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ORIGINAL ARTICLE

The Addenbrooke's Cognitive Examination Revised (ACE-R) and its sub-scores: normative values in an Italian population sample

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Abstract The Addenbrooke's Cognitive Examination Revised (ACE-R) is a rapid screening battery, including five sub-scales to explore different cognitive domains: attention/orientation, memory, fluency, language and visuospatial. ACE-R is considered useful in discriminating cognitively normal subjects from patients with mild dementia. The aim of present study was to provide normative values for ACE-R total score and sub-scale scores in a large sample of Italian healthy subjects. Five hundred twenty-six Italian healthy subjects (282 women and 246 men) of different ages (age range 20–93 years) and educational level (from primary school to university) underwent ACE-R and Montreal Cognitive Assessment (MoCA). Multiple linear regression analysis revealed that age and education significantly influenced performance on ACE-R total score and sub-scale scores. A significant effect of gender was found only in sub-scale attention/orientation. From the derived linear equation, a correction grid for raw scores was built. Inferential cut-offs score were estimated using a non-parametric technique and equivalent scores (ES) were computed. Correlation analysis showed a good significant correlation between ACE-R adjusted scores with MoCA adjusted scores ($r = 0.612$, $p < 0.001$). The present study provided normative data for the ACE-R in an Italian population useful for both clinical and research purposes.

Keywords Addenbrooke's Cognitive Examination Revised · ACE-R · Normative values · Mild cognitive impairment cognitive dysfunctions · Normative data

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Introduction

Many brief screening tests have been developed to improve early diagnosis of dementia in primary care settings or in large-scale studies, when administration of comprehensive neuropsychological batteries is not feasible [1]. Ideally such screening tools should be brief, inexpensive and sensitive in identifying Mild Cognitive Impairment (MCI), and in disentangling dementias of different types, for instance in distinguishing Alzheimer-type disease from dementias in which frontal/executive deficits are prominent [2, 3].

Mini Mental State Examination (MMSE) is likely the most widely used screening test for detecting cognitive deterioration [4], but it has well-known limitations in screening multiple cognitive domains and in detecting early dementia [5, 6].

Based on the above considerations, the Addenbrooke's Cognitive Examination (ACE), [7] was developed to distinguish MCI from cognitive changes of normal aging [8] and types of dementia among each other [9–12].

The Addenbrooke's Cognitive Examination Revised (ACE-R), specifically developed to improve sensibility and specificity of the ACE, is a brief (15–20 min) cognitive test

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including the same subtests as MMSE, but with additional measures that allow obtaining five sub-scores, each for a single cognitive domain: attention/orientation, memory, fluency, language and visuospatial. This revision proved to be useful in screening patients with possible degenerative dementias, or with MCI [2, 8]. Moreover, the availability of sub-scores extended possible employment of ACE-R even to early assessment of patients with vascular brain lesions. For instance, ACE-R has been demonstrated useful to detect impairment in visuospatial, attention and executive domains in acute stroke patients [13]. Moreover, the language sub-scale of ACE-R has a satisfactory sensitivity and specificity, as a screening tool for aphasia in stroke patients compared with other screening tests [14].

ACE-R has been translated into different language [15–17], including Italian [18]. The Italian version maintained good sensitivity and specificity for identifying early dementia in the young-old and old-old population [19]. Recently, the normative data for the total score of ACE-R Italian version have been derived from a sample of cognitively healthy subjects ranging from 60 to 93 years [20], whereas normative data for sub-scores are not available yet.

The present study was designed to provide normative data for the total score and the five domain sub-scores of ACE-R Italian version [18] in a large sample of cognitively healthy subjects covering a wide age-range (20–93 years), similar to that assessed for other screening tools usually used in Italian clinical practice (e.g., [21–24]).

Following consolidated analytical procedures [25], a correction grid is proposed to take into account the influence of the main sociodemographic variables (gender, age and education) on raw scores and a transformation of adjusted scores into equivalent scores (ES) is proposed to compare the performance on ACE-R Italian version with other tests. Moreover, inferential cut-off scores are provided for ACE-R total score and for each cognitive domain.

