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Validation Study of the Italian Addenbrooke's Cognitive Examination Revised in a Young-Old and Old-Old Population

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Key Words

Addenbrooke's cognitive examination · Elderly · Dementia · Cognitive assessment · Young-old · Old-old

old-old population, which represents not only the fastest growing age group but also the group at the highest risk of dementia in Western countries. Copyright © 2012 S. Karger AG, Basel

Abstract

Aims: The main aims of the study were the translation and the subsequent validation in Italian of the Addenbrooke's Cognitive Examination Revised (ACE-R), and the evaluation of its usefulness in discriminating cognitively normal subjects from patients with mild dementia in an elderly population. **Methods:** The ACE-R was translated and adapted into Italian. The Italian ACE-R was administered to a group of 179 elderly subjects (72 cognitively healthy and 107 subjects with mild dementia, mean age 75.4 ± 6.4 years). The group was stratified into two subsamples according to age, i.e. a young-old (<75 years) and an old-old (≥ 75 years) group, in order to evaluate the sensitivity and specificity of the test in detecting dementia in different age strata of elderly subjects. **Results:** The reliability of the Italian ACE-R was extremely good (α -coefficient = 0.85). Two different cutoffs were identified for young-old (cutoff 79; sensitivity 90% and specificity 80%) and old-old subjects (cutoff 60; sensitivity 82% and specificity 100%). **Conclusions:** The Italian ACE-R is a valid screening tool to detect dementia, especially in the

Introduction

Many studies have been performed to improve methods for assessing cognitive functions in the elderly and to differentiate dementia and mild cognitive impairment from physiological age-related changes. Individuals older than 75 years represent the fastest growing group in developed countries and, in the meantime, the group at the highest risk of dementia [1].

Different psychometric tests have been proposed for screening purposes [2, 3]. The Mini Mental State Examination (MMSE) is the most popular and is widely used to follow cognitive decline along with time as well as to monitor the effects of drug treatments [4]. The MMSE is brief and easy to administer, but it has shown poor sensitivity in early detection of dementia, particularly in people over 75 years [5], and it is unable to differentiate dementia subtypes [4]. Several other screening tools have been developed over the years, although they have not

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become as popular as the MMSE: most of them are too lengthy and complex, requiring specialized trained personnel for administration, or too brief and simple, lacking in sensitivity.

Hodges and his group [6] proposed the Addenbrooke's Cognitive Examination (ACE), which includes the MMSE, as a simple bedside test battery designed to detect mild dementia and differentiate Alzheimer's disease from frontotemporal dementia (FTD). The ACE – lately translated into Malayalam [7], French [8], Spanish [9], German [10], Hebrew [11], Danish [12] and Japanese [13] – was then revised (ACE-R) [14] in order to make the test easier to administer and to increase its sensitivity and specificity. In addition, three parallel forms were developed to avoid practice effects [14]. The ACE-R has been published in Portuguese [15, 16], German [17], Greek [18], Korean [19] and Spanish [20].

The ACE-R consists of five components evaluating different cognitive domains, with separate scores, i.e. attention/orientation (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial functions (16 points), with a maximum score of 100 as the sum of scores of all domains. The ACE-R can be administered in about 15 min in a clinical setting.

Although the psychometric properties of the ACE-R are well documented in the literature, no information is available on the sensitivity and specificity of this screening instrument in the old-old population.

The aims of this study were: (1) to translate the ACE-R into Italian and to assess its validity in the elderly in order to have at one's disposal a new screening test for dementia; (2) to evaluate the sensitivity and specificity of the ACE-R in detecting dementia in the elderly, specifically in young-old (<75 years) and old-old (≥75 years) subjects.

Methods and Subjects

Italian Version of the ACE-R

The ACE-R was translated and adapted into Italian according to the guidelines for cross-cultural adaptation by Guillemin et al. [21]. The Italian ACE-R, therefore, went through translation and back-translation. A pretesting phase was conducted in order to study two versions of the Italian ACE-R. A group of 10 cognitively healthy elderly people were tested with two versions of the test and were asked about the suitability and clearness of both. Then, a review committee composed by two psychologists and two geriatricians chose the final version of the Italian ACE-R. The Italian MMSE counterpart replaced ACE-R components referring to the MMSE. Some adaptations concerning memory, verbal fluency, language and visuospatial domains were made. For example, in

