Screening for Early Alzheimer's Disease: Is There Still a Role for the Mini-Mental State Examination?

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Background: The objective of this study was to compare the performance of the Mini-Mental State Examination (MMSE) total score as well as item scores in separating 4 groups of elderly (55–85 years of age) subjects—normal controls, subjects with mild cognitive impairment (MCI), subjects with mild Alzheimer's disease, and subjects with depression.

Method: The MMSE scores of 86 subjects (25 normal elderly controls, 26 subjects with MCI, 10 subjects with mild Alzheimer's disease, and 25 subjects with depression) were analyzed. Statistically significant differences between groups in both overall MMSE score and individual item scores were documented. Receiver operating characteristic curves were constructed to yield further data.

Results: The overall MMSE scores of the mild Alzheimer's disease group were significantly below those of subjects in the control, MCI, and depression groups ($p < .001$). The overall MMSE scores of MCI subjects were significantly lower than those of control subjects ($p = .005$) but not different from those of subjects with depression. Furthermore, individual item responses were not significantly different between MCI subjects and controls. The delayed recall item scores were statistically lower in the mild Alzheimer's disease group versus the other 3 groups but did not separate the control, MCI, and depression groups from each other.

Conclusion: The MMSE effectively separates those with mild Alzheimer's disease from the other 3 groups and MCI from normal aging, but it is relatively ineffective in separating normal elderly individuals from those with depression and individuals with MCI from those with depression. Measures other than the MMSE may need to be implemented to evaluate mental status to more effectively separate MCI from depression and depression from normal aging.

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In light of the continuing rise in the population of elderly individuals in the United States and the threat of impaired cognitive function to diminish one's quality of life, accurate and effective screening for early recognition and differentiation between normal age-related cognitive decline, mild cognitive impairment (MCI), mild Alzheimer's disease, and other causes of cognitive decline is desirable. The Mini-Mental State Examination (MMSE)[1] is one of the most widely used tools implemented by physicians to evaluate a patient's cognitive status.[2] Common use among physicians occurs because the MMSE, in general, has fulfilled its original goal of providing a bedside screening test of cognitive impairment in hospitalized patients.[1] Also contributing to its popularity among physicians is the MMSE's feasibility in terms of the time required to administer a test assessing a patient's degree of cognitive impairment, as opposed to longer mental status tests or neuropsychological batteries that may require a neuropsychologist or other trained experts several hours to administer and evaluate scoring.

The MMSE correlates significantly with other cognitive batteries such as the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS) (a standard cognitive outcome in Alzheimer's disease drug trials), and an equation to predict ADAS scores from the MMSE (and

vice versa) has been published for patients with mild to moderate Alzheimer's disease.[3] Over the past 2 decades, there have also been numerous studies examining the clinical utility of the MMSE, and many attempts have been made to improve its sensitivity and specificity.[2,4–10] The MMSE was developed at a time when only patients in more advanced stages of dementia were being evaluated, and thus the MMSE's usefulness in separating normal aging from MCI and depression (a common differential diagnosis dilemma in the elderly) was not originally well studied. Yet, while most clinicians do not utilize the MMSE in the capacity of a diagnostic tool, the MMSE remains the conventional choice for the initial assessment of patients' mental status by primary care physicians and many specialists. Therefore, determination of the MMSE's utility in screening for cognitive decline in various clinical diagnostic states is needed.

The objective of this study was to compare the ability of the MMSE total score, as well as item scores, to separate 4 clinically important groups of elderly subjects—normal elderly controls, subjects with MCI, subjects with mild Alzheimer's disease, and subjects with depression—in order to assess its use as a screening tool for cognitive impairment in the elderly. The MMSE scores, both overall and individual items, were expected to be significantly different between the control and mild Alzheimer's disease and MCI groups, while comparisons of control versus depression groups were not expected to be significant.

