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Optimal Cutoff Scores for Alzheimer's Disease Using the Chinese Version of Mini-Mental State Examination Among Chinese Population Living in Rural Areas

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Abstract

To explore the optimal cutoff score for initial detection of Alzheimer's Disease (AD) through the Chinese version of Mini-Mental State Examination (CMMSE) in rural areas in China, we conducted a cross-sectional study within the Linxian General Population Nutritional Follow-up study. 16,488 eligible cohort members participated in the survey and 881 completed the CMMSE. Among 881 participants, the median age (Interquartile range) was 69.00 (10.00), 634 (71.92%) were female, 657 (74.57%) were illiterate, 35 (3.97%) had 6 years of education or higher, and 295 (33.48%) were diagnosed with AD. By reducing the CMMSE criteria for illiterate to 16 points, primary school to 19 points, and middle school or higher to 23 points, the efficiency of Chinese version of Mini-Mental State Examination can be significantly improved for initial detection of AD in rural areas in China, especially in those nutrition deficient areas.

Keywords

Alzheimer's disease, Chinese version Mini-Mental State Examination, Chinese population, cutoff scores, rural areas, ROC analysis

Introduction

In 2015, over 46 million people live with dementia worldwide, and this number will almost double every 20 years, to 74.7 million in 2030 and 131.5 million in 2050.[1] Approximate 94% of these people living in low- and middle-income countries are cared for at home, because the incomplete health and care systems often provide limited or no support to these people or their families according to the World Alzheimer Report 2015.[1] However, China had over 9.5 million people diagnosed with dementia and over 5.69 million diagnosed with Alzheimer's disease (AD), placing China with the most diagnosed cases of AD in the world.[2-4] China's AD burden will only increase over the coming years due to the 1-child policy, aging population, large amounts of internal migration, and fewer working adults able to provide continuing care, especially in rural areas.[2] Previous estimates by the World Alzheimer Report 2010 may have underestimated the burden of disease by half in China.[2,5] Given the increasing age of the Chinese population, the Chinese State Council estimates that there will be over 300 million Chinese people over the age of 60 by 2025 and more than 20 million diagnosed with AD in 2050.[6-8] Therefore, it is necessary to find an efficiency screening method, which can identify early signs of AD.

The Mini-Mental State Examination (MMSE) is the most widely used cognitive test for screening cognitive disorders.[9-11] Several studies have been conducted in China during the past few decades to assess the efficiency of culturally adapted Chinese version of MMSE (CMMSE) for identifying participants with dementia using different optional cutoff scores.[12-14]

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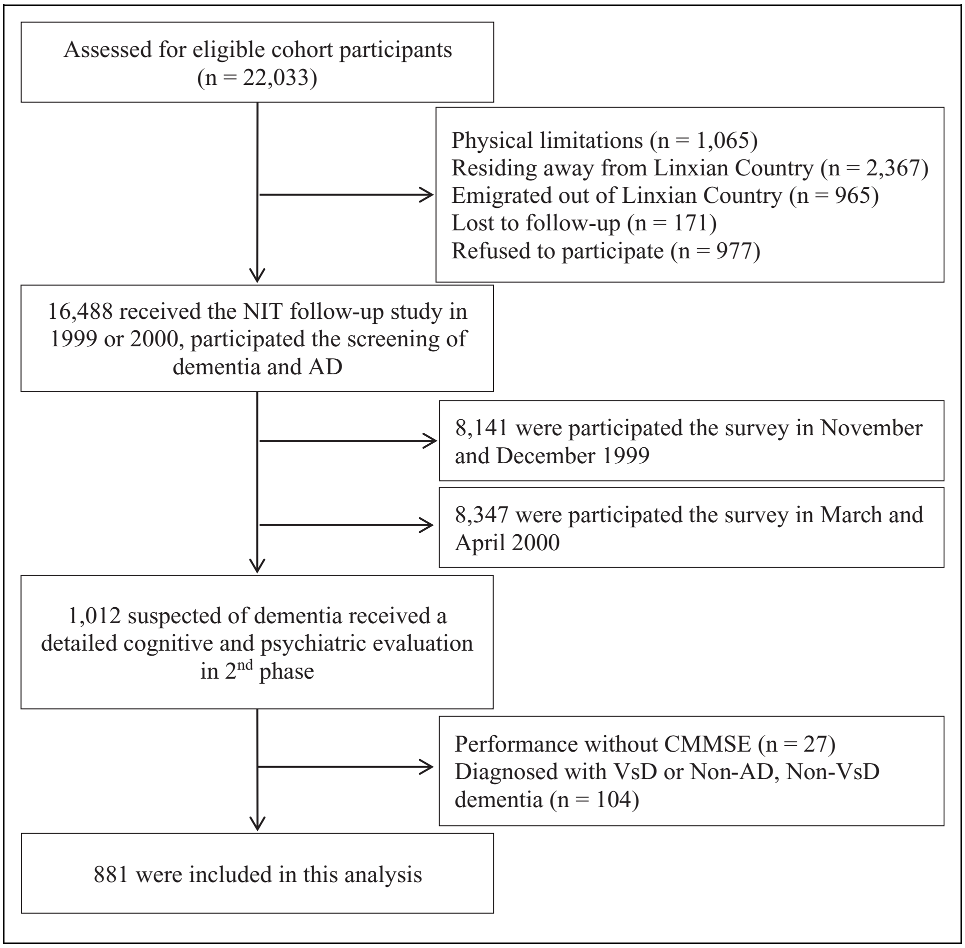