Table 1. Composition of the study population according to age

	Young-old (age <75)	Old-old (age ≥75)	Total
Controls	41	31	72
Alzheimer's disease	11	35	46
Frontotemporal dementia	15	3	18
Vascular dementia	4	18	22
Dementia with Lewy bodies	10	11	21

the memory domain, the name and address task (anterograde memory) was modified to be consistent with the Italian system. In the retrograde memory task, the name of the English Prime Minister and the name of the woman who was Prime Minister in England were replaced by the name of the President of the Italian Republic and the name of the previous Pope of the Catholic Church. The distractors in the recognition task maintained the same difficulties because the selected items were chosen to be semantically, phonologically and spatially related to the correct answers. In the verbal fluency 'F', which is commonly used in the Italian fluency tests, replaced the letter 'P'. In the repetition test, Italian multisyllabic infrequently used words were selected. In the reading test, words with irregular accentuation were chosen since there are no irregular words in Italian. In the visuospatial domain, for the clock drawing test, we used the same scoring as the original version, but asked to set the clock hands to '10 past 11', because this analogical clock time has been reported to be the most sensitive for detecting cognitive dysfunctions [22, 23]. In the perceptual abilities test, we changed the letter 'K' with 'R', because 'K' does not belong to the Italian alphabet.

Participants and Assessment Procedure

The Italian ACE-R was validated in 179 subjects (101 women, 78 men, mean age 75 ± 6.4 years): 72 cognitively normal subjects as controls, 46 patients with Alzheimer's disease, 18 patients with FTD, 22 patients with vascular dementia and 21 patients with dementia with Lewy bodies. Subjects with dementia were consecutive patients attending the memory clinic. Controls were recruited from relatives of patients or from social centers in Perugia. The a priori sample size calculation for one-tailed nonparametric analysis was performed considering an α -level of 0.05, an anticipated effect size (Cohen's *d*) of 0.5 and a statistical power of 0.90.

Controls and subjects with dementia were stratified into two samples according to age (<75 and ≥75) and defined as young-old and old-old (table 1).

Subjects with dementia were assessed at the Memory Clinic of the Institute of Gerontology and Geriatrics, University of Perugia, and of the Department of Neurology, Regina Apostolorum Hospital, Rome, between October 2009 and October 2010. After a clinical interview, all participants were tested using a standard neuropsychological battery including Digit Span Forward and Digit Span Backward, Trail Making Test, Controlled Oral Word Association, Raven's Colored Progressive Matrices, Auditory Verbal Learning Test, Visual Search Test, Copying Drawings, Category fluency, Token Test, and the Babcock Story Recall Format described in Lezak et al. [24]. For each test, details on administra-

Table 2. Demographic data of the study population

	Age <75		p value	U	Age ≥75		p value	U
	control (n = 41)	dementia (n = 40)			control (n = 31)	dementia (n = 67)		
Gender, male	43%	40%	n.s.	–	35%	37%	n.s.	–
Age, years	69.6 ± 2.8	70.8 ± 3.6	n.s.	628.0	80.7 ± 3.6	80.9 ± 3.6	n.s.	1,030.5
Education, years	8.9 ± 4.6	7.1 ± 3.7	n.s.	800.5	7.7 ± 3.9	7.1 ± 4.8	n.s.	714.0

Data are expressed as percentages or mean ± SD as needed. n.s. = Not significant.

tion procedures and Italian normative data for score adjustment for age and education as well as normality cutoff scores are available [25–28].

In addition, we used the Geriatric Depression Scale [29] and the Neuropsychiatric Inventory [30] to assess mood and behavioral disturbances in the elderly. All subjects underwent a neuro-radiological evaluation (brain CT or MR scan) and laboratory examinations. The diagnosis was made on the basis of a multidisciplinary consensus (neuropsychologists and geriatricians). The *Diagnostic and Statistical Manual of Mental Disorders* criteria [31] were used for the diagnosis of dementia. Exclusion criteria were depression, schizophrenia or psychiatric disorders and causes of cognitive impairment other than neurodegenerative diseases (epilepsy, head injury, alcoholism and drug abuse). Alzheimer's disease patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association – (NINCDS-ADRDA) criteria [32]. As in previous studies [6, 14], the diagnosis of FTD was made in accordance with the Lund-Manchester consensus criteria [33]. The diagnosis of vascular dementia was based on the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [34]. Dementia with Lewy bodies (DLB) was diagnosed in accordance with criteria by McKeith et al. [35].

The severity of dementia was scored with the Clinical Dementia Rating Scale [36] and only patients with scores ≤1 (mild dementia) were included in the study.