METHOD

Subjects

There were 86 elderly subjects (Table 1) who participated in 2 different research studies that had been approved by an ethics committee. Subjects were recruited from the community through advertisements for people with memory problems or depression. All subjects gave written consent. The data used for the present study represent a subset of data that was originally considered demographic information for the larger studies, which are ongoing long-term projects. The 86 elderly subjects were chosen due to completeness of their data sets. They comprised the following 4 groups: 25 normal elderly control subjects, 26 subjects with MCI, 10 subjects with early Alzheimer's disease, and 25 subjects with depression. Subjects underwent clinical and neurologic evaluations, computed tomographic or magnetic resonance imaging (MRI) scans, and review of laboratory data.

General inclusion criteria. Subjects (1) were 55 to 85 years old, (2) were fluent in English, and (3) had a minimum of 8 years of formal education.

Exclusion criteria. Exclusion criteria were (1) depression not controlled by medication (as indicated by scores on the Beck Depression Inventory[11] or Montgomery-Asberg Depression Rating Scale [MADRS],[12] as well as an evaluation by a psychiatrist [P.M.D.]), or other psychiatric illness (for the first 3 groups); (2) use within 24 hours of psychoactive medications known to significantly affect memory (particularly anxiolytics and hypnotics); (3) presence of a confounding central neurologic disease (e.g., brain tumor, stroke, epilepsy); or (4) presence of a substance abuse disorder or substance dependence.

Table 1. Demographics and Clinical Information for Elderly Subjects in 4 Groups

Variable	Control (N = 25)	MCI (N = 26)	Mild AD (N = 10)	Depression (N = 25)
Age, mean (SE), y	71.1 (1.03)	76.0 (1.38)[a]	75.4 (2.23)	69.0 (1.05)
Sex, male/female, N	12/13	11/15	4/6	17/8
Race, N				
White	18	22	8	24
African American	5	4	1	1
Other	2	0	1	0
Education, mean (SE), y	16.0 (0.53)	15.0 (0.51)	13.7 (0.68)	14.2 (0.52)
MMSE score, mean (SE)	28.4 (0.25)	26.5 (0.38)	22.8 (0.72)	27.9 (0.31)
CDR score	0	0.5	1.0	
BDI score, mean (SE)	5.5 (0.90)	5.2 (0.73)	6.2 (1.30)	
MADRS score, mean (SE)				25.0 (0.86)

[a]Age of MCI group was significantly older than that of both the control and depression groups.
Abbreviations: AD = Alzheimer's disease, BDI = Beck Depression Inventory, CDR = Clinical Dementia Rating scale, MADRS = Montgomery-Asberg Depression Rating Scale, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination.

Control group inclusion criteria. In addition to meeting the exclusion criteria, the fulfillment of the following criteria was required for inclusion within the control group. Subjects (1) did not meet National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[13] criteria for clinical Alzheimer's disease or *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[14] criteria for dementia, (2) had normal/near normal independent function, (3) had no objective memory impairment demonstrated by performance on a word learning list (the California Verbal Learning Test-II [CVLT-II][15]) and story or picture recall tests (logical memory and visual reproduction subtests from the Wechsler Memory Scale-III (WMS-III),[16] (4) had a Clinical Dementia Rating scale (CDR)[17] global score of 0 (a rating based on cognitive and functional abilities as reported by an informant and interview of the subject), and (5) did not meet criteria for MCI (as stated in the next section).

Mild cognitive impairment group inclusion criteria. In addition to the exclusion criteria, fulfillment of the following criteria was required for inclusion within the MCI group: (1) a recent history of symptomatic worsening in

memory, which was supported by information from an informant; (2) an objective memory impairment (at least 1 standard deviation below normal) as demonstrated by performance on the CVLT-II and/or logical memory and/or visual reproduction tests from the WMS-III; (3) normal/near normal performance on other cognitive tests; (4) a CDR global score of 0.5 (questionable dementia) with a memory score of at least 0.5; (5) failure to meet NINCDS-ADRDA criteria for clinical Alzheimer's disease or DSM-IV criteria for dementia; and (6) absence of other factors that may provide a better explanation for memory loss (e.g., depression).

Mild Alzheimer's disease group inclusion criteria. In addition to the exclusion criteria, fulfillment of the following criteria was required for inclusion within the early Alzheimer's disease group: (1) a history of progressive cognitive worsening for at least 1 year, (2) a Hachinski score[18] of < 4 (indicating an insignificant vascular component to the memory loss), (3) a CDR global score of 1 with a memory score of at least 1 (mild Alzheimer's disease), and (4) NINCDS-ADRDA criteria for probable Alzheimer's disease after full workup including neurologic, imaging, and laboratory tests.