Figure 1. Flow diagram of the eligible nutritional invention cohort members in 1999 to 2000.

There is still no unified conclusive criteria used.[15-18] Previous studies have shown that different cutoff scores are necessary for different education levels.[18-20] This is especially true in China where there exists wide gaps in elderly population education levels.[21,22] Given this information, the current investigation aims to explore the optimal criteria for the CMMSE stratified for different education levels in which clinicians may consider referring their patients for further evaluation of possible AD diagnosis.

Materials and Methods

Ethics Statement

The Linxian Alzheimer and Parkinson's Study (LAPS) and the additional work described here were approved by the Human Subjects Review Board of Cancer Hospital Chinese Academy of Medical Sciences. Participants in the LAPS underwent a written informed consent process indicating their willingness to participate and their understanding of the procedure and general aim of the study at enrollment. For illiterate participants, informed consent was explained by investigators until participant fully understood the purpose and their involvement in the study; participants were given sufficient time to understand and ask any question regarding the study, once completed, participants then gave a fingerprint as verification of understanding of informed consent. All participants' consent was obtained prior to the survey, and all the studying process obeyed the Declaration of Helsinki without violation of any ethical principle.

Original Studies and Study Population

The original substudy "Linxian Alzheimer and Parkinson's Study (LAPS)" was a cross-sectional study conducted among participants in the Linxian Nutritional Intervention Trial (NIT) in 1999 to 2000 by the Cancer Institute Chinese Academy of Medical Sciences, Dalian Medical University, and Institute of Mental Health Peking University cooperates with National Cancer Institute of American.[17,19,23] The NIT began in 1986 due to the high mortality of esophageal cancer in Linxian, a rural area of Henan province of China.[19,23-26] This trial sought to supplement the diets of 29 584 participants with vitamins to study the effects of nutrition supplementation on the incidence of esophageal cancer. These initial participants were studied from 1986 to 1991 and were adults aged between 40 to 69 years with no history of malignancy or other debilitating disease, taking any vitamin, mineral supplements regularly, or were taking any medications. In 1999, 22 033 of the original study participants were available for a cross-sectional LAPS substudy examining the prevalence of AD and other dementias. A total of 16 488 chose to participate in this study, which was completed between December 1999 and April 2000.[17,19] Additional enrollment details are shown in Figure 1.

Diagnostic Procedure

To diagnose participants with AD, a 2-phase procedure was used. In the first phase, all participants underwent a dementia screening using either the CMMSE or, if unable to complete CMMSE due to physical inability, Adult Daily Living (ADL). In addition to the CMMSE or ADL screen, participants had demographic medical history information taken and underwent a brief neurologic examination. The CMMSE is a culturally adapted version of MMSE and has been tested in Chinese population and found to have excellent reliability and validity; most of the items on the CMMSE can be directly applied in Linxian, which has been published elsewhere.[19] Considering a larger proportion of illiterate participants in this study, changes were necessary for the CMMSE's items, which require participants to read or write. The item – "please write a sentence item" was changed to "please write or say a complete sentence", and the read and obey item "close your eyes" was also changed so that participants were told to "close their eyes".

Participants who scored >16 on the ADL scale were considered screen positive.[19,27] For CMMSE, positive screen was stratified by education level, which adopted cutoff points according to the respondent's level of education in Linxian—illiterate (<1 year of education) score: 18, primary school (1-6 years of education) score: 21, and middle school or higher (>6 years of education) score: 25.[9,19,27] The ADL and CMMSE were administered face-to-face by research associates trained by Doctor of Philosophy psychologists.