Methods

Subjects

We selected for the study subjects who were in good health, had no brain injury, depression, alcohol or/and drug abuse, severe medical conditions (e.g., neoplasms, severe organ insufficiency), stroke, clinically evident dementia and achieved a normal score on Montreal Cognitive Assessment (MoCA age- and education-adjusted score >15.5) [23]. Individuals with mild hypertension and well-compensated type II diabetes were not excluded. Five hundred and twenty-eight healthy Italian volunteers, distributed across age classes (age range 20–93 years), gender (282 women and 246 men) and education levels (from primary school to university) took part in this study. Mean age of the sample was 52.33 years (SD 18.12), and mean formal education was 10.87 years (SD 5.15). Adjusted MoCA score was 23.80 (SD 3.27). The distribution of the sample for age and education is reported in Table 1.

Informed consent was obtained from all individual participants included in the study.

Materials and procedure

After having completed MoCA, all subjects were individually assessed on the ACE-R in a quiet room. ACE-R incorporates all items of MMSE (and it is possible to calculate a MMSE total score after administration of ACE-R), but it has been expanded to encompass 26 components that are combined to produce five sub-scores exploring the following cognitive domains: attention/orientation (score range 0–18), memory (score range 0–26), fluency (score range 0–14), language (score range 0–26) and visuospatial (score range 0–16). ACE-R maximum score is 100, obtained by adding the above sub-scores [8]. In the present study, we adopted standardized administration and scoring procedures [18].

Statistical analysis

ACE-R total score and sub-scale scores have been analyzed by means of simultaneous multiple regressions to check the influence of age, education and gender. After transforming the concomitant variables, a linear regression model was computed for each score to reduce the residual variance. The effects of age and education level (expressed as years of schooling) were explored after logarithmic, quadratic and reciprocal transformation and the effect of each variable was weighed within the complete model by partialing out the effect common with the other variables. Bonferroni correction for multiple comparisons was applied to reduce possibility of type-I error, and variables were included in the model only when the significance level related to each of them was lower than or equal to 0.017. We, adopting the results of the best regression models, developed a regression equation for computing an adjusted score for each subject. We considered a non-parametric procedure [26] to evaluate unidirectional tolerance limits that can classify a given score as normal or abnormal with confidence set at 95 % [27]. According to the procedure described by Ackerman [28], we have computed separately the outer and inner tolerance, while the scores including between the inner and outer limits are defined “borderline scores”, because a controlled judgment cannot be expressed. Cut-

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Table 1 Demographic distribution of the sample

Education (years)	Age (years)														
	20–29		30–39		40–49		50–59		60–69		70–79		80–		Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
1–3	–	–	–	–	5	2	4	8	4	4	6	6	4	8	51
4–5	1	3	–	2	2	5	4	7	5	19	3	9	3	12	75
6–8	6	5	7	7	8	10	6	12	12	11	8	6	6	3	107
9–13	10	14	11	10	12	15	23	20	8	8	4	6	3	3	147
>13	22	14	20	13	10	8	8	16	14	10	5	4	2	2	146
Total	39	36	38	32	37	40	45	63	43	52	26	31	18	28	528

off value was defined the score at which or below which the probability than an individual belongs to the normal population is less than 0.05 [29]. Since the use of the adjusted scores is more informative when it is standardized, we have converted the adjusted scores into Equivalent Scores (ES) [27]. ES correspond to a five-point interval scale divided as follows: 0 indicates a performance to the worst 5 % of the population; 4 indicates scores higher than the median value of the whole sample; 1, 2 and 3 are obtained by dividing into three equal parts the area of the distribution between 0 and 4 with reference to the percentile partition of the left half of a "divert" normal distribution [25]. A correction grid was built for any combination of age level (by 10-year steps), educational level (according to the Italian schooling system) and gender, to allow adjustment of the raw scores of newly tested individuals according to demographic variables. Spearman's non-parametric correlation analysis was performed to investigate the association of adjusted ACE-R total score with adjusted MoCA total score and adjusted MMSE total score (computed from the corresponding items included in ACE-R). Effect size for the correlation coefficient was defined by the following criteria: $r_{rho} < 0.3$ weak; $r_{rho} = 0.3$–0.5 moderate; $r_{rho} > 0.5$ strong [30].