The control group consisted of people recruited from a recreation center for the elderly in Perugia or among spouses/relatives of patients attending the Memory Clinics in Perugia and Rome. All subjects had a normal social functioning in the community and none had a history of psychiatric or neurological diseases. They did not have a history of head injury, drug or alcohol abuse or depressive symptoms, subjective memory complaints or identifiable cognitive impairment. Their MMSE ranged from 26 to 30.

Demographic characteristics of controls and subjects with dementia in the two age groups are reported in table 2.

Data Analysis

Statistical Package for the Social Sciences 12 (SPSS Inc., Chicago, Ill., USA) and MedCalc 11.2 (MedCalc software bvba, Belgium) for Windows were used. The reliability of the Italian ACE-R was measured in terms of internal consistency using Cronbach's α -coefficient [37]. Concurrent and convergent validity were cal-

culated with the two-tailed Spearman correlation test between Italian ACE-R final scores and MMSE scores [37, 38]. The sample was stratified into two groups according to age (<75 and ≥75). The χ^2 test and the Mann-Whitney test were carried out to compare control and dementia groups on demographics, Italian ACE-R total score, Italian ACE-R subscores and MMSE. Receiver operating characteristic curve (ROC) analysis was applied to define sensitivity and specificity at different cutoffs and to compare the Italian ACE-R with the MMSE in the two groups. Positive predictive values (PPV) and negative predictive value (NPV) were calculated in order to identify the optimal cutoff points in the two subsamples. Sensitivity, specificity, PPV and NPV values for diagnosing dementia were calculated at different prevalence rates (5, 10, 20, 40%).

Results

In this study, taking into consideration the study population, controls and subjects with mild dementia did not differ for age, gender distribution and education. The neuropsychological characteristics (MMSE, ACE-R total and subscores) of controls and subjects with dementia in the two age samples are reported in table 3. In both groups, subjects with dementia had statistically significantly lower scores than controls in all components.

In order to assess concurrent and convergent validity, the Italian ACE-R was correlated with MMSE. The Spearman ρ correlation coefficient between Italian ACE-R and MMSE was statistically significant ($r = 0.90$, $p < 0.01$). Cronbach's α for the Italian ACE-R was 0.85, an excellent result in terms of internal consistency [37, 38].

ROC curves for the Italian ACE-R and MMSE were constructed in the young-old and old-old samples.

In the young-old group, the area under the ROC curve (AUC) was 0.933 (95% CI = 0.855–0.977) for the Italian ACE-R and 0.904 (95% CI = 0.818–0.958) for the MMSE (fig. 1), suggesting that the former slightly better distinguishes controls from subjects with mild dementia. A

Table 3. MMSE, Italian ACE-R total score and Italian ACE-R subscores in control and subjects with mild dementia among the young-old (<75 years) and old-old (≥75 years) groups

	Age <75				Age ≥75			
	control (n = 41)	dementia (n = 40)	p value	U	control (n = 31)	dementia (n = 67)	p value	U
MMSE	28.7 ± 1.5	23.0 ± 4.4	<0.001	158.0	27.7 ± 2.0	20.6 ± 4.2	<0.001	142.0
ACE-R total score (range 0–100)	87.1 ± 9.3	63.3 ± 13.2	<0.001	109.5	80.5 ± 10.7	53.6 ± 12.2	<0.001	115.5
Attention and orientation (range 0–18)	17.7 ± 0.8	13.3 ± 3.7	<0.001	195.0	17.3 ± 1.0	12.6 ± 3.1	<0.001	168.0
Memory (range 0–26)	20.8 ± 4.7	13.8 ± 7.9	<0.001	354.0	17.9 ± 5.2	8.8 ± 5.4	<0.001	205.5
Fluency (range 0–14)	9.8 ± 2.8	4.2 ± 2.5	<0.001	127.0	8.4 ± 3.0	3.9 ± 2.3	<0.001	263.0
Language (range 0–26)	24.3 ± 2.4	21.6 ± 4.4	<0.01	507.0	23.1 ± 2.6	18.3 ± 5.2	<0.001	483.0
Visuospatial (range 0–16)	14.6 ± 1.7	10.4 ± 2.5	<0.001	135.0	13.7 ± 2.0	10.2 ± 2.3	<0.001	273.0

Data are expressed as means ± SD.

