

Normative Data for the Montreal Cognitive Assessment in a Japanese Community-Dwelling Older Population

Kenji Narazaki^a Yu Nofuji^b Takanori Honda^a Eri Matsuo^b Koji Yonemoto^c
Shuzo Kumagai^b

^aGraduate School of Human-Environment Studies and ^bInstitute of Health Science, Kyushu University, and
^cBiostatistics Center, Kurume University, Fukuoka, Japan

Key Words

Cognitive decline · Cognitive screening · Dementia ·
Cross-sectional study · Community-based study · Elderly ·
Mild cognitive impairment

Abstract

Background: Although the Montreal Cognitive Assessment (MoCA) is acknowledged as a promising neuropsychological tool, its normative data for older populations have not been established yet. The purpose of this study was to provide normative data for the MoCA in Japanese community-dwelling older people. **Methods:** In a Japanese town, 1,977 participants aged 65 years or older (mean age 73.6 years; male 41.3%) completed MoCA tests. After descriptive and regression analyses, normative data were developed for MoCA scores in the population. **Results:** The mean MoCA score observed (21.8 points) was lower than that for normal controls (27.4 points) in the original validation study of the MoCA. Additionally, 82.6% of MoCA scores fell below the standard cutoff of 26 points for detecting mild cognitive impairment (MCI). The regression analysis showed that higher age and fewer years of formal education were associated with lower MoCA scores ($p < 0.001$). Normative data for MoCA scores were presented with respect to age and education. **Conclusion:** This study provided normative data for the MoCA in a

Japanese community-dwelling older population. This research also suggests that conventional use of the MoCA as a screening tool for MCI might be problematic in cultures different from that in which the cutoff was developed.

Copyright © 2012 S. Karger AG, Basel

Introduction

Mild cognitive impairment (MCI) represents an intermediate clinical state between normal cognitive aging and Alzheimer's disease or other types of dementia [1]. Although it is not always the case, MCI has been reported to often develop into either Alzheimer's disease or other forms of dementia and, therefore, recognized as a high-risk state for dementia development [2]. In recent discussions, community-based screening of MCI is considered one of the crucial steps to enable wide-reaching interventions for preventing or slowing the onset of dementia [3].

Montreal Cognitive Assessment (MoCA) is a brief neuropsychological tool designed for screening MCI in community health care [4] and is acknowledged as a promising instrument worldwide [5–7]. Given the need for ethnic-specific versions of neuropsychological tests [8, 9], 38 versions of the MoCA are currently developed in 31 languages (www.mocatest.org). MoCA has also

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2012 S. Karger AG, Basel
0251-5350/13/0401-0023\$38.00/0

Accessible online at:
www.karger.com/ned

Dr. Shuzo Kumagai
Institute of Health Science, Kyushu University
6-1 Kasugakoen, Kasuga
Fukuoka 816-8580 (Japan)
Tel. +81 92 583 7853, E-Mail shuzo@ihs.kyushu-u.ac.jp

been reported to have higher sensitivity to a subtle cognitive decline than conventional tools such as the Mini-Mental State Examination [4, 10, 11]. To date, two cohort studies reported normative MoCA data in population-based samples including a multiethnic US population [12] and a Portuguese population [13]. Both studies, however, were conducted with subjects of a wide age range, and thus, the sample sizes were scarce for the older age groups.

Because older people are the primary subjects of MCI screening and subsequent interventions, their scoring characteristics on the MoCA should be examined and demonstrated with a larger sample size. This is an urgent matter, especially for a Japanese society undergoing the world's fastest aging with the highest life expectancy. Therefore, the aim of the present study was to provide normative MoCA data specific to community-dwelling older people in a Japanese town.

