

Brief version of the CAMCOG for illiterate older adults with Alzheimer's dementia

Versão breve do CAMCOG para idosos analfabetos com doença de Alzheimer

Juliana Francisca CECATO^{1,2}, Everton BALDUINO¹, José Eduardo MARTINELLI¹, Ivan APRAHAMIAN¹

ABSTRACT

Background: The Cambridge Cognition Examination (CAMCOG) is one of the most used cognitive assessment batteries for older adults. **Objective:** To evaluate a brief version of the CAMCOG for illiterate older adults (CAMCOG-BILL) with Alzheimer's dementia (AD) and healthy controls (CG). **Methods:** Cross-sectional case-control study with 246 illiterate older adults (AD [n=159] and CG [n=87], composed by healthy seniors without cognitive complaints) who never attended school or took reading or writing lessons. Diagnosis of AD was established based on the NIA-AA and DSM-5 criteria. All participants were assessed with the CAMCOG by a researcher blinded for diagnosis. To assess the consistency of the chosen CAMCOG-BILL sub-items, we performed a binary logistic regression analysis. **Results:** Both the CAMCOG and the CAMCOG-BILL had satisfactory psychometric properties. The area under the curve (AUC) was 0.932 ($p < 0.001$) for the original version of CAMCOG and 0.936 for the CAMCOG-BILL. Using a cut-off score of ≥ 60 (CAMCOG) and ≥ 44 (CAMCOG-BILL), both instruments had the same sensitivity and specificity (89 and 96%, respectively). **Conclusion:** The CAMCOG-BILL may be a preferred tool because of the reduced test burden for this vulnerable subgroup of illiterate patients with dementia.

Keywords: Alzheimer Disease; Education; Neuropsychological Tests; Aging.

RESUMO

Antecedentes: O Cambridge Cognition Examination (CAMCOG) é uma das baterias de avaliação cognitiva mais usadas para idosos. **Objetivos:** Avaliar uma versão breve do CAMCOG para idosos analfabetos (CAMCOG-BILL) com demência de Alzheimer (DA) em comparação com controles saudáveis não demenciados (GC). **Métodos:** Estudo caso-controle transversal com 246 idosos analfabetos (AD [n=159] e GC [n=87], composto por idosos saudáveis sem queixas cognitivas) que nunca frequentaram a escola ou fizeram aulas de leitura ou redação. O diagnóstico de DA foi estabelecido pelos critérios NIA-AA e DSM-5. Todos os participantes foram avaliados por meio do CAMCOG por avaliador cego, para o diagnóstico dos grupos. Para avaliar a consistência dos subitens escolhidos do CAMCOG-BILL, realizou-se uma análise de regressão logística binária. **Resultados:** Tanto o CAMCOG quanto o CAMCOG-BILL apresentaram propriedades psicométricas satisfatórias. A área sob a curva (AUC) foi de 0,932 ($p < 0,001$) para a versão original do CAMCOG e de 0,936 para o CAMCOG-BILL. Usando-se uma pontuação de corte de ≥ 60 (CAMCOG) e ≥ 44 (CAMCOG-BILL), ambos os instrumentos tiveram a mesma sensibilidade e especificidade (89 e 96%, respectivamente). **Conclusão:** O CAMCOG-BILL pode ser preferido para reduzir a sobrecarga do teste para esse subgrupo vulnerável de pacientes analfabetos com demência.

Palavras-chave: Doença de Alzheimer; Educação; Testes Neuropsicológicos; Envelhecimento.

INTRODUCTION

Educational level is an important determinant of cognitive performance^{1,2}. More years of formal education contribute to cognitive reserve and may support coping with aging-related cognitive decline^{3,4,5,6,7}. Higher intellectuality is another neuroprotective factor. Intellectually stimulant

activities, e.g. traveling, reading and writing, language classes, among others, also improve cognitive abilities during life and thereby protect against aging-related cognitive decline^{5,6}. Thus, alterations observed in neuropsychological assessment of seniors with high educational level or high intellectuality may indicate the presence of a neurodegenerative disease^{8,9,10}. However, those with low or no formal

¹Faculdade de Medicina de Jundiaí, Departamento de Medicina Interna, Divisão de Geriatria, Group of Investigation on Multimorbidity and Mental Health in Aging, Jundiaí SP, Brazil.

