Variability in Annual Mini-Mental State Examination Score in Patients With Probable Alzheimer Disease

A Clinical Perspective of Data From the Consortium to Establish a Registry for Alzheimer’s Disease

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Objective: To determine the variability in annual Mini-Mental State Examination scores of patients with Alzheimer disease enrolled in the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD).

Patients: A total of 372 patients with probable Alzheimer disease with 1 or more years of follow-up.

Setting: Twenty-one CERAD clinical sites throughout the United States.

Results: An average annual decline of 3.4 points in CERAD patients returning for longitudinal reassessments was close to the SD of the measurement error of 2.8 points for the Mini-Mental State Examination. There was wide variability in individual rates of decline. Even with 4 years of follow-up, 15.8% of the patients had no clinically meaningful decline in Mini-Mental State Examination score (defined as a change in initial score $>3$, ie, 1 SD of measurement error). Validity of measurements of the rate of change in Mini-Mental State Examination scores improved with longer observation intervals and was reliable for most patients when observations were separated by 3 or more years.

Conclusions: Although the Mini-Mental State Examination is a useful screening instrument to assess level of cognitive function, it has limited value in measuring the progression of Alzheimer disease in individual patients for periods less than 3 years because of a large measurement error and substantial variation in change in annual score.
Change in MMSE was determined by 2 methods. In the traditional clinical approach, change was defined as the difference between 2 scores separated by time. In the statistical model, change was estimated using a random slope and intercept model and fit using SAS PROC-MIXED. The model estimated an average entry MMSE score and change in MMSE score over time for the patients as a group (fixed effects), and then estimated subject-specific slope and intercept terms to reflect how each individual deviated from the group average (random effects). Additional covariates were included so that fixed effects could vary by demographic or prognostic factors, such as age, sex, comorbidity, and age of onset. We added terms to the fixed-effect model to determine whether comorbid conditions reported by the subjects or caregivers (hypertension, cardiac disease, thyroid disease) and age at which the symptoms of dementia were first noted (onset age) affected MMSE score at entry or its rate of change over time.

Continuous predictors, specifically, age at first evaluation and symptom duration, were included in the model and centered at a value close to the mean or median. This aids interpretation of the model, since every coefficient must be interpreted as conditional on other predictors in the model. We used age, centered at the average age of 71 years, for patients who were followed up annually. Likewise, we centered symptom duration at the median of 4 years. To ensure adequate control for the possibly confounding effects of age, we also included quadratic age terms as appropriate. Centering age also increased the stability of the model when polynomial terms were included because this technique reduced the correlation between the linear and quadratic terms.

Data from some subjects described in this article have been published previously. However, all analyses reported herein were performed independent of prior analyses.

Median length of follow-up was 2.4 years for patients and 4.1 years for controls. The proportion of each group returning annually decreased steadily over time (Figure 1).

Patients who did not return to clinic for follow-up evaluations were evaluated by caregivers via a telephone interview. Comparison of the 82 patients in cohort 2 who returned for a fourth-year follow-up with members of the cohort who did not showed no differences with respect to age, sex, marital status, education, or comorbid conditions at entry. However, patients who did not return for their fourth annual assessment had a greater degree of cognitive impairment at the time of enrollment (MMSE mean score, 17.3 vs 20.6; $P<.001$) and more functional impairment (mean Blessed Dementia Scale score, 4.3 vs 3.8; $P<.05$). The primary reasons patients did not return were entry into nursing homes (54.3%) or death (37.1%). The reasons for drop out by controls were less clear, but many stopped coming when their spouses became too severely impaired to return to the clinic.

We estimated the reliability of the MMSE score by comparing data obtained at entry with that obtained 1 month later in a subsample of 331 patients and 317 controls. Test-retest Pearson correlations were 0.87 and 0.67, respectively. The lower correlation for controls reflects a more limited range of scores due to a ceiling...
effect. Changes in score among patients ranged from an increase of 7 points to a decrease of 8 points, with an average change of −0.5 (SD, 2.8). During the 1-month interval, 95% of retest MMSE scores for patients were within 6 points of their original scores. Analysis of the test-retest reliability data provided no evidence of a learning effect or measurable deterioration in cognitive function (Figure 2). Changes in scores among controls ranged from +4 points to −6 points (average change, +0.1; SD, 1.3). Ceiling effects reduced the change feasible for them.

Figure 3 demonstrates the distribution of MMSE score changes seen during sequential visits. Each dot represents 1 or more patients with the same score change. The MMSE score change indicated is the difference between 2 contiguous visits, adjusted for the number of years between visits.

Figure 4 shows the overall rate of change for each patient. This was estimated as the difference between the last and first MMSE scores, divided by the number of years between testing. Follow-up intervals ranged from 1 to 6 years. For patients with only 1 year of follow-up, MMSE score changes ranged from a decline of 23 points to an improvement of 7 points. As follow-up interval increased, the range of score changes narrowed, but even after 4 years, 13 (15.8%) of the 82 patients returning had no meaningful decline.