Materials and Methods

Participants

The present study involved analysis of data from the baseline phase of the Sasaguri Genkimon Study (SGS) conducted from May to August 2011. The SGS is an ongoing community-based prospective cohort study in a Japanese local town, Sasaguri, aiming to explore modifiable lifestyle factors causing older people to require nursing care. Subjects of the baseline study (SGS-1) were all residents of the town who were aged 65 years or older and not certified as individuals requiring nursing care by the town in January 2011 ($n = 4,979$). Sixty-six subjects were excluded due to being dead or moving out by the onset of the study. A set of study information sheets and a questionnaire were mailed to all remaining subjects ($n = 4,913$), and 2,629 individuals, hereafter referred to as the participants of the SGS-1, responded to the mail by (1) visiting a community center to submit the questionnaire and undergo multiple physical and cognitive tests in one of 31 group-testing sessions of the SGS-1, (2) contacting study coordinators to set up an appointment for an individual home-testing session or (3) visiting the city office to submit the questionnaire (recruitment rate: 53.5%). Of these, 2,129 individuals took part in the MoCA tests. After the testing, we excluded 32 individuals who were unable to complete the MoCA properly, 12 individuals with missing information about their years of formal education, and 108 individuals with self-reported medical histories of stroke, depression, Parkinson's disease and dementia. Accordingly, data from 1,977 participants (75.2% of the total participants of the SGS-1) were involved in the present study.

Standard Protocol Approvals, Registrations and Patient Consents

All the participants provided written informed consent to participate in the present study. The study protocol and the informed consent form were approved by the Institutional Review Board of the Institute of Health Science, Kyushu University.

Measurements

We used the Japanese version of the MoCA for all measurements. The details of the Japanese version are described elsewhere [5]. Briefly, it was developed and validated by investigators, including the inventor of the original MoCA (Dr. Nasreddine). As in the original one [4], the Japanese version of the MoCA was designed as a 30-point screening instrument administered in about 10 min and consists of the following 12 cognitive tasks: a five-item delayed recall task (5 points), a clock-drawing task (3 points), a cube-copying task (1 point), a trail-making task (1 point), a phonemic fluency task (1 point), a two-item verbal abstraction task (2 points), a target-tapping task (1 point), a serial subtraction task (3 points), a two-item digits-reading task (2 points), a three-item naming task (3 points), a two-item sentence-repeating task (2 points) and a six-item temporal and locational orientation task (6 points). In the standard procedure of the original as well as the Japanese versions, 1 point is added to the total score of the cognitive tasks if an individual has 12 years or fewer of formal education, and a final total score falling below 26 points is judged to have probable MCI.

Procedures

All MoCA tests were administered to the participants by trained personnel as part of the group-testing and home-testing sessions of the SGS-1. After the testing, MoCA scores were independently evaluated by two authors (K.N. and T.H.) and double-checked between the two before being finally determined. The interevaluator reliability, shown as a percentage of agreement in the MoCA scores, was 93.3% in the initial evaluation. To demonstrate normative data in participants with a wide range of years of formal education, the preferred 1-point correction for education was not adopted.

Statistical Analyses

All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, N.C., USA). The Wilcoxon rank-sum test and the χ^2 test were conducted to compare age and sex, respectively, between the participants of the present study and the rest of the subjects ($n = 2,936$). The Wilcoxon rank-sum test was also performed to assess the difference in years of formal education between the participants of the present study and the rest of the participants of the SGS-1 answering educational history in the questionnaire ($n = 608$). Descriptive statistics were calculated for MoCA scores and for scores of respective cognitive tasks. A multiple regression analysis was performed with the MoCA score as a dependent variable and age, sex and years of formal education as independent variables. Additionally, to visualize changes in MoCA scores, simple regression analyses were conducted between the MoCA score and age in three education levels (≤ 9 , 10–12, and ≥ 13 years of formal education). Subsequently, normative data for MoCA scores in the community-dwelling older population were developed with respect to age and education. Overlapping age categories of 65–75, 70–80, 75–85, and ≥ 80 years, accompanied by the aforementioned three education levels, were adopted in the normative data based on the rationale previously described for practical use of the normative data in community health care [12, 14]. A significance level was set at two-sided $\alpha = 0.05$.

