteristics that are typical of LAMIC. Another strength is its sample size, which was large enough to enable us to obtain fairly precise estimates of validity parameters and misclassification bias. Of note, we did not use split half analysis because the test investigated (MMSE) was not part of the gold standard assessment, and such procedure would greatly reduce the precision of the estimates of the validity parameters. We acknowledge that our participants were sampled from one area of the city of Sao Paulo, which may raise questions regarding the generalizability of our results. However, the socioeconomic and education profiles of our sample and the Brazilian elderly population are very similar [22, 23], which suggests that our findings are likely to be representative.

As expected, we found that older adults with dementia have lower MMSE scores than those without dementia. However, among older adults without dementia, MMSE scores were independently influenced by education, age, gender and income, corroborating results of normative population-based studies undertaken in high- and middle-income countries [6, 7, 11, 18, 25, 36]. The ROC analysis showed that validity parameters were better for participants with at least some degree of literacy, when compared with participants with no formal education, even when using different cut-points for each group, as indicated by the areas under the ROC curve. Interestingly, a MMSE cut-point of 17/18 showed very good sensitivity and specificity for participants with one or more years of formal education; these results are comparable to those reported by previous validity studies in high-income countries [37], even though most of our participants had substantially less years of formal education than what is usually statutory in high-income countries. The PPV derived from our analyses (19.3% no formal education and 21.9% one or more years of formal education) were lower than those reported by studies of selected samples [1, 26]. However, the PPV is influenced by the prevalence of the disease in the study population, and validation studies based on selected samples usually include higher proportions of individuals with dementia than what we found in our population based sample.

The threshold scores for dementia caseness that we found were somewhat lower than the cut-points adopted by two previous validation studies carried out in health services settings in Brazil (18/19 and 19/20 for the group with no formal education and 23/24 and 24/25 for the group with some formal education, respectively) [1, 26]. This may be due, at least in part, to differences in the study populations. Samples drawn from health services are likely to present more severe dementia than samples from the general population, and this can influence the validity estimates of the MMSE [37]. Another study in Brazil evaluated the performance of the MMSE in an outpatient clinic in Sao Paulo, and reported cut-off points similar to those found in our study [4]. However, that study included a sample drawn from a health service, aged 15 years-old or over, what makes the comparison of results difficult.

Our results also showed that older adults with no literacy have lower MMSE scores and that the psychometric properties of the instrument are less robust, even after the lowering of the cut-point to establish the presence of cognitive impairment associated with dementia. This is a worrying finding, as misclassification of older adults screened with the MMSE in LAMIC may have substantial clinical and public health implications. The use of the cut-off points suggested by the ROC curves in our study resulted in 20% misclassification of older adults with dementia and 15% for those without. In addition, if the MMSE had been used as the solo instrument of an epidemiological study to estimate the prevalence of dementia in the population, the obtained estimate would have been four times greater than the actual prevalence.

Another concern in epidemiological studies is the possibility of non-random misclassification of the outcome, dependent on the exposure status of the study participant, because that may bias the estimate of the association between the exposure and outcome [33]. We found that older participants, women, those with no formal education, and people with lower personal income tended to have lower scores (false-positive) on the MMSE. This differential misclassification may give overestimations of the associations between these variables and of the prevalence of dementia, with similar practical implications for health service planning and individuals, as previously discussed.

Conclusion

The MMSE has been used worldwide for decades, and our results support its utility with older adults with at least minimum literacy skills. However, the test results are strongly influenced by education and sociodemographic status, and the misclassification ratio for dementia caseness is unacceptably high for older adults who are illiterate, regardless of the cut-point used to determine the presence of cognitive impairment. Older adults are the group with the lowest educational attainment in most LAMIC and this reality will persist for a few more generations [9, 38]. As Cummings pointed out two decades ago, *errors of omission, not of commission* are important when examining the cognitive state of older adults. The challenge to develop a simple and valid screening instrument to determine the presence of dementia in LAMIC remains [12].

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