²Universidade São Francisco, Departamento de Psicologia, Bragança Paulista SP, Brazil.

JFC  <http://orcid.org/0000-0002-2783-772X>; EB  <https://orcid.org/0000-0001-9310-9491>; JEM  <https://orcid.org/0000-0003-2766-1987>;

IA  <https://orcid.org/0000-0003-3806-7895>

Correspondence: Juliana F. Cecato; Email: cecatojuliana@hotmail.com.

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education may obtain false-positive results in cognitive assessment.

UNESCO¹¹ has estimated that around 161 million older persons (≥ 65 years old) are illiterate worldwide. Seven of the ten most important economically emerging countries (classified by Columbia Center on Sustainable Investment¹²) present illiteracy rates of older adults equal or higher than 20% (Morocco: 66%; India: 55%; South Africa: 45%; Indonesia: 26%; Brazil: 21%; Turkey: 20%; and Mexico 20%)¹¹. Even though in Brazil, Mexico, and Turkey these estimates showed a decreasing trend in the last 5 years, this is still a major concern considering the impact of illiteracy in autonomy and health of older adults¹¹. As a primary phenomenon, written language skills results in a reorganization of cognition, with changes in visual and spatial perception, logical reasoning, recall strategies, improved memory skills, metalinguistic awareness, among others¹³. Recently, we demonstrated the influence of illiteracy and low educational level over cognitive performance among seniors, based on the results of different cognitive screening instruments, including the Cambridge Cognition Examination (CAMCOG)³.

The CAMCOG is a valid instrument to detect suspected cases of Alzheimer's disease (AD), which is the most common cause of dementia worldwide^{14,15}. This instrument showed good accuracy in discriminating healthy individuals from AD patients with a sensitivity of 100% and specificity of 95%^{14,15}. Even a shorter version of the battery with only half of the items (CAMCOG-R) showed a sensitivity of 98% and a specificity of 100%¹⁴. The CAMCOG also presented good interrater reliability and internal consistency for different stages of dementia^{9,10}. These evidences depict that the CAMCOG is a useful cognitive battery for the identification of AD cases. Nonetheless, whether the CAMCOG would be suitable for illiterate persons with suspected dementia remains unknown. While several instruments have been developed for neuropsychological testing of older adults with low or no educational background^{9,10,14,15,16}, specific validation studies in illiterate samples have not been performed.

Finally, feasible and reliable instruments for diagnostic investigation of illiterate seniors with different cognitive issues are needed. Our objective was to evaluate a brief version of the CAMCOG for illiterate older adults (CAMCOG-BILL) with Alzheimer's disease (AD) and healthy controls (CG).

METHODS

Study design and participants

We conducted a cross-sectional case-control study with 246 illiterate older adults (60 to 97 years old). Illiteracy was defined as never having learned to read or write in a school environment. A convenient sample was selected from an outpatient geriatrics clinic at the Faculdade de Medicina

de Jundiaí and included those with 60 years of age or older that were healthy (CG, $n=87$) or had AD ($n=159$); data collection occurred between January 2015 and December 2019. The diagnosis of AD was made through a multidisciplinary consensus meeting according to both the NIA-AA¹⁷ and the DSM-5¹⁸ diagnosis criteria of AD and major neurocognitive disorder, respectively. Severity of dementia was clinically evaluated by the Clinical Dementia Rating (CDR). The participants in the AD group had mild and moderate disease stages (according to CDR, stages 1 and 2). All patients received acetylcholinesterase inhibitors alone or in combination to memantine for mild and moderate AD, respectively.