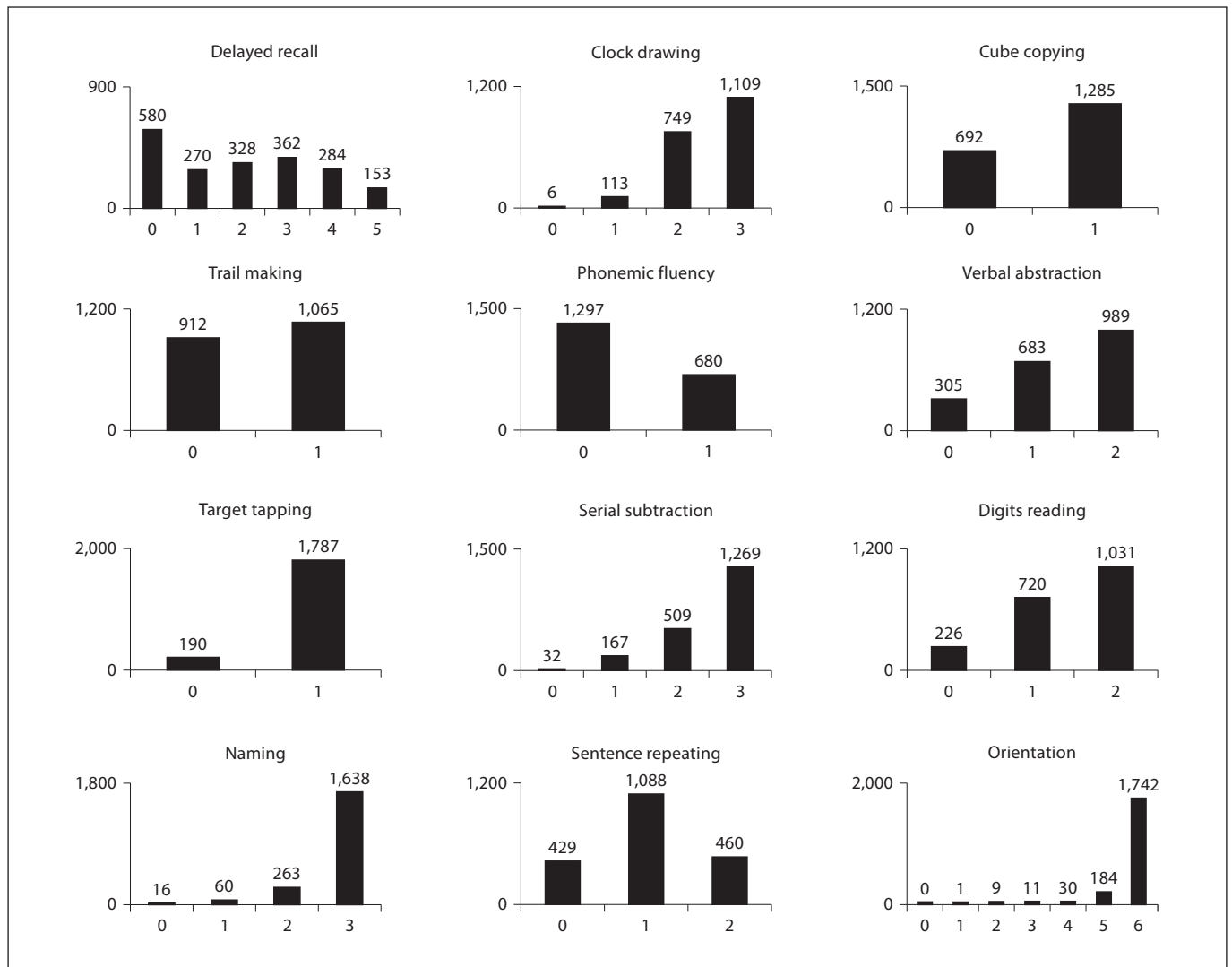


Fig. 1. Histograms of scores for respective cognitive tasks in MoCA. Each panel shows a histogram for one of the 16 cognitive tasks in the MoCA. Horizontal and longitudinal axes of each panel indicate points scored and frequency count for each point, respectively.