Depression group inclusion criteria. In addition to the exclusion criteria, fulfillment of the following criteria was required for inclusion within the depression group: (1) current major depressive disorder criteria of the DSM-IV, (2) a minimum score of 21 on the MADRS,[12] (3) MRI and neurologic examination not suggestive of other causes of depression, and (4) absence of dementia by DSM-IV criteria.

Materials

A standard MMSE form was administered to each of the 86 elderly subjects comprising the 4 separate groups. The MMSE was composed of 20 questions designed to assess the patient's mental status in the following 5 categories[1,7]: 10 orientation questions (year, season, date, day, month, state, country, city, floor, and location), 1 memory item (delayed recall of apple, table, penny), 1 attention-concentration item (spelling "world" backward), 6 language items ("watch-pencil" [naming], registration of 3 words and "No ifs, ands, or buts" [repetition], 3-step command [comprehension], "close your eyes" [reading], and "write a sentence" [writing]), and 1 constructional item (copy overlapping pentagons).

Statistical Method

First-level (general linear model) analysis. For both the overall MMSE scores and individual item scores, a 1-way analysis of covariance (ANCOVA) was conducted on scores between groups (controls, MCI, mild Alzheimer's disease, and depression) with age, sex, and education used as covariates. To determine whether a statistically significant difference existed between the scores of the groups, an α of 0.05 was used to test the omnibus null hypothesis.

Second-level (post hoc) analysis. The post hoc analysis involved pairing groups for comparisons of statistically significant data, indicated by the 1-way ANCOVA conducted at the first-level analysis. Statistically significant differences between scoring items of 2 groups were determined via ANCOVA, applying a Bonferroni-corrected α-coefficient of 0.0083 (to correct for multiple comparisons) to the following 6 between-group comparisons: control versus MCI, control versus mild Alzheimer's disease, control versus depression, MCI versus mild Alzheimer's disease, MCI versus depression, and mild Alzheimer's disease versus depression.

The same between-group comparisons of data were used to construct receiver operating characteristic (ROC) curves. An ROC curve is a graphical representation of the trade-off between the false-negative and false-positive rates for every possible cutoff for a test. It allows us to establish the most appropriate threshold for a test, based on how well it classifies subjects into the relevant groups.

The "cutoff" MMSE score for each group was determined from the ROC curves, following which, sensitivity (the probability that a patient will be accurately classified by the test), specificity (the probability that a nonpatient will be accurately classified by the test), positive predictive value (the probability that a subject classified as a patient by the test belongs in the patient group), and negative predictive value (the probability that a subject classified as a nonpatient by the test belongs in the nonpatient group) were calculated. The area under the ROC curve (AUC) was also calculated as a measure of efficacy of the test.

RESULTS

Demographic profiles for each of the 4 groups are shown in Table 1. Sex and education were not significantly different between the 4 groups. The mean age of the MCI group was greater than that of the control and depression groups, $F = 2.153$, $df = 1$, $p = .007$, and $F = 1.330$, $df = 1$, $p = .001$, respectively. As a conservative measure in the data analyses, all 3 factors (age, education, sex) were applied as covariates when conducting the ANCOVA.

The results of overall MMSE score between-group comparisons are shown in Table 2. The overall MMSE scores of the mild Alzheimer's disease group were significantly lower than those of the other 3 groups, and the total MMSE score of the MCI group was significantly lower than that of the control group. The MMSE scores of the depression subjects were not significantly different than those of control or MCI subjects.