All patients were interviewed at the outpatient clinic by a team of geriatric and psychiatric specialists, physical therapists, and neuropsychologists. In order to acquire information regarding functional disability, cognition, and behavior, all patients (including controls) were asked to attend to consultation with a relative or caregiver. Laboratory (hemogram, renal and hepatic function, electrolytes, vitamin B12 and folate, TSH, free T_4 , and VDRL) and imaging exams (magnetic resonance or a computerized tomography of the brain if the patient had a pacemaker or claustrophobia) were done in all patients.

The participants in the CG group were completely independent for activities of daily living (ADL), had no neuropsychiatric disorder, no subjective memory complains, nor Mild Cognitive Impairment¹⁸. These patients were followed at our clinic for routine care, such as control of chronic diseases or health maintenance.

We excluded from this study participants with any kind of disorder that could compromise the neuropsychological evaluation or that would suggest another etiology for dementia other than AD. Thus, we excluded patients with any plegia or paresis, important tremor, functional impairment in hands, severe visual or auditory impairment, any addictive disorder, any depression syndrome (Geriatric Depression Scale score ≥ 5 points)¹⁹, Parkinson's disease, any stroke history or those who refused to complete any of the tests. We also excluded patients with alterations in laboratorial exams (e.g., vitamin B12 and thyrotropin) that suggested reversible dementia and neuroimaging alterations (magnetic resonance) that suggested moderate microvascular ischemia (i.e., Fazekas 2 or 3), hydrocephalus or neoplasm. All patients agreed to participate by signing an informed consent form approved by the local Ethics Committee (protocol number: 1.012.851).

Instruments and procedures

In our routine clinical evaluation, all patients had a complete clinical, neurological, and psychiatric evaluation by geriatricians with special focus in neuropsychiatry and also by geriatric psychiatry specialists. Additionally, the Cambridge Examination of Mental Disorder of the Elderly (CAMDEX), a semi-structured interview that yields diagnostic information on neuropsychiatric disorders of late life was used²⁰.

A neuropsychologist conducted the cognitive and functional evaluation. The Mini-Mental State Examination (MMSE) was used as a cognitive screening test before proceeding to CDR^{21,22}. The Geriatric Depression Scale (GDS) with 15 items¹⁹ and the Pfeffer's Functional Activities Questionnaire (PFAQ)²³ were also applied to assess depressive symptoms and ADL, respectively. The PFAQ was applied to a relative or caregiver. In a separated session, all participants were assessed with the CAMDEX and the CAMCOG by an assessor blinded for any results of previous examinations. The CAMCOG is the B part of the CAMDEX and includes subtests for several cognitive domains, such as memory, attention, concentration, orientation, language, abstract thinking, calculation, praxis, and perception. The multidisciplinary team responsible for the final diagnosis of dementia was blinded for the CAMCOG score²⁰. The CAMCOG score did not contribute to the clinical diagnosis. The MMSE, the CDR, and clinical and functional evaluations were taken into account for establishing the AD diagnosis.

Development of the Cambridge Cognition Examination - brief version for illiterate individuals

For the CAMCOG-BILL development, we considered the most successful subtests scored by the CG as well as excluded the subtests with most correct answers in the AD group. The included subtests after the correctness analysis were: motor response (to follow verbal commands); definitions (to explain the meaning of 4 sentences); figure naming (to name correctly 6 figures); verbal fluency (to verbalize the greatest number of animals in one minute); sentence repetition and writing of address; memory (remote, recent, evocation, and recognition); countdown and calculation; and orientation (temporal and spatial). The maximum score was 60 points, and the estimated duration of the test was 35 minutes in a single session.