Results

The participants of the present study differed from the rest of the subjects in terms of sex (percentage of males, 41.3 vs. 45.3%; $p = 0.008$), but not in terms of age (median, 72 years for both groups; interquartile range, 68–78 years for both groups; $p = 0.860$). Also, the number of years of formal education was not different between the participants of the present study and the rest of the participants of the SGS-1 answering educational history in the questionnaire (median, 12 years for both groups; interquartile range, 9–12 years for both groups; $p = 0.216$). The mean

age of the participants was 73.6 years (standard deviation, SD, 6.2; median, 72; range, 65–96) and the number of years of formal education was 11.0 years (SD, 2.5; median, 12; range, 2–23); 41.3% of the participants were male ($n = 817$). The mean MoCA score was 21.8 points (SD, 3.9; median, 22; range, 5–30), with 82.6% of scores falling below the preferred cutoff of 26 points for probable MCI. Histograms with scores of the respective cognitive tasks are summarized in figure 1.

In the multiple regression analysis, significant associations with the MoCA score were found for age (regression coefficient, -0.21 ; 95% confidence interval, CI, -0.23

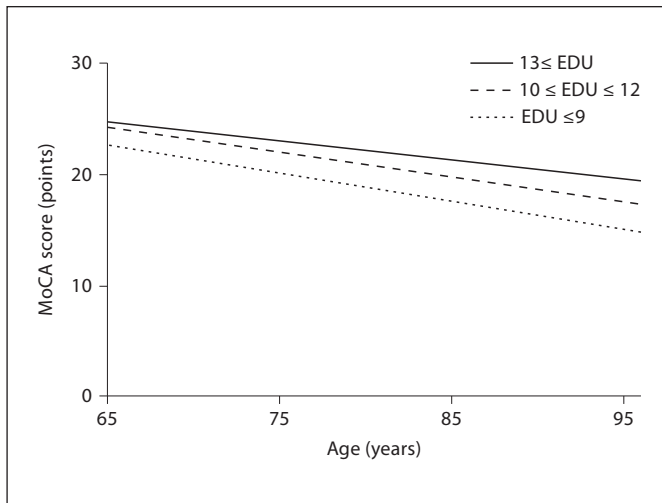


Fig. 2. Regression lines between age and MoCA scores in three education levels. EDU denotes years of formal education. Intercepts (at 65 years) and slopes for respective regression lines are as follows: 24.73 and -0.17 in $13 \leq \text{EDU}$; 24.30 and -0.22 in $10 \leq \text{EDU} \leq 12$; 22.66 and -0.25 in $\text{EDU} \leq 9$.

Table 1. Normative data for MoCA scores

	Education level			Total by age
	≤ 9 years	10–12 years	≥ 13 years	
<i>Age category</i>				
65–75 years	371 21.4 \pm 3.7 22 (9–29)	659 23.3 \pm 3.1 23 (14–30)	248 24.0 \pm 3.0 24 (13–30)	1,278 22.9 \pm 3.4 23 (9–30)
70–80 years	406 20.2 \pm 3.8 20 (6–29)	471 22.1 \pm 3.4 22 (12–30)	157 23.2 \pm 3.0 23 (13–29)	1,034 21.6 \pm 3.7 22 (6–30)
75–85 years	327 19.2 \pm 4.0 19 (5–28)	320 21.3 \pm 3.4 21 (12–29)	83 22.6 \pm 3.1 23 (16–29)	730 20.5 \pm 3.9 21 (5–29)
≥ 80 years	161 18.0 \pm 4.4 19 (5–28)	170 20.5 \pm 3.5 21 (8–29)	35 22.1 \pm 4.0 23 (12–29)	366 19.6 \pm 4.2 20 (5–29)
Total by education	692 20.1 \pm 4.1 20 (5–29)	964 22.5 \pm 3.4 23 (8–30)	321 23.6 \pm 3.2 24 (12–30)	1,977 21.8 \pm 3.9 22 (5–30)

Data are expressed as number, mean \pm SD and median (with range in parentheses).

to -0.18 ; $p < 0.001$) and education (regression coefficient, 0.42; 95% CI, 0.36–0.49; $p < 0.001$) but not for sex (regression coefficient, 0.21; 95% CI, -0.10 to 0.52; $p = 0.186$). Figure 2 demonstrates the results of the simple regression analyses showing significant associations between the MoCA score and age in all three education levels ($p < 0.001$). Specifically, higher age was associated with lower MoCA scores in all the education levels. Finally, normative data for MoCA, specific to the community-dwelling older people, were determined with respect to the four age categories and three education levels (table 1).