The between-group comparisons of individual MMSE item scores following the second-level analysis are displayed in Table 2. Items proving to be significantly dif-

Table 2. Between-Group Comparisons of MMSE Overall Score and Individual Items (p values)[a]

Measure	Control vs MCI	Control vs Mild AD	Control vs Depression	MCI vs Mild AD	MCI vs Depression	Mild AD vs Depression
Overall score	.005[b]	< .001[b]	.636	< .001[b]	.038	< .001[b]
Orientation						
Year	…[c]	.014	…[c]	.010	…[c]	.054
Season	.114	.372	.260	.003[b]	.311	.260
Date	.239	< .001[b]	.351	.011	.036	< .001[b]
Day of week	.117	< .001[b]	…[c]	.007[b]	.030	< .001[b]
City	.490	.141	.057	.079	.369	.392
Floor of building	.014	.404	< .001[b,d]	.845	< .001[b,d]	.002[b]
Name of place	.474	.023	…[c]	.023	.736	.041
Delayed recall						
0 Correct	.381	< .001[b]	…[c]	.002[b]	.886	.001[b,e]
1 Correct	.039	.121	.293	.944	.034	.024
2 Correct	.864	.303	.011	.094	.050	.006[b]
3 Correct	.036	.022	.049	.382	.812	.761
Total correct	.017	< .001[b]	.260	.023	.392	.005[b]

[a]Post hoc analysis of statistically significant comparisons by analysis of covariance. Age, sex, and education were covariates.
[b]Statistically significant difference (α-coefficient = 0.0083).
[c]No incorrect responses were given by subjects of either group in the comparison.
[d]More correct responses from depression group.
[e]More mild AD subjects with zero correctly recalled.
Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination.

ferent between the groups following first-level analysis came only from the categories of orientation and memory. Second-level post hoc analyses were then conducted. There were no significant differences between individual item scores of the MMSE in the control group and the MCI group, despite a significant difference in total MMSE scores between the 2 groups. The item scores for the MCI group also demonstrated little difference from those of the depression group. However, the subjects of the MCI group incorrectly answered the floor item significantly more frequently than did those of the depression group ($F = 29.305$, $df = 1$, $p < .001$).

The results from ANCOVA showed many areas of significant difference between the mild Alzheimer's disease subjects and the subjects of the other 3 groups. The most notable items in which the mild Alzheimer's disease subjects had significant deficits compared with the other 3 groups were date, day of the week, and delayed recall. In terms of the delayed recall item, mild Alzheimer's disease subjects recalled zero out of the 3 words (apple, table, penny) significantly more often than did any one of the other 3 groups, while the total number of words recalled correctly by subjects of the mild Alzheimer's disease group was significantly fewer than that of either the control subjects or depression subjects (see Table 2). In terms of delineating between items of particular importance on the MMSE when evaluating groups of elderly individuals with cognitive decline, incorrect responses to certain individual items (date, day of the week, delayed recall) were correlated to subjects with mild Alzheimer's disease. The floor item discriminates depression from both MCI and controls (see Table 2). There do not, however, appear to be any individual items on the MMSE that alone discern between all 4 groups.