Statistical analyses

We analyzed the data using the IBM® Statistical Package for Social Sciences (SPSS) software version 19.0. We performed normality tests (histogram analysis and Kolmogorov-Smirnov test), which indicated a non-parametric distribution of the CAMCOG subtests scores. Percentages and means (and standard deviation) were calculated for sex and age. We used the Mann-Whitney test to compare differences between groups for age and chi-squared test for sex. Additionally, we evaluated the correlation between cognitive tests (MMSE and CAMCOG-BILL) and PFAQ through Spearman's correlation coefficient. To assess the consistency of the CAMCOG-BILL subitems of choice, we performed a binary logistic regression analysis using a stepwise forward likelihood ratio method, based on a model with all cognitive domains (language, memory, calculation, praxis, perception, orientation). Finally, we analyzed the sensitivity and specificity of cognitive tests (the CAMCOG-BILL and the original CAMCOG) using

the Receiver Operating Characteristic (ROC) curve analyses. We performed this specific analysis in the MedCalc software version 15.8. We considered p-values lower than 0.05 as statistically significant.

RESULTS

The total sample presented a mean age of 79.3 years (60 to 97 years; standard deviation [SD]=7.3) and 76.5% (n=189) were women. Table 1 shows the clinical characteristics of AD and CG participants. We did not find significant differences concerning age and sex. All CAMCOG sub-items were significantly different between the two groups.

Table 2 shows the correlation between the CAMCOG-BILL, the MMSE, and the PFAQ. The correlation was high between the CAMCOG-BILL and the MMSE in the total sample and was moderate in the two groups. We observed a negative moderate correlation between the CAMCOG-BILL and the PFAQ in the total sample and AD group. The correlation between the CAMCOG-BILL and the PFAQ was also negative but weak in the CG.

We evaluated the CAMCOG-BILL sub-items through a binary logistic regression analysis using a stepwise backward likelihood ratio. Language (OR=0.617, 95%CI 0.444–0.858; p=0.004), temporal orientation (OR=0.315; 95%CI 0.197–0.506; p<0.001), and spatial orientation (OR=0.354; 95%CI 0.192–0.652; p=0.001) demonstrated a significant association (Table 3). The psychometric results showed that this proposed model had statistical significance corroborating the likelihood

Table 1. Characteristics of control group and Alzheimer disease participants.

		CG	AD	p-value
		78.1 (±7.91)	79.9 (±7.25)	0.075
Age (years), mean (SD)	Female	69.6%	79.4%	0.152
	Male	30.4%	24.6%	
Sex	CAMCOG	69.12 (±11.92)	45.08 (±12.41)	*<0.001
	MMSE	22.73 (±2.88)	14.51 (±3.51)	*<0.001
	PFAQ	1.30 (±1.57)	18.36 (±8.64)	*<0.001
CAMCOG subtests	Language	10.8 (±1.7)	8.0 (±1.9)	*<0.001
	Memory	10.6 (±2.7)	6.8 (±3.1)	*<0.001
	Praxis	8.2 (±2.0)	6.5 (±1.6)	*<0.001
	Perception	6.4 (±1.6)	4.8 (±1.6)	*<0.001
	Temporal orientation	4.2 (±0.8)	2.0 (±1.4)	*<0.001
	Spatial orientation	4.6 (±0.5)	3.0 (±1.3)	*<0.001
	Calculate	1.6 (±0.5)	1.1 (±0.5)	*<0.001

CG: control group; AD: Alzheimer disease; CAMCOG: Cambridge Cognition Examination; MMSE: Mini-Mental State Exam; PFAQ: Pfeffer's Functional Activities Questionnaire; SD: standard deviation; CAMCOG: Cambridge Cognition Examination; *p: Mann-Whitney.

Table 2. Correlation analyses between Cambridge Cognition Examination brief version for illiterate individuals and Mini-Mental State Exam and Mini-Mental State Exam for the total sample, Alzheimer disease group and control group participants.

	Total sample (n)	rho	p-value	CG (n)	rho	p	AD (n)	rho	p-value
CAMCOG-BILL and MMSE	246	0.85	<0.001	87	0.70	<0.001	160	0.68	<0.001
CAMCOG-BILL and PFAQ	246	-0.67	<0.001	87	-0.31	0.005	160	-0.53	<0.001

CG: control group; AD: Alzheimer disease; MMSE: Mini-Mental State Exam; PFAQ: Pfeffer's Functional Activities Questionnaire; rho: Spearman correlation coefficient; CAMCOG-BILL: Cambridge Cognition Examination brief version for illiterate individuals.