Discussion

Population-based screening for MCI is recognized as a key step in establishing sound wide-reaching intervention programs for preventing or delaying older people from developing dementia [3]. Although the MoCA has great promise as a screening tool for MCI, knowledge regarding its scoring characteristics in population-based older samples has still been limited. To our knowledge, the present study was the first to demonstrate normative MoCA data specific to community-dwelling older people not only in Japanese society but worldwide. Reflecting the world's highest population aging rate in Japan, the normative data were formed with a relatively high proportion of old-old and oldest-old samples (table 1), which should be informative for other societies besides Japan. The present study also examined the associations of socio-demographic factors, including age, sex and years of formal education with MoCA scores in the older population.

In an attempt to develop normative data reflecting cognitively normal samples, we excluded individuals from the present analyses if they self-reported medical history of diseases contributing to or reflecting the development of clinical cognitive decline [2, 10, 15, 16]. There exists an argument that normative values should be representative and, therefore, should be developed from samples including both cognitively normal and abnormal individuals [17]. However, we made the exclusion based on the promise that the sensitivity of screening or detecting cognitively impaired individuals can be enhanced by comparing a patient's score to that of a reference group free of any clinical cognitive decline [18]. The exclusion of individuals requiring nursing care in the subject selection process may also be conducive to enhancing the sensitivity.

The mean MoCA score of 21.8 points observed in the present study was lower than that for the normal controls

($n = 90$; mean, 27.4 points; SD, 2.2) and was indeed close to that for the patients with MCI ($n = 94$; mean, 22.1 points; SD, 3.1) in the original normative study performed by the development group of the MoCA [4]. These trends were unchanged even after the preferred 1-point correction of MoCA scores for formal education (mean, 22.7 points; SD, 3.8). Furthermore, more than three quarters of the scores (82.6% without the correction or 75.1% with the correction) fell below the preferred cutoff of 26 points for detecting MCI while the reported prevalence of MCI in older populations ranges from 15 to below 30% [19–23]. This percentage is still high even considering the potential inclusion of patients with undiagnosed dementia. Because multiple population-based studies have also observed MoCA scores comparable to the present one [12, 13, 24], this discrepancy may not be attributed to some administrative issues in the present study but to a low external validity of the cutoff score due to the limited number of samples and/or possible selection bias for the non-population-based samples in the original study [4]. Other possible causes of the discrepancy are some cultural and linguistic artifacts occurring in the translation process of the original MoCA into the Japanese version [8, 18]. Although the cross-cultural and cross-linguistic adaptations appear to be taken into account during the development process of the Japanese version [5], the validity of the adaptations was examined with a limited number of clinical-based subjects and, therefore, the possibility of cultural and linguistic artifacts in population-based use cannot be ruled out.

As observed in previous population-based studies with subjects in a wide age range [12, 13], the present results show significant associations of age and education with the MoCA scores in older samples. Specifically, MoCA scores were lower in participants with higher age and/or fewer years of formal education. In contrast, no association was found between sex and the MoCA score. The effects of age and education have been well documented for neuropsychological tests in population-based studies and have been taken into account with age- and education-specific norms when the obtained scores have been evaluated [17, 18]. Because both age and education are now recognized as risk factors of cognitive decline [25, 26] rather than just biasing factors of the tests, it can be misleading and problematic to count the effects by adjusting an obtained score for these variables and evaluate the adjusted score using a single cutoff [17, 27]. In the light of this discussion, the current MoCA procedure, comprising a 1-point adjustment for 12 or fewer years of formal education and a subsequent evaluation with a single

cutoff of 25/26, may not be the best for screening MCI in population-based samples.