Results

The distribution of ACE-R total score and of the five sub-scores was skewed, with a longer left tail. The individual regression analyses (Table 2) showed that the square root or reciprocal transformation of education (in years) and the logarithmic transformation of age [log10 (100 − age)] were the most effective in reducing residual variance, while the effect of the gender was maximum when it was not transformed. The influence of age and education was always significant, whereas gender significantly affected only the attention and orientation domains, with an advantage for men. On these bases, we calculated the best linear models relating the dependent variable (ACE-R total score and sub-scale scores) and including the most suitable transformations of independent variables (Table 3). By reversing the signs of the regression coefficients, the adjustment factors for each level of age, education and, if needed, gender can be derived. For a sample of 528 subjects and using a non-parametric procedure, outer and inner tolerance limits are defined by values corresponding to the 19th and 35th worst observations (Table 4). Adjusted ACE-R total score and sub-scale scores lower than or equal to outer tolerance limit, or cut-off point, can be considered abnormal because the region of tolerance includes also value of 19th worst observation [27]. Adjusted ACE-R total score and sub-scale scores higher than 35th indicate a normal performance, while intermediate scores indicate a borderline performance, which in our study was obtained by 3.03 % of the sample.

We computed the corrections grids for any combination of age (by 10-year steps), educational level (according to the Italian schooling system) and gender (when necessary) to allow adjustment of raw scores of newly tested individuals (Table 5). For individuals with demographic characteristics not included in the correction grid the, it is possible to use the original linear models shown in Table 4 (after reversing the signs of the parameters), but in this case adjustment factors should be treated with caution. ES, the number of subjects included within each ES (density) and cumulative frequency of subjects comprised from 0 to 1, 2, 3 and 4 are shown in Table 6.

Adjusted ACE-R total score was positively correlated with adjusted MoCA total scores ($r_{rho} = 0.568$, $p < 0.001$) and adjusted MMSE score ($r_{rho} = 0.596$, $p < 0.001$; mean adjusted MMSE score was 28.33 (SD 1.78) in the present sample).

Discussion

ACE-R, as well as MoCA, is considered useful for screening degenerative dementias when shorter tests are inconclusive [31], and its sub-scales can be useful to screen impairments in specific areas of cognitive functioning [13, 14]. Based on the above considerations, in the present

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Table 2 Mean scores (±SD) and the effects of age, education and gender on Addenbrooke's Cognitive Examination Revised (ACE-R) total score and cognitive domain sub-scores