Table 3. Forward stepwise logistic regression of the Cambridge Cognition Examination subitems.

Subtests	SE	p-value	OR	95%CI OR	
				Lower	Upper
Language	0.168	0.004	0.617	0.444	0.858
Memory	0.091	0.062	0.844	0.706	1.008
Countdown	0.289	0.436	0.799	0.453	1.407
Praxis	0.159	0.565	1.096	0.802	1.497
Calculation	0.502	0.157	0.491	0.184	1.315
Perception	0.165	0.126	0.777	0.563	1.073
Temporal orientation	0.241	<0.001	0.315	0.197	0.506
Spatial orientation	0.311	0.001	0.354	0.192	0.652

CAMCOG: Cambridge Cognition Examination; SE: standard error; OR: Odds Ratio; 95%CI: 95% confidence interval.

value (Model Likelihood) found in the regression analysis ($p < 0.001$) with a predictive value of 83.3%. We performed another forward stepwise logistic regression for the memory subtests considering that the CAMCOG's memory sub-item was not significant ($p = 0.062$) and the memory impairment is a cornerstone cognitive dysfunction in AD (Table 4). The recent memory subtest (OR=0.444; 95%CI 0.335–0.589; $p < 0.001$) and the memory recall (OR=0.746; 95%CI 0.602–0.923; $p = 0.007$) were significant for AD identification.

The area under the curve (AUC) of ROC for the original CAMCOG and the CAMCOG-BILL were similar and significantly discriminated between cases and controls (Figure 1). The original CAMCOG presented a cut-off value of equal or less than 60 points for AD (AUC=0.936, standard error [SE]=0.015). The cut-off score for the CAMCOG-BILL was equal or less than 44 points (AUC=0.932, standard error [SE]=0.016). Both instruments showed high sensitivity and specificity values (89 and 96%, respectively).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate a shorter version of the CAMCOG adapted to illiterate groups of AD patients and cognitively healthy older adults. The subtests of the CAMCOG-BILL included the items assessing temporal and spatial orientation, recent memory,

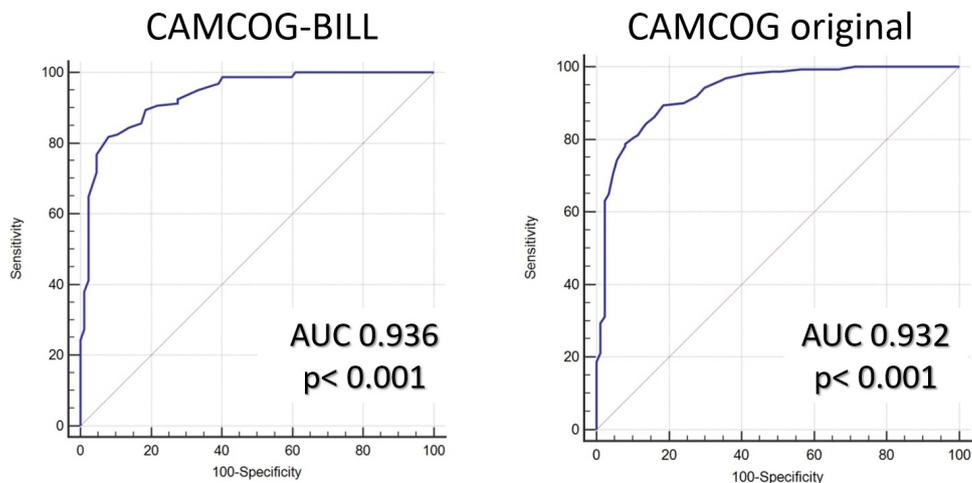
Table 4. Forward stepwise logistic regression of the Cambridge Cognition Examination memory subtests.