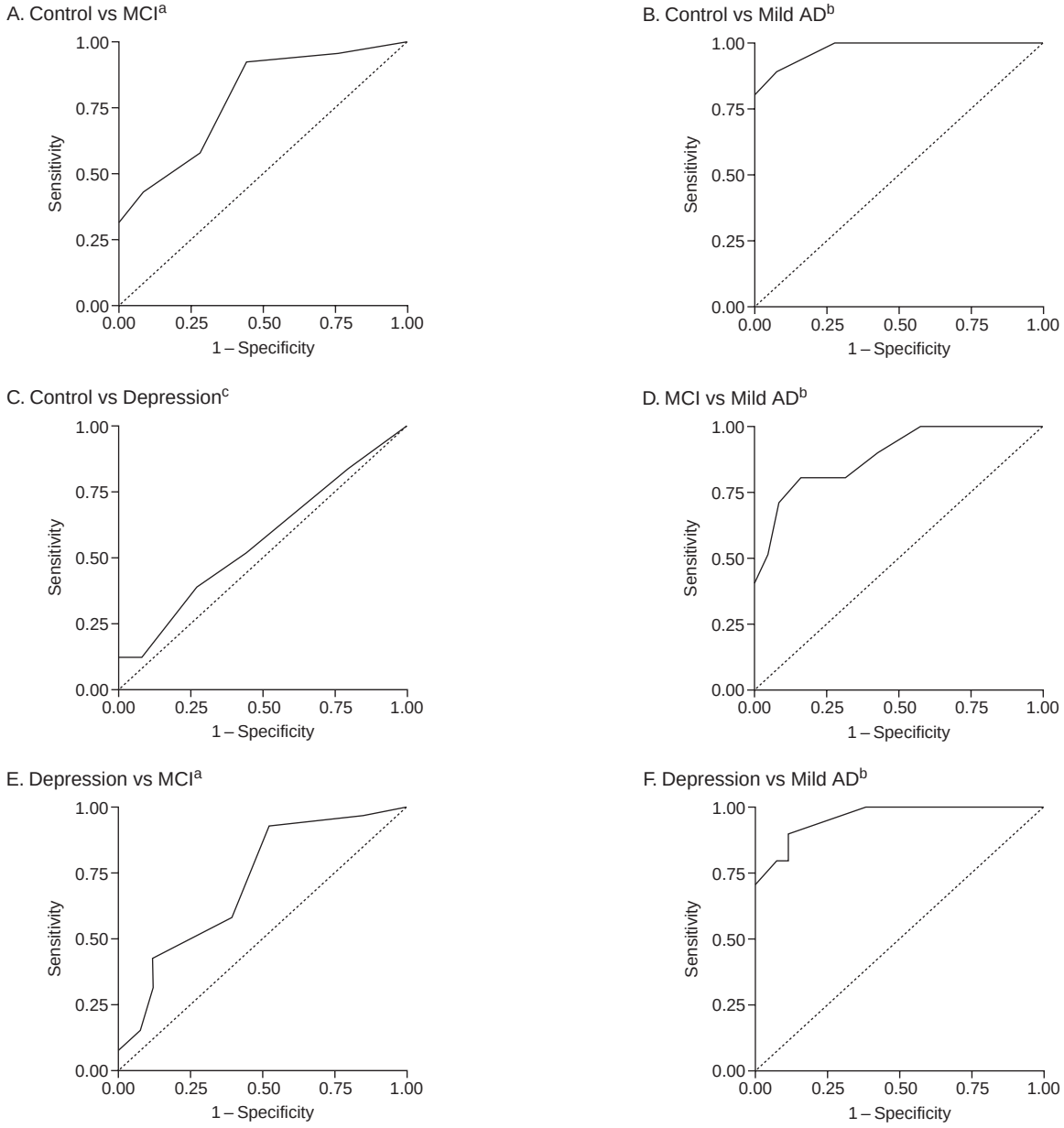
Between-group comparisons of total MMSE scores were used to construct ROC curves (Figure 1), which permitted data analysis (Table 3) via those ROC curves. The ROC curves showing the largest AUC and accuracy values (among other values as well) are those comparing any one of the groups of nondemented states to the mild Alzheimer's disease group as the positive state. However, the values calculated from the ROC curves comparing the control, MCI, and depression groups with each other are markedly lower than those with the mild Alzheimer's disease group as the positive state.

DISCUSSION

The results of this study demonstrate that the MMSE can still play an effective role in the primary care physician's cognitive screening of the elderly. Out of the 4 groups studied, our results show that the MMSE appears best suited to identify cognitive impairments caused by mild Alzheimer's disease. Both the total score and incorrect responses for the individual date, day of the week, and delayed recall items could be useful to the primary care physician in detecting cognitive changes associated with mild Alzheimer's disease. The MMSE total score may differentiate between normal age-associated memory symptoms and MCI (a possible prodromal state of Alzheimer's disease) and also separate MCI from mild Alzheimer's disease.[19]

While we have shown that incorrect responses for the items date, day of the week, and delayed recall can indi-

Figure 1. ROC Curves for Overall MMSE Scores



[a]MCI was the positive state used in the comparison.
[b]Mild AD was the positive state used in the comparison.
[c]Depression was the positive state used in the comparison.
Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, ROC = receiver operating characteristic.

cate mild Alzheimer's disease, the other items individually showed little sensitivity or specificity, consistent with several other studies.[8–10] Depression, an important differential diagnosis in the elderly population, was not well separated from normal elderly controls or MCI by the MMSE. Other studies have shown that detecting cognitive impairment due to depression requires more complex tasks involving executive function or speed.[20] Due to the overlap in cutoff scores on the MMSE that separated controls from MCI (≤ 27) and from depression (≤ 28) subjects, caution should be exercised when patients' overall score falls in this range. This finding also demonstrates that additional specific testing of mood is important for an elderly person with suspected cognitive decline.