Total ACE-R score	Mean score: 87.91 ± 11.15		
Individual regression analysis	$\log_{10}(100 - \text{age})$	$F(1526) = 350.447$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1526) = 304.503$	$p < 0.001$
	Gender	$F(1526) = 9.110$	$p = 0.003$
Simultaneous regression analysis	$\log_{10}(100 - \text{age})$	$F(1524) = 206.634$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1524) = 163.463$	$p < 0.001$
	Gender	$F(1524) = 1.647$	ns
Attention and orientation	Mean score: 17.45 ± 1.29		
Individual regression analysis	$\log_{10}(100 - \text{age})$	$F(1526) = 93.711$	$p < 0.001$
	$1/\text{education}$	$F(1526) = 93.743$	$p < 0.001$
	Gender	$F(1526) = 9.775$	$p = 0.002$
Simultaneous regression analysis	$\log_{10}(100 - \text{age})$	$F(1524) = 47.248$	$p < 0.001$
	$1/\text{education}$	$F(1524) = 47.737$	$p < 0.001$
	Gender	$F(1524) = 5.812$	$p = 0.016$
Memory	Mean score: 21.66 ± 4.52		
Individual regression analysis	$\log_{10}(100 - \text{age})$	$F(1526) = 257.215$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1526) = 239.272$	$p < 0.001$
	Gender	$F(1526) = 9.041$	$p = 0.003$
Simultaneous regression analysis	$\log_{10}(100 - \text{age})$	$F(1524) = 138.230$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1524) = 118.956$	$p < 0.001$
	Gender	$F(1524) = 1.937$	ns
Fluency	Mean score: 10.18 ± 2.68		
Individual regression analysis	$\log_{10}(100 - \text{age})$	$F(1526) = 195.269$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1526) = 214.885$	$p < 0.001$
	Gender	$F(1526) = 1.671$	ns
Simultaneous regression analysis	$\log_{10}(100 - \text{age})$	$F(1525) = 95.617$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1525) = 112.496$	$p < 0.001$
Language	Mean score: 24.28 ± 2.87		
Individual regression analysis	$\log_{10}(100 - \text{age})$	$F(1526) = 234.936$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1526) = 144.959$	$p < 0.001$
	Gender	$F(1526) = 9.626$	$p = 0.002$
Simultaneous regression analysis	$\log_{10}(100 - \text{age})$	$F(1524) = 135.642$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1524) = 54.605$	$p < 0.001$
	Gender	$F(1524) = 3.160$	ns
Visuospatial	Mean score: 14.31 ± 2.05		
Individual regression analysis	$\log_{10}(100 - \text{age})$	$F(1526) = 147.077$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1526) = 134.727$	$p < 0.001$
	Gender	$F(1526) = 3.312$	ns
Simultaneous regression analysis	$\log_{10}(100 - \text{age})$	$F(1525) = 72.882$	$p < 0.001$
	$\sqrt{\text{education}}$	$F(1525) = 61.852$	$p < 0.001$

study, we provided normative data valid for a wide age range both for ACE-R total scores and for single sub-scores, thus allowing Italian clinicians to fully exploit this tool.

Since one of the major features of the ACE-R is its sensitivity in identifying MCI, in the present study we took care to enroll participants without possible cognitive decline, and for this purpose we adopted as an inclusion criterion a normal score on the Italian version of the MoCA [23], which is considered sensitive to detect MCI. Moreover, we excluded subjects without any formal education, to avoid the huge and not necessarily linear effect of illiteracy on performance on neuropsychological measures [32]. Last, although we excluded participants affected by

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Table 3 Best linear models relating Addenbrooke's Cognitive Examination Revised (ACE-R) total score and cognitive domain sub-scores to the most suitable transformation of age, education and gender

Test	Best linear model	R	R^2
Total ACE-R score	$87.91 + 26.701\ x\ [\log_{10}(100 - \text{age}) - 1.64] + 5.577\ x\ (\sqrt{\text{education}} - 3.18)$	0.739[a]	0.546
Attention and orientation	$17.45 + 1.887\ x\ [\log_{10}(100 - \text{age}) - 1.64] - 3.655\ x\ (1/\text{education} - 0.12) - 0.240\ x\ (\text{gender} - 0.53)$	0.482[a]	0.232
Memory	$21.66 + 9.704\ x\ [\log_{10}(100 - \text{age}) - 1.64] + 2.119\ x\ (\sqrt{\text{education}} - 3.18)$	0.676[a]	0.457
Fluency	$10.18 + 5.027\ x\ [\log_{10}(100 - \text{age}) - 1.64] + 1.261\ x\ (\sqrt{\text{education}} - 3.18)$	0.632[a]	0.399
Language	$24.28 + 6.539\ x\ [\log_{10}(100 - \text{age}) - 1.64] + 0.988\ x\ (\sqrt{\text{education}} - 3.18)$	0.615[a]	0.378
Visuospatial	$14.31 + 3.608\ x\ [\log_{10}(100 - \text{age}) - 1.64] + 0.769\ x\ (\sqrt{\text{education}} - 3.18)$	0.549[a]	0.301

[a] In the F tests p is in all cases <0.001

Table 4 One-tailed non-parametric tolerance limits for the upper 5 % (worse performance) of the adjusted times 95 % confidence