Taken together, it is considered reasonable to assume that the current MoCA procedure is somewhat premature for MCI screening in community-dwelling older people. However, because we didn't employ a clinical diagnosis of MCI in the research design, the present study is unable to further propose any alternative criteria for population-based MCI screening. Instead, at this stage, the normative data demonstrated in the present study can allow clinicians and researchers to detect individuals with abnormal cognitive decline from the community-dwelling older samples while taking into account the influence of age and education. For example, if a 75-year-old patient with 9 years of formal education scored 12 points on the MoCA test, his or her personal physician can appreciate that the score was lower than the mean minus $2 \times \text{SD}$ [i.e. $20.2 - (2 \times 3.8) = 12.6$] for the age- and education-matched normal group and can suspect the patient's clinical cognitive decline. Similarly, the normative data may be useful for professionals when monitoring subtle cognitive change within a patient in longitudinal observations. It should be noted here that the definition of normal or abnormal needs to be carefully made in practical use, depending on the context and circumstances in which the MoCA test is administered.

Our report has some limitations which are worth noting here. First, the sample of the present study was affected to some extent by the nonresponse, withdrawal and exclusion of originally designated subjects. Specifically, the participants of the present study differed from the rest of the subjects in terms of sex distribution. However, we believe the influence of this discrepancy on the present results was not considerable because the regression analysis showed no association between sex and the MoCA score. Second, because the present study was performed in a single Japanese town, generalizability of the results is somewhat limited. Nevertheless, the present normative data can be considered applicable to other places in Japan because ethnicity and educational system are almost homogeneous across Japan. Finally, in the normative data, some strata were formed with relatively small numbers of samples and, thus, are probably less reliable in terms of age-education relationships.

Associations of MoCA scores with other socio-demographic factors, such as ethnicity, culture, language, financial security and family configuration, remain to be explored by future investigations in order to generalize the findings of this research. Obtaining these types of re-

search findings might be essential before establishing the cutoff for population-based MCI screening. In parallel with exploring the future use of the MoCA as a population-based MCI screening tool, we are going to follow the present participants in prospective observations of the SGS to determine the ability of the test to predict the future onset of dementia in the community-dwelling older population.

Conclusion

In summary, the present research reported normative data for MoCA scores derived from a relatively large-scale community-dwelling older population in Japan and proposed practical applications of the normative data in community health care. This research also suggests that

conventional use of the MoCA as a screening tool for MCI might be problematic in cultures different from that in which the cutoff was developed.

Acknowledgements

The present study was supported in part by Sasaguri town, Fukuoka, Japan. We are grateful for the support of the municipal staff of Sasaguri town, especially of Ms. Kumiko Gunjima who helped us coordinate the study. We would also like to thank Dr. Yoshihiro Fujiwara and Dr. Hiroyuki Suzuki of the Tokyo Metropolitan Institute of Gerontology for giving us suggestions on the administration of the Japanese version of the MoCA.

Disclosure Statement

The authors declare that there are no conflicts of interest.