All participants who were screened positive by CMMSE or ADL underwent a detailed cognitive and psychiatric evaluation by Doctor of Medicine neurologists. Then these participants were officially diagnosed based on the detail examination according to the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria.[28,29]

Statistical Analysis

Demographics of the study population were determined using the McNemar test and χ^2 test. Interquartile range (IQR) was calculated to determine the median scores on the CMMSE stratified by age-group, sex, and education. These data were then analyzed with a nonparametric 1-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA[30] to determine whether there was a significant difference between age, sex, and education on CMMSE scores.

To identify optimal CMMSE cutoff scores, data were reanalyzed, and receiver operating characteristic (ROC) analysis was performed.[31,32] After identifying optimal CMMSE scores, the sensitivity, specificity, and area under the ROC curve (AUC) were used as indicators. Sensitivity, specificity, and AUC were also calculated for original CMMSE cutoff score used at the time of LAPS substudy, Peking Union Medical College Hospital (PUMCH) criteria, the Shanghai Mental Health Center (SHMHC). After calculating these indicators, a *Z* test was used to compare the differences between the AUCs for detecting AD or Non-AD.

Due to the possible presence of confounding variables, subgroup analysis was used to analyze the education level and age to determine the generality of the study. All calculations were conducted using SAS version 9.4 service pack 1 (SAS Institute Inc, Cary, North Carolina). All reported *P* values are 2 sided, and *P* value <.05 was considered statically significant.

Results

Participants

Figure 1 describes the recruitment process of the original LAPS substudy and subsequent analysis. Of the original cohort, 22 033 individuals were eligible for the substudy and only 16 488 were able and agreed to participate in the study. One thousand twelve were suspected of dementia based on the CMMSE and ADL scoring criteria and received a detailed cognitive psychiatric evaluation.[17,19,23] Twenty-seven of those were screened positive based on the ADL and were excluded from the final analysis, and of the 985 participants screened by CMMSE, 104 were diagnosed with vascular dementia (VsD), non-AD, or non-VsD dementia and then excluded from the final analysis, leaving 881 total participants included in the final analysis. Of these 881 included, 301 were diagnosed by neurologists using the NINCDS-ADRDA criteria as having AD.

Table 1 displays the major demographic characteristics of 881 participants included in the analysis. Median age for participants with AD was 72, for those without AD, age was 68 and was statistically significant. Difference in age-groups was also statistically significant. There existed no significant differences between sex and education level.

Table 2 displays the median CMMSE scores and IQR based on age, sex, and education level for participants with AD versus non-AD participants. Median scores based on the education levels for illiterate with dementia: 14.50, primary school: 17.00, and for middle school or higher education: 22.00. In comparison to the non-AD group, median scores were illiterate: 16.00, primary school: 19.00, and middle school or greater: 24.00, and all results were statistically significant.

Outcome Data

Based on the clinical diagnosis, 295 (33.48%) of the 881 were diagnosed with AD and 586 (66.52%) were deemed nondementia. Before adjustment of CMMSE screening criteria, 742 (84.22%) of the 881 were deemed positive; after adjustment in criteria, 392 (44.49%) of the participants were

Table 1. Major Demographic Characteristics of the 881 Participants in AD and No-Dementia Group.

Demographic Characteristics	Eligible Participants (N = 881)		*P* Value
	AD (N1 = 295)	No Dementia (N2 = 586)	
Age, median (IRQ[a]), years	72.00 (10.00)	68.00 (11.00)	<.0001[b]
Age category, n (%), years			<.0001[c]
<55	2 (7.14)	26 (92.86)	
55-64	39 (18.31)	174 (81.69)	
≥65	254 (39.69)	386 (60.31)	
Sex, n (%)			.6670[d]
Male	80 (32.39)	167 (67.61)	
Female	215 (33.91)	419 (66.09)	
Educational level, n (%), years			.0779[e]
Illiterate (<1 year)	232 (35.31)	425 (64.69)	
Primary school (1-6 years)	56 (29.63)	133 (70.37)	
Middle school or higher (>6 years)	7 (20.00)	28 (80.00)	

Abbreviations: AD, Alzheimer's disease; IQR, interquartile range.
[a]The age was presented as median (IQR).
[b]Z value: 6.4813.
[c]χ^2 value: 41.8012.
[d]χ^2 value: 0.1851.
[e]χ^2 value: 5.1036.