Test	Outer limits ($\beta t \geq 0.95$, nineteenth observation)	Borderline scores	Inner limits ($\beta t \leq 0.95$, thirty-fifth observation)
Total ACE-R score	≤71.78	71.79–76.47	≥76.48
Attention and orientation	≤14.73	14.74–15.65	≥15.66
Memory	≤14.47	14.48–16.01	≥16.02
Fluency	≤6.01	6.02–6.74	≥6.75
Language	≤18.83	18.84–20.37	≥20.38
Visuospatial	≤10.73	10.74–11.44	≥11.45

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severe medical conditions, we included in our sample patients with mild hypertension or non-complicated diabetes to avoid assessing a "hyper-normal" sample [24].

In the first validation study of the ACE-R Italian version, two cut-offs have been established for young-old and old-old subjects (79 and 60) [19], whereas in a subsequent study a single age- and education-adjusted cut-off point ≤66.92 for ACE-R total score has been proposed, but this only applies to subjects aged 60–93 years [20]. The cut-off value of ≤71.78 for ACE-R total score found in the present study is higher than that reported in the original study on older subjects (≤66.92) [20], but such values are considerably lower than the three cut-offs identified in literature for English-speaking populations (88, 82 and 75) [33]. These discrepancies may depend on cultural and linguistic factors related to the Italian translation of original ACE-R, whereas the higher cut-off value observed in our study, compared to previous Italian normative study [20] might depend on younger age of our sample (mean age 52.33 vs 72.91). Consistent with previous studies in several ethnic groups [33], we observed that the ACE-R total score is significantly affected by age and schooling but not by gender.

Since ACE-R allows producing five sub-scores for selected cognitive domains, here we evaluated the possible effects of sociodemographic variables on such sub-scores and provided normative data that were not yet available for the Italian version. As often reported in Italian normative studies [27], we observed that age and education influence performance on all cognitive sub-scores, thus underlining those demographic features must be taken into account in evaluation of raw scores obtained by old and/or less educated individuals.

As in the Brazilian normative study [34], gender had a significant effect on the attention/orientation sub-score only, with higher scores in males than in females. This finding is consistent with that reported in an Italian normative study on a paper-and-pencil attentional test [25], and in a recent Italian normative study on MoCA, as far as the attention domain is concerned [23]. Interestingly, gender did not affect the remaining sub-scores of ACE-R, analogously to what observed for the Italian version of MoCA [23].

The correlation between adjusted ACE-R total score and adjusted MoCA total scores demonstrated a significant and good association between the two instruments, consistent with the idea that they are useful in evaluating cognitive status, although the ACE-R contains more memory and language items, whereas the MoCA also includes abstraction and has more attentional tests [2]. A positive correlation, of similar magnitude as the previous one, has also been found between adjusted ACE-R total score and adjusted MMSE total score. This last finding is explained by the partial overlap of the two scales.

In conclusion, the present study provided Italian clinicians with normative data for ACE-R total score and sub-

Table 5 Correction grid for Addenbrooke's Cognitive Examination Revised (ACE-R) total score and cognitive domain sub-scores, according to age, education and gender