Because this was a pilot study with a relatively small sample size, the findings need to be interpreted cautiously

Table 3. Overall MMSE Score ROC Curve Statistical Results

Result	Control vs MCI[a]	Control vs Mild AD[b]	Control vs Depression[c]	MCI vs Mild AD[b]	Depression vs MCI[a]	Depression vs Mild AD[b]
Cutoff score	≤ 27	≤ 24	≤ 28	≤ 24	≤ 27	≤ 24
AUC	0.785	0.978	0.574	0.888	0.715	0.962
Sensitivity, %	57	75	52	80	58	80
Specificity, %	72	100	56	85	60	96
PPV, %	69	100	39	50	71	89
NPV, %	88	93	29	90	88	92
Accuracy, %	75	94	36	72	77	91

[a]MCI was the positive state used in the comparison.
[b]Mild AD was the positive state used in the comparison.
[c]Depression was the positive state used in the comparison.
Abbreviations: AD = Alzheimer's disease, AUC = area under curve, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic.

and may not yet be generalizable. The MMSE item scores were not originally developed to discriminate diagnostic groups, but we examined them here to investigate whether they could provide clinical value. Overall, our analyses were intended to further assist physicians in utilizing the strengths of the MMSE as a cognitive screening tool and, at the same time, emphasize its weaknesses.

The MMSE appears to be useful as a good first step in the evaluation of cognitive status and maintains its original purpose in detecting cognitive decline over time. The utility of the MMSE extends to effectively recognizing mild Alzheimer's disease and, in the absence of depression, discriminates between MCI and normal aging. The MMSE is therefore capable of providing useful information necessary for physicians to pursue early treatment and/or referral of patients displaying early signs of cognitive decline.

REFERENCES

1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
2. Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: a comprehensive review. J Am Geriatr Soc 1992;40:922–935
3. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364
4. Somerfield MR, Weisman CS, Ury W, et al. Physician practices in the diagnosis of dementing disorders. J Am Geriatr Soc 1991;39:172–175
5. Tang-Wai DF, Knopman DS, Geda YE, et al. Comparison of the Short Test of Mental Status and the Mini-Mental State Examination in mild cognitive impairment. Arch Neurol 2003;60:1777–1781
6. Stuss DT, Meiran N, Guzman DA, et al. Do long tests yield a more accurate diagnosis of dementia than short tests? a comparison of 5 neuropsychological tests. Arch Neurol 1996;53:1033–1039
7. Pasqualetti P, Moffa F, Chiovenda P, et al. Mini-Mental State Examination and Mental Deterioration Battery: analysis of the relationship and clinical implications. J Am Geriatr Soc 2002;50:1577–1581
8. Feher EP, Mahurin RK, Doody RS, et al. Establishing the limits of the Mini-Mental State: examination of "subtests." Arch Neurol 1992;49: 87–92
9. Braekhus A, Laake K, Engedal K. The Mini-Mental State Examination: identifying the most efficient variables for detecting cognitive impairment in the elderly. J Am Geriatr Soc 1991;40:1139–1145
10. Klein LE, Roca RP, McArthur J, et al. Diagnosing dementia: univariate and multivariate analyses of the Mental Status Examination. J Am Geriatr Soc 1985;33:483–488
11. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
12. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
13. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
15. Delis DC, Kramer JH, Kaplan KE, et al. California Verbal LearningTest—2nd ed. (CVLT-II). New York, NY: Psychological Corporation; 2000
16. Wechsler D. Wechsler Memory Scale—3rd ed. (WMS-III). New York, NY: Psychological Corporation; 1997
17. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414
18. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol 1975;32:632–637
19. Petersen RC, Stevens JC, Ganguli M, et al. Practice parameter: early detection of dementia: mild cognitive impairment: an evidence-based review. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142
20. Tarbuck AF, Paykel ES. Effects of major depression on the cognitive function of younger and older subjects. Psychol Med 1995;25:285–296

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