Subtests	SE	p-value	OR	95%CI OR	
				Lower	Upper
Recent memory	0.144	<0.001	0.444	0.335	0.589
Memory recall	0.109	0.007	0.746	0.602	0.923
Memory recognition	0.146	0.090	0.780	0.586	1.039

CAMCOG: Cambridge Cognition Examination; SE: standard error; OR: Odds Ratio; 95%CI: 95% confidence interval.

memory recall, and language of the original CAMCOG scale. The original CAMCOG and the CAMCOG-BILL presented good psychometric properties to assess these patients, significantly discriminating the two groups. Both instruments showed similar diagnostic accuracy with the same sensitivity and specificity, and a cut-off of less than 44 points in the CAMCOG-BILL is suggested to differentiate AD patients from controls.

The CAMCOG is a sensitive battery and widely used to assess different levels of cognitive impairment in older adults^{9,10,15,16,24,25}. However, CAMCOG's cut-off score appears to be affected by age and education level, and performance may be modulated by sociodemographic characteristics²³. Therefore, there is a need for adapting this instrument for use in the oldest old or individuals with little formal education. Previously, a cut-off score of 65 points was proposed for a sample of illiterate healthy seniors with more than 80 years³, and lower performance, especially in memory, praxis, and abstraction subtests, was described for seniors with 90 years or more²⁶. Since its description, the CAMCOG battery showed cut-off scores that increased with higher educational levels²³. In a previous study evaluating the association between sociodemographic variables and CAMCOG scores, educational level influenced language and abstract thinking scores²⁷. In another Brazilian study, memory, language, visual perception, and abstract thinking distinguished three different levels of education²⁸, but illiterates were not included. In our study, all CAMCOG subtests were significantly different between the two groups. Aprahamian et al. reported a cut-off score of 79 points for older adults (mean age 75.7 years) with low educational level (1 to 4 years of formal education), with sensitivity of 88% and specificity of 83% for detecting mild AD¹⁶. Moreover, in a sample of older adults from low



ROC: receiver operating characteristic; AUC: area under the curve; CAMCOG: Cambridge Cognition Examination; CAMCOG-BILL: Cambridge Cognition Examination brief version for illiterate individuals.

Figure 1. ROC curves, AUC, and accuracy values for the original Cambridge Cognition Examination and the Cambridge Cognition Examination brief version for illiterate individuals.

to middle-income countries, CAMCOG's language subtests were highly affected by educational level²⁸. Finally, a previous study compared CAMCOG scores of 189 low-educated Brazilian older adults with dementia to those of healthy controls¹⁰. Most participants were illiterate (mean educational level of 3.1 ± 2.2 years). The best cut-off score to discriminate between dementia and control groups was 50/51 with a sensitivity and specificity of 69%. The cut-off value of 44 was established for proposed CAMCOG-BILL, but the scale had different AUC (0.936 versus 0.750) and diagnostic accuracy values (69 versus 89% sensitivity and 96% specificity) than the original scale.

Several arguments could explain these differences such as the strict diagnostic criteria in this study to include only AD patients and the use of an adapted brief version of the CAMCOG without language constraints for illiterate seniors. Furthermore, another important characteristic of our sample is that it was entirely composed of illiterate people, i.e., never attended school, learned to read or write, or attended supplementary school or similar programs to compensate for the absence of formal education in childhood.

Brief versions of the CAMCOG can be of high clinical value and save time when assessing mild cognitive impairment and early dementia¹⁶. Previously, some of the CAMCOG's subtests were shown to have better discrimination ability of mildly impaired older adults and controls than the total score, in both cross-sectional and longitudinal studies^{16,29,30,31}. Orientation and memory subtests, especially delayed recall, are more implicated with AD than other subtests^{16,29,30,31}. Most of the CAMCOG-BILL items assess orientation and memory outcomes, which could explain the high AUC and diagnostic accuracy in AD patients. Even among older adults with cerebrovascular disease (e.g. carotid occlusion and history of brain stroke) but not dementia, orientation (OR=2.25; 95%CI 1.40–3.61),