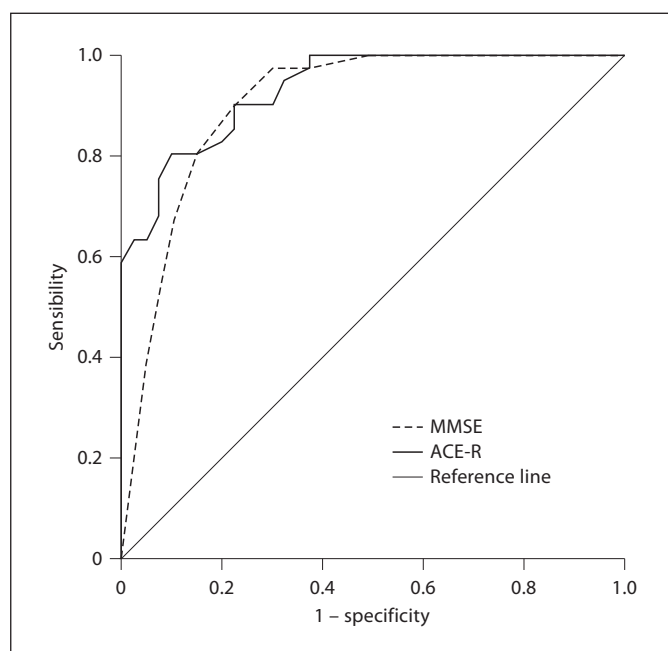


Fig. 1. Comparison of ROC curves of the Italian ACE-R and MMSE in the young-old group.

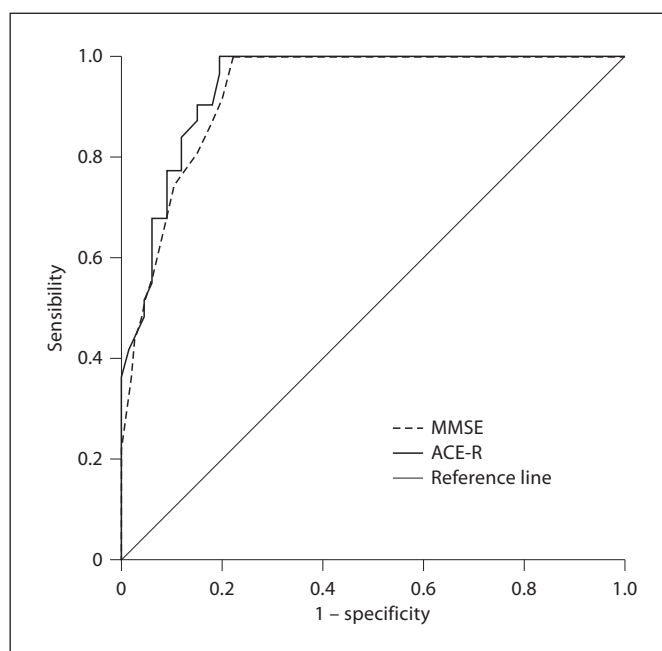


Fig. 2. Comparison of ROC curves of the Italian ACE-R and MMSE in the old-old group.

cutoff of 79/100 (sensitivity of 90% and specificity of 80%) was chosen for the ACE-R based on the calculations of sensitivity, specificity and PPV at different prevalence rates in the young-old sample (table 4).

ROC curves demonstrated that both the Italian ACE-R (AUC 0.944; 95% CI = 0.877–0.980) and MMSE (AUC 0.931; 95% CI = 0.860–0.972) discriminate controls from subjects with mild dementia in the old-old group (fig. 2).

A cut-off score of 60/100 for the ACE-R was associated with maximum sensitivity (82%) and specificity (100%) and was selected based on the calculations of sensitivity, specificity and PPV at different prevalence rates (table 4).

Table 4 also lists alternative cutoff scores along with their sensitivities, specificities, PPV and NPV in the young-old and old-old groups.

Table 4. Sensitivity, specificity, AUC and PPV at different prevalence rates of the cutoff of the Italian ACE-R total score in the young-old and in the old-old groups. Values in parentheses represent the respective NPV

Group	Cutoff	Sensitivity	Specificity	AUC	5%	10%	20%	40%
Age <75	78	87.5	80.5	0.936	19.1 (99.2)	33.3 (98.3)	52.9 (96.3)	74.9 (90.6)
	79*	90.0	80.5		56.8 (98.3)	73.5 (96.4)	86.2 (92.3)	94.3 (81.8)
	80	92.5	75.6		16.6 (99.5)	29.6 (98.9)	48.6 (97.6)	71.6 (93.8)
Age ≥75	59	75.7	100.0	0.931	100 (98.7)	100 (97.4)	100 (94.2)	100 (86.0)
	60*	81.8	100.0		100 (99.0)	100 (98.0)	100 (95.6)	100 (89.2)
	61	81.8	96.7		56.6 (99.0)	73.4 (97.9)	86.1 (95.5)	100 (88.8)

Discussion

The ACE-R can be considered a simple but highly valuable bedside test battery, easy to administer, with values of sensitivity and specificity good enough to be proposed as a screening tool for mild dementia in the elderly population.