Table 2. Major Demographic Characteristics of the CMMSE Scores Among 881 Participants.

Demographic Characteristics	CMMSE Scores			*P* Value
	Total (IQR[a])	AD (IQR)	No Dementia (IQR)	
Age category, years				<.0001[b]
<55 (n = 28)	18.00 (3.50)	14.00 (8.00)	18.50 (4.00)	
55-64 (n = 213)	17.00 (4.00)	15.00 (4.00)	17.00 (5.00)	
≥65 (n = 640)	16.00 (3.50)	15.00 (4.00)	17.00 (4.00)	
Sex				<.0001[c]
Male (n = 247)	18.00 (6.00)	16.00 (4.50)	19.00 (6.00)	
Female (n = 634)	16.00 (3.00)	15.00 (3.00)	16.00 (2.00)	
Educational level, years				<.0001[d]
Illiterate (<1 year; n = 657)	16.00 (3.00)	14.50 (3.00)	16.00 (2.00)	
Primary school (1-6 years; n = 189)	19.00 (3.00)	17.00 (3.00)	19.00 (4.00)	
Middle school or higher (>6 years; n = 35)	23.00 (3.00)	22.00 (4.00)	24.00 (1.00)	

Abbreviations: AD, Alzheimer's disease; CMMSE, Chinese version of Mini-Mental State Examination; IQR, interquartile range.
[a]The CMMSE scores were presented as median (IQR).
[b]*F* value: 23.87.
[c]Z value: 10.946.
[d]*F* value: 144.42.

deemed positive screen. Table 3 displays the diagnosis of AD stratified by education level and number screened positive based on the original cutoff scores and adjusted cutoff scores.

Adjusted Criteria Results

The ROC analysis displays AUC before cutoff score adjustment and after CMMSE criteria adjustment. Preadjustment AUC was 0.588 (95% confidence interval [CI]: 0.555-0.621), and AUC after adjustment was 0.6888 (95% CI: 0.656-0.718). The sensitivity and specificity of preadjustment were 95.93% (95% CI: 93.0%-97.9%) and 21.67% (95% CI: 18.4%-25.2%), respectively, with positive predicted value (PPV) of 38.1% and negative predicted value (NPV) of 91.4%. After adjustment, the sensitivity, specificity, PPV, and NPV were 69.49% (95% CI: 63.9%-74.7%), 68.09% (95% CI: 64.1%-71.8%), 52.3%, and 81.6%, respectively. In addition, preadjusted CMMSE resulted in 12 (4.1%) false negatives and 459 (79.3%) false positives, and after adjustment, CMMSE yielded 90 (30.5%) false negatives and 187 (31.9%) false positives. Although referral rate for pre- and postadjustment CMMSE score was 33.5%, the actual detection rate of disease was much higher in the postadjustment CMMSE score (45.3%) versus preadjustment (68.6%). More detailed data regarding CMMSE pre- and postadjustment can be found in Table 4.

Table 3. Diagnosis of AD Based on Different Cutoff Scores of CMMSE.

		Before Adjustment		After Adjustment	
Educational Level, years	Clinical Diagnose of AD (%)[a]	Cutoff Scores	AD (%)[b]	Cutoff Scores	AD (%)[c]
Illiterate (<1 year; n = 657)	232 (78.64)	≤18	562 (75.74)	≤16	300 (76.53)
Primary school (1-6 years; n = 189)	56 (18.98)	≤21	152 (20.49)	≤19	82 (20.92)
Middle school or higher (>6 years; n = 35)	7 (2.37)	≤25	28 (3.77)	≤23	10 (2.55)

Abbreviations: AD, Alzheimer's disease; CMMSE, Chinese version of Mini-Mental State Examination.
[a]χ^2value: 5.1036, *P* value: .0779.
[b]χ^2value: 3.3812, *P* value: .1844.
[c]χ^2value: 4.0498, *P* value: .1320.

Table 4. Comparison of Different Cutoff Scores for Detecting the Alzheimer's Disease Based on CMMSE.