References

- 1 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–308.
- 2 Petersen RC: Clinical practice. Mild cognitive impairment. *N Engl J Med* 2011;364:2227–2234.
- 3 Stephan BC, Kurth T, Matthews FE, Brayne C, Dufouil C: Dementia risk prediction in the population: are screening models accurate? *Nat Rev Neurol* 2010;6:318–326.
- 4 Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H: The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–699.
- 5 Fujiwara Y, Suzuki H, Yasunaga M, Sugiyama M, Ijuin M, Sakuma N, Inagaki H, Iwasa H, Ura C, Yatomi N, Ishii K, Tokumaru AM, Homma A, Nasreddine Z, Shinkai S: Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal Cognitive Assessment. *Geriatr Gerontol Int* 2010;10:225–232.
- 6 Lee JY, Dong Woo L, Cho SJ, Na DL, Hong Jin J, Kim SK, You Ra L, Youn JH, Kwon M, Lee JH, Maeng Je C: Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. *J Geriatr Psychiatry Neurol* 2008;21:104–110.
- 7 Rahman TT, El Gaafary MM: Montreal Cognitive Assessment Arabic version: reliability and validity prevalence of mild cognitive impairment among elderly attending geriatric clubs in Cairo. *Geriatr Gerontol Int* 2009;9:54–61.
- 8 Escobar JI, Burnam A, Karno M, Forsythe A, Landsverk J, Golding JM: Use of the Mini-Mental State Examination (MMSE) in a community population of mixed ethnicity. Cultural and linguistic artifacts. *J Nerv Ment Dis* 1986;174:607–614.
- 9 Mungas D, Marshall SC, Weldon M, Haan M, Reed BR: Age and education correction of Mini-Mental State Examination for English and Spanish-speaking elderly. *Neurology* 1996;46:700–706.
- 10 Dong Y, Sharma VK, Chan BP, Venketasubramanian N, Teoh HL, Seet RC, Tanicala S, Chan YH, Chen C: The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci* 2010;299:15–18.
- 11 Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM: Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. *Stroke* 2010;41:1290–1293.
- 12 Rossetti HC, Lacritz LH, Cullum CM, Weiner MF: Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology* 2011;77:1272–1275.
- 13 Freitas S, Simoes MR, Alves L, Santana I: Montreal Cognitive Assessment (MoCA): normative study for the Portuguese population. *J Clin Exp Neuropsychol* 2011;33:989–996.
- 14 Pauker JD: Constructing overlapping cell tables to maximize the clinical usefulness of normative test data: rationale and an example from neuropsychology. *J Clin Psychol* 1988;44:930–933.
- 15 Bhalla RK, Butters MA, Becker JT, Houck PR, Snitz BE, Lopez OL, Aizenstein HJ, Raina KD, DeKosky ST, Reynolds CF 3rd: Patterns of mild cognitive impairment after treatment of depression in the elderly. *Am J Geriatr Psychiatry* 2009;17:308–316.
- 16 Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, Melzer TR, Kirwan J, Keenan R, Wells S, Porter RJ, Watts R, Anderson TJ: The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology* 2010;75:1717–1725.
- 17 Crum RM, Anthony JC, Bassett SS, Folstein MF: Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA* 1993;269:2386–2391.
- 18 Bravo G, Hebert R: Age- and education-specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population. *Int J Geriatr Psychiatry* 1997;12:1008–1018.
- 19 Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG: Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology* 2006;67:2176–2185.

- 20 Di Carlo A, Lamassa M, Baldereschi M, Inzitari M, Scafato E, Farchi G, Inzitari D: CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. *Neurology* 2007;68:1909–1916.
- 21 Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, Breitner J, Lyketsos C, Jones B, Kawas C, Carlson M, Kuller LH: Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study. Part 1. *Arch Neurol* 2003;60:1385–1389.
- 22 Manly JJ, Bell-McGinty S, Tang MX, Schupf N, Stern Y, Mayeux R: Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. *Arch Neurol* 2005;62:1739–1746.
- 23 Manly JJ, Tang MX, Schupf N, Stern Y, Vonsattel JP, Mayeux R: Frequency and course of mild cognitive impairment in a multiethnic community. *Ann Neurol* 2008;63:494–506.
- 24 Luis CA, Keegan AP, Mullan M: Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *Int J Geriatr Psychiatry* 2009;24:197–201.
- 25 Daviglus ML, Plassman BL, Pirzada A, Bell CC, Bowen PE, Burke JR, Connolly ES Jr, Dunbar-Jacob JM, Granieri EC, McGarry K, Patel D, Trevisan M, Williams JW Jr: Risk factors and preventive interventions for Alzheimer disease: state of the science. *Arch Neurol* 2011;68:1185–1190.
- 26 Nithianantharajah J, Hannan AJ: The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Prog Neurobiol* 2009;89:369–382.
- 27 Holsinger T, Deveau J, Boustani M, Williams JW Jr: Does this patient have dementia? *JAMA* 2007;297:2391–2404.