The first aim of this study was to translate, adapt and validate the ACE-R into Italian in order to obtain a reliable screening test for detecting dementia. The second one was to evaluate the sensitivity and specificity of the Italian ACE-R in the elderly at different ages, specifically in young-old (<75 years) and old-old (≥75 years) subjects.

For the first aim, our results confirmed the psychometric properties of the Italian version of the ACE-R as well as its diagnostic accuracy. According to Swets' classification, $0.9 < AUC < 1$ is an index of a highly accurate test [39]. In this study, an AUC of 0.933 in the young-old and of 0.904 in the old-old was found, suggesting that the battery is excellent to detect mild dementia in both groups.

Although the MMSE emerges as the most commonly used screening test worldwide, its advantages and disadvantages in evaluating cognitive functions are still debated [40, 41]. The MMSE is widely translated and internationally used, quickly administered and easily scored also by nonexperts, suitable for comparison between studies, effective to measure general cognitive ability, available with different norms, statistically robust and freely available. At the same time, it has been found that it has an unstable interrater reliability, heavy reliance on total scores while differing cutoff scores are used, too lengthy for general practice, little sensitive to differentiating type of dementia, with important ceiling and floor effects and a limited range score [40]. The ACE-R is an expansion of the MMSE, proposed to maintain its advantages and compensate for its disadvantages. The ACE-R

explores more cognitive domains compared to MMSE [41] and the different subcores offer a more complete description of the patient's cognitive profile to clinicians, both from a qualitative and a quantitative point of view. Like the MMSE, the ACE-R is brief, easy to administer, freely and widely available and different alternative versions have been developed in order to avoid the learning effect in follow-up studies. Since it contains the MMSE items, ACE-R can be used to be comparable with previous studies allowing calculation of the MMSE score.

Regarding the second goal of the study, to our knowledge this is the first research specifically focused on the use of ACE-R in old-old subjects – the fastest growing age group with the maximum prevalence and incidence of dementia particularly in western countries [42] – to evaluate its reliability as a screening test for dementia. For these epidemiological reasons, it is extremely important to propose and validate simple but accurate screening tools for detecting cognitive problems in the elderly and to define normative data on cognitive performances in the old-old group [43–45].

In this study, two different cutoffs, 79 for the young-old group and 60 for the old-old group, discriminate cognitively healthy subjects from those with mild dementia well. The two cutoff points did not match exactly those previously proposed in studies performed in other countries [14–20]. This can be explained by the differences related to setting, type and severity of dementia as well as to age, educational level and social-cultural background of the studied populations, factors that heavily influence cognitive functions in the elderly. In fact, studies on the cognitive reserve hypothesis [46–48] have demonstrated that education, adult-life occupational work complexity as well as late-life social network and leisure activities act at different periods across the life course contributing to increasing the neural reserve and promoting functionally more efficient cognitive networks to cope or compensate

sate with brain pathology and delay the onset of clinically evident dementia.

Our data confirm the need for different cutoff points reflecting sociodemographic and age effects for a correct use of the test when screening for dementia. With respect to sensitivity, the Italian ACE-R obtained a better value in the young-old (90%) than in the old-old group (82%), an aspect probably due to the different representations of dementia subtypes in the two samples FTD being observed more frequently in the young-old group, in accordance with the epidemiology of this type of dementia. Nevertheless, the specificity in discriminating subjects with dementia in the old-old group reached 100% regardless the rate of prevalence.

Some limitations of the study must be acknowledged. Firstly, the frequency of types of dementia was not comparable in the two age-stratified samples, with a lower representation of vascular dementia in the young-old and of FTD in the old-old group. Secondly, our population had a low educational level which limits the applicability of these results in more educated subjects, although nowadays 5–8 years of schooling is the most commonly observed educational level in the Italian elderly population. According to the above limitations, future studies should

be carried out in larger samples of subjects with dementia to evaluate the specificity and sensitivity of ACE-R for different dementia types. Furthermore, these studies should be planned taking into account differences in education and age strata.

In conclusion, the Italian ACE-R is an easily administrable, reliable and sensitive screening tool, useful in discriminating cognitively healthy subjects from patients with mild dementia in a young-old and, above all, in an old-old population in which confounding variables, such as old age and low educational level, frequently obscure the diagnosis in clinical settings. To promote the clinical use of the Italian ACE-R, we are currently performing hospital-based as well as population-based studies that will provide normative data for the Italian population of different ages, educational levels and sociocultural backgrounds.

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