Education (years)	Age (years)						
	20–29	30–39	40–49	50–59	60–69	70–79	80–
Total ACE-R score							
1–3	3.74*	5.39*	7.32	9.63	12.52	16.39	22.30
4–5	−0.35	1.29	3.21	5.52	8.42	12.29	18.19
6–8	−3.27	−1.62	0.29	2.60	5.50	9.37	15.27
9–13	−7.00	−5.35	−3.42	−1.11	1.77	5.64	11.55
>13	−10.48	−8.83	−6.91	−4.60	−1.70	2.16	8.06
Attention and orientation (male)							
1–3	1.18*	1.29*	1.43	1.59	1.80	2.07	2.49
4–5	−0.23	−0.11	0.02	0.18	0.38	0.66	1.08
6–8	−0.52	−0.40	−0.27	−0.10	0.09	0.37	0.78
9–13	−0.71	−0.59	−0.46	−0.29	−0.09	0.17	0.59
>13	−0.57	−0.45	−0.32	−0.16	0.04	0.31	0.73
Attention and orientation (female)							
1–3	1.42*	1.53*	1.67	1.83	2.04	2.31	2.73
4–5	0	0.12	0.26	0.42	0.62	0.90	1.32
6–8	−0.28	−0.16	−0.03	0.13	0.33	0.61	1.02
9–13	−0.47	−0.35	−0.22	−0.05	0.14	0.41	0.83
>13	−0.57	−0.45	−0.32	−0.16	0.04	0.31	0.73
Memory							
1–3	1.52*	2.12*	2.82	3.66	4.71	6.12	8.82
4–5	−0.03	0.56	1.26	2.10	3.15	4.56	6.71
6–8	−1.14	−0.54	0.15	0.99	2.05	3.45	5.60
9–13	−2.55	−1.95	−1.25	−0.41	0.63	2.04	4.18
>13	−3.88	−3.28	−2.58	−1.74	−0.68	0.71	2.86
Fluency							
1–3	1.08*	1.39*	1.75	2.19	2.73	3.46	4.58
4–5	0.15	0.46	0.83	1.26	1.81	2.54	3.65
6–8	−0.50	−0.19	0.17	0.60	1.15	1.88	2.99
9–13	−1.34	−1.03	−0.67	−0.23	0.30	1.03	2.14
>13	−2.13	−1.82	−1.45	−1.02	−0.47	0.25	1.36
Language							
1–3	0.23*	0.63*	1.11	1.67	2.38	3.33	4.77
4–5	−0.49	−0.08	0.38	0.94	1.65	2.60	4.05
6–8	−1.00	− 0.60	−0.13	0.43	1.14	2.08	3.53
9–13	−1.67	−1.26	−0.79	−0.22	0.48	1.42	2.87
>13	−2.28	−1.88	−1.41	−0.84	−0.13	0.81	2.25
Visuospatial							
1–3	0.53*	0.75*	1.01	1.32	1.72	2.24	3.04
4–5	−0.03	0.19	0.45	0.76	1.15	1.67	2.47
6–8	−0.43	−0.21	0.04	0.36	0.75	1.27	2.07
9–13	−0.94	−0.72	−0.46	−0.15	0.23	0.76	1.55
>13	−1.42	−1.20	−0.94	−0.63	−0.24	0.28	1.07

Values marked by the asterisk (*) should be taken cautiously because they were obtained by extrapolation from the formulas below

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Table 6 Equivalent scores (ES) for adjusted values on Addenbrooke's Cognitive Examination Revised (ACE-R) total score and cognitive domain sub-scores

ES	Interval	Cumulative frequency	Density
Total ACE-R score			
0	≤71.78	19	19
1	71.79–79.86	61	42
2	79.87–84.75	145	84
3	84.76–88.89	264	119
4	>88.89	528	264
Attention and orientation			
0	≤14.73	19	19
1	14.74–16.34	61	42
2	16.35–17.30	145	84
3	17.31–17.64	264	119
4	>17.64	528	264
Memory			
0	≤14.47	19	19
1	14.48–17.85	61	42
2	17.86–20.16	145	84
3	20.17–21.99	264	119
4	>21.99	528	264
Fluency			
0	≤6.01	19	19
1	6.02–7.54	61	42
2	7.55–9.13	145	84
3	9.14–10.37	264	119
4	>10.37	528	264
Language			
0	≤18.83	19	19
1	18.84–21.83	61	42
2	21.84–23.62	145	84
3	23.63–24.57	264	119
4	>24.57	528	264
Visuospatial			
0	≤10.73	19	19
1	10.74–12.32	61	42
2	12.33–13.68	145	84
3	13.69–14.64	264	119
4	>14.64	528	264

scale scores, applicable to a population aged 20–93 years. Since age, education and gender significantly influence performance on ACE-R total score and on sub-scale scores, specific reference values must be applied when using ACE-R in research and clinical contexts.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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