language (OR=1.80; 95%CI 1.10–2.95), memory (OR=1.67; 95%CI 1.05–2.65), perception (OR=1.74; 95%CI 1.02–2.98), and praxis (OR=1.64; 95%CI 1.03–2.62) were more frequently impaired and associated with vascular dementia after 2 years of follow-up²⁵. Additionally, brief versions of the CAMCOG could be used as alternatives to other brief cognitive tests such as the Mini Mental State Examination, the Addenbrooke test, and the Rowland Universal Dementia Assessment Scale (RUDAS). Of these scales, the first two have adapted scores for people with low educational level or illiterate, and thus require more in-depth evaluation for illiterate patients with dementia^{32,33}. The RUDAS is designed for patients with low educational background but presents specific cut-off scores for different populations³⁴.

Formal education has a strong effect on the construction of cognitive reserve, and elderly with higher educational level received more brain stimuli contributing to a greater cognitive reserve and consequently, decreasing their risk of dementia^{1,2,3}. In fact, several studies demonstrated that a few years of formal education might elicit better cognitive performance, owing to the neurocognitive development and brain network reorganization^{35,36,37,38,39}. As there are approximately eight hundred million illiterate people in the world, the interpretation of the cognitive performance in traditional neuropsychological tests, which are developed to assess the literate population, can be a challenge⁷. Our study presented valid psychometric data indicating that the CAMCOG-BILL has adequate sensitivity and specificity to assess illiterate elderly with possible AD. Our instrument also presented convergent validity compared to the MMSE (a similar cognitive instrument), with the tools presenting significant and robust correlations. The original CAMCOG has a broad applicability but it is time-consuming and illiterate seniors might be unfamiliar with subtests because of reading, writing, calculating, and abstract thinking impairments. CAMCOG-BILL

demonstrated high sensitivity for the assessment of memory, language, and orientation, whilst demanding less time to be completed, keeping the patients motivated throughout the test. In fact, maintaining the focus of older adults during an entire neuropsychological session is a challenge. Leite et al.⁴⁰ used a brief version of a cognitive instrument for illiterate seniors and found that the attention of the participants was maintained throughout the assessment⁴⁰. In clinical practice, the results of such tests in older adults with low or no formal education can indicate a false mild dementia because most instruments need reading and logical thinking abilities. In our region, for example, the percentage of illiteracy among older adults is 9.7%⁴¹, which is an important reason for the development of cognitive instruments adapted for this population.

Some potential limitations of this study must be addressed. The CAMCOG-BILL might still be too complex for illiterate people to understand as the original CAMCOG was not developed specifically for this population. Moreover, the ecological validity of the CAMCOG-BILL has not been assessed and its verisimilitude and veridicality need to be explored in future studies to consolidate the use of this instrument for this specific and cognitively complex population. Adjusting some items may further increase the tool's specificity. Furthermore, we did not evaluate other components of cognitive reserve beyond years of education, such as intelligent coefficient, occupational status, engagement

in leisure activities, and the strength of social relationships. Illiteracy results in a complex heterogeneous cognitive reserve and cannot be fully characterized based on years of schooling alone. Our research is a case-control study, which used a convenient sample of illiterate seniors from our specialized clinic. Moreover, information regarding multimorbidity, frailty, and prescription drugs was not collected, which could better characterize the sample. Additionally, we included only older adults with AD and more studies are recommended to assess the properties of the CAMCOG-BILL in people with other cognitive disorders. Finally, cognitive performance in illiterate people is heterogeneous and samples from different regions of our country and abroad may show different results.

In conclusion, the present study showed that the CAMCOG-BILL is a feasible instrument for the evaluation of illiterate people with suspected AD. The instrument showed high accuracy in diagnosing AD, close to that of the original CAMCOG battery, but the verbal responses, the reading, and the perception sub-items of the original CAMCOG were removed.

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