	Cutoff Scores of CMMSE for Detecting AD			
	Before Adjustment	After Adjustment	PUMCH[a]	SHMHC[b]
Sensitivity (%, 95% CI)	95.93 (93.0-97.9)	69.49 (63.9-74.7)	98.64 (96.6-99.6)	84.07 (79.4-88.1)
Specificity (%, 95% CI)	21.67 (18.4-25.2)	68.09 (64.1-71.8)	18.60 (15.5-22.0)	44.88 (40.8-49.0)
+LR	1.22	2.18	1.21	1.53
−LR	0.19	0.45	0.07	0.35
PPV (%)	38.1	52.3	37.9	43.4
NPV (%)	91.4	81.6	96.5	84.8
AUC (95% CI)	0.588 (0.555-0.621)	0.688 (0.656-0.718)	0.586 (0.553-0.619)	0.645 (0.612-0.676)

Abbreviations: AD, Alzheimer's disease; AUC, area under receiver-operating characteristic curve; CI, confidence interval; CMMSE, Chinese version of Mini-Mental State Examination; NPV, negative predicted value; +LR, positive likelihood ratio; PPV, positive predicted value; PUMCH, Peking Union Medical College hospital; SHMHC, Shanghai Mental Health Center.
[a]PUMCH in 3 educational levels (illiterate [<1 year], primary school [1-6 years], and middle school or higher [>6 years]) and the optimal CMMSE scores for detecting AD were ≤17, ≤19, and ≤21, respectively.
[b]SHMHC in 3 educational levels (illiterate [<1 year], primary school [1-6 years], and middle school or higher [>6 years]) and the optimal CMMSE scores for detecting AD were ≤19, ≤22, and ≤26, respectively. Difference AUCs between after adjustment and before adjustment (*P* < .001), PUMCH (*P* < .001), and SHMHC (*P* = .016).

Table 5. Cutoff Scores, Sensitivities, Specificities, and AUCs (95% CI) for Detecting AD Strategy by Educational Levels and Age Category.

AD Versus No Dementia	Cutoff Scores	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	AUC (95% CI)
Educational levels				
Illiterate (<1 year; n = 657)	16	69.40 (63.0-75.3)	67.29 (62.6-71.7)	0.683 (0.646-0.719)[a]
Primary school (1-6 years; n = 189)	19	71.34 (57.8-82.7)	68.42 (59.8-76.2)	0.699 (0.628-0.764)[a]
Middle school or higher (>6 years; n = 35)	23	57.14 (18.8-89.6)	78.57 (59.0-91.7)	0.769 (0.500-0.826)[b]
Age category, years				
<65 (n = 241)	[c]	68.85 (49.4-79.9)	73.50 (66.8-79.5)	0.697 (0.634-0.754)[a]
≥65 (n = 640)	[c]	70.08 (64.0-75.6)	65.28 (60.3-70.0)	0.677 (0.639-0.713)[a]

Abbreviations: AUC, area under receiver-operating characteristic curve; AD, Alzheimer's disease; CI, confidence interval.
[a]Significance level *P* value (area = 0.500) < .0001.
[b]Significance level *P* value (area = 0.677) = .1433.
[c]Cutoff scores from different educational levels—illiterate, cutoff scores = 18; primary school, cutoff scores = 21; middle school or higher, cutoff scores = 25.

Table 4 compares adjusted criteria versus preadjusted criteria, PUMCH, and SHMHC criteria. The PUMCH criteria yielded a sensitivity of 98.64% (95% CI: 96.6%-99.6%) and SHMHC 84.07% (95% CI: 79.4%-88.1%). The specificity for PUMCH and SHMHC was 18.60% (95% CI: 15.5%-22.0%) and 44.88% (95% CI: 40.8-49.0), respectively. The PPV for PUMCH and SHMHC was 37.9% and 43.4%, respectively. The NPV for PUMCH and SHMHC was 96.5% and 84.8%, respectively. The AUC for PUMCH and SHMHC was 0.586 (95% CI: 0.533-0.619) and 0.645 (95% CI: 0.612-0.676), respectively.

Subgroup Analysis

Table 5 displays subgroup analysis among education levels and age. There was no significant difference between age-group <55 and age-group 55 to 64, so these 2 were combined for subgroup analysis. Among participants <65 years of age (n = 241), use of the adjusted CMMSE resulted in sensitivity of 68.85% (95% CI: 49.4%-79.9%), specificity of 73.50 (95% CI: 66.8%-79.5%), and AUC of 0.697 (95% CI: 0.634-0.754). Among participants aged

≥65 years, sensitivity was 70.08% (95% CI: 64.0%-75.6%), specificity 65.28% (95% CI: 60.3%-70.0%), and AUC 0.677 (95% CI: 0.639-0.713).

Discussion

The purpose of this study was to determine the optimal cutoff score for the CMMSE to detect the presence of AD in elderly Chinese population stratified for education levels in rural areas. The sensitivity and specificity of the varying thresholds were analyzed and compared to the already established criteria for the CMMSE including the PUMCH criteria, SHMHC, and initially established LAPS CMMSE criteria. During the data analysis, we found that adjusted criteria had an increased specificity, PPV, and AUC over preadjusted criteria, PUMCH, and SHMHC criteria while maintaining a relatively high NPV.[33-36]

The optimization of a method that increases sensitivity and specificity is important and in a nonspecialist setting, striving to maintain a high NPV is very important statistically.[32] Therefore, the reduction in false-positive rates while improving the specificity of the CMMSE was our desired outcome. Adjusting the criteria increased the specificity from 21.67% to 68.09%. This new adjusted specificity is also higher than other models such as the PUMCH and SHMHC criteria with specificities of 18.60% and 44.88%, respectively. Although sensitivity decreased after our adjustment from 95.93% to 69.49% and it is lower than the PUMCH and SHMHC which were 98.64% and 84.07%, respectively, our PPV increased from 38.1% to 52.3% and was higher than PUMCH and SHMHC PPVs, which were 37.9% and 43.4%, respectively. Finally, the NPV, while it did decrease after the adjustment from 91.4% to 81.6%, was also lower than the PUMCH and SHMHC NPVs, which were 96.5% and 84.8%, respectively, however, the adjustment to the criteria did yield a higher AUC than the other criteria including the PUMCH and SHMHC (Table 5).

Overall, our specificity, positive likelihood ratio, PPV, and AUC after adjustment were significantly higher than before. Given these results, this criterion may be optimal for the evaluation of cognition in rural Chinese population. Although we found a high prevalence of disease (33.48% of the study population) that can have an effect on the performance of screening examinations, this high prevalence of disease should only affect the PPV and the NPV of screening test while the sensitivity and specificity of the examinations should be unaffected.[37,38] This high prevalence should act to increase the PPV and lower the NPV but should have the same effect on all criteria (SHMHC, PUMCH, and LAPS original criteria). It has also been found in rural settings that there is an increased prevalence of dementia in China, given this finding, our criteria may have optimal performance in rural settings of China versus the other studied and proposed CMMSE criteria.

In addition, age and educational level have been demonstrated to be 2 most important risk factors for the diagnosis of AD.[1,39] Therefore, we conduct the subgroup analyses trying to avoid pitfalls. Finally, we found the refined definition of criteria presented here had better performance among the participants receiving middle school or higher education than others. There was no significant difference between age-groups (<65 years of age vs ≥65 years of age).

Finally, it is essential to take the cost-effectiveness into consideration and seeking optional cutoff points suiting local situations, in which the prevalence of AD and scale of aging population are rapidly increasing in China, as the sensitivity and specificity are generally inversely related. This is especially true in the rural populations of China where still over 48% of the Chinese population resides.[3] Accounting for this point, the refined definition of criteria presented here is important for both public health and clinical practice for the rural population of China.

It is also important to consider the limitations of this study when interpreting the findings. First, the result was based on the data of Linxian County, a rural population found to be a nutritionally deficient population with limited ethnic minority groups.[40,41] Previous studies show a variety of nutritional deficiencies among these population, especially in rural areas throughout China.[40,42,43] Those nutritionally deficient among the population should be considered in future research. Second, ADL-screened positive participants were excluded from the final analysis, which could potentially have altered final calculations. Also, this was 1 cohort set of data, which may explain the equivalent referral rates between pre- and postadjusted CMMSE criteria. Third, keeping the screening processes and clinical diagnostic processes independent plays a significant role in assessing the different screening cutoff points. However, in this study, we failed to take this into consideration, which may also alter the final results. Finally, our analysis for AUC of our adjusted criteria yielded a result of 0.688, the highest general AUC compared to the other analyzed criteria which is less than an AUC of 0.7, which is usually necessary to make conclusions,[44] but we used AUC as a comparative measure to differentiate the performances of all criteria.

Overall, we focused on the efficiency of CMMSE for the initial detection of AD in rural areas, especially in nutritional-deficiency areas. We found that by reducing the cutoff score of CMMSE in 3 educational levels (illiterate, primary school, and middle school or higher) to 16, 19, and 23, respectively, the efficiency for initial detection of AD was improved. These data provide evidence that CMMSE for initial detection of AD in nutritional-deficiency areas needs future development.

Authors' Note

Zhao Yang and Hunter K. Holt contributed equally to this work.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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