Table 1. Characteristics of the Study Population (Control and Patient Cohorts) at Entry

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n = 343)</th>
<th>Patient Cohort 1 (n = 119)</th>
<th>Patient Cohort 2 (n = 372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry, mean ± SD, y</td>
<td>68.5 ± 7.7</td>
<td>71.8 ± 7.9</td>
<td>70.9 ± 7.8†</td>
</tr>
<tr>
<td>Male, %</td>
<td>33</td>
<td>40</td>
<td>49†</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-11 y</td>
<td>10</td>
<td>25</td>
<td>20†</td>
</tr>
<tr>
<td>12 y</td>
<td>28</td>
<td>35</td>
<td>32†</td>
</tr>
<tr>
<td>&gt;12 y</td>
<td>62</td>
<td>40</td>
<td>48†</td>
</tr>
<tr>
<td>Marital status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>66</td>
<td>66</td>
<td>78†</td>
</tr>
<tr>
<td>Widowed</td>
<td>8</td>
<td>27</td>
<td>17†</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>7</td>
<td>5†</td>
</tr>
<tr>
<td>MMSE score, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>100</td>
<td>38†‡</td>
<td>48†‡</td>
</tr>
<tr>
<td>16-19</td>
<td>0</td>
<td>21†‡</td>
<td>25†‡</td>
</tr>
<tr>
<td>10-15</td>
<td>0</td>
<td>23†‡</td>
<td>21†‡</td>
</tr>
<tr>
<td>&lt;10</td>
<td>0</td>
<td>18†‡</td>
<td>6†‡</td>
</tr>
<tr>
<td>BDS score, mean ± SD</td>
<td>NA</td>
<td>4.4 ± 2.3</td>
<td>4.1 ± 2.3</td>
</tr>
<tr>
<td>CDR score, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0†</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>51†‡</td>
<td>58†‡</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>41†‡</td>
<td>39†‡</td>
</tr>
<tr>
<td>&gt;2</td>
<td>0</td>
<td>8†‡</td>
<td>3†‡</td>
</tr>
</tbody>
</table>

*MMSE indicates Mini-Mental State Examination; BDS, Blessed Dementia Scale; CDR, Clinical Dementia Rating scale; and NA, not administered.
†Cohort 2 significantly different from the control group at P < .05 based on the χ² analysis for categorized variables and t test for continuous measures.
‡Significant difference between the 2 patient cohorts (P < .05) based on the χ² analysis for categorized variables.
had no significant decline (\(P = .11\)). By the fourth year of follow-up, 15.8% still remained within 3 points of their initial score. At the first annual evaluation, 53.9% of the patients had no significant decline during 1 or more years in a patient with AD, we reviewed the data for the 82 patients with 4 years of follow-up to determine the proportion whose scores remained within 3 points of their initial score. At the first annual evaluation, 53.9% of the patients had no significant decline. By the fourth year of follow-up, 15.8% still had no significant decline.

To evaluate how often an MMSE score remains stable during 1 or more years in a patient with AD, we reviewed the data for the 82 patients with 4 years of follow-up to determine the proportion whose scores remained within 3 points of their initial score. At the first annual evaluation, 53.9% of the patients had no significant decline. By the fourth year of follow-up, 15.8% still had no significant decline (Table 2).

Because of the variable length of follow-up and number of MMSE scores available for each patient with AD, we used a random-effects linear regression model to estimate the average rate of change within patients. Model 1 represents the result of fitting MMSE scores on years in the study, sex, and age (with both linear and quadratic terms). The interaction between years in the study and the effects of sex and age (linear term only) are presented in Table 3.

The MMSE score declined by an average of 3.41 points per year (\(P < .001\)) at age 71 years. Age had a statistically significant impact, with a 0.06-point-per-year (\(P < .001\)) additional decline for every year greater than 71 or a corresponding reduction in the rate of decline for every year less than 71. Sex had no significant effect (\(P = .43\)).

Random-effect variances may be interpreted as those of the subject-specific slopes and intercepts. The random “years in study” effect was of particular interest. It had a variance of 3.65, indicating that 95% of the subjects should have had a rate of change in the range of \(-7.15 \pm 0.33\) MMSE points per year (ie, \(-3.41 \pm 1.96 / 3.65\), compared with the 95% confidence interval on the population average rate of change of \(-4.23 \pm 2.59\). The correlation of 0.33 between the subject-specific slopes and intercepts indicates that subjects with higher initial MMSE scores tended to have an individual rate of decline that was somewhat flatter (ie, they have less decline) than individuals with lower initial MMSE scores. This relationship between initial MMSE score and rate of change was also observed in an earlier analysis of this same cohort.14

Model 2 represents the final model after including comorbidity and age at symptom onset as fixed effects. Each variable was assessed both alone and as an interaction with years in the study. All fixed-effect terms not statistically significant at the \(P = .1\) level were dropped. With this model, 95% of the subjects had a rate of change between \(-7.27 \pm 2.59\). Other explanatory variables that affected the rate of change were age, with a change of 0.05 points per year of age \((P = .001); duration of disease, with an increase of 0.12 points per additional year \((P = .008); and presence of thyroid disease, with a decrease of 0.90 points per year when present \((P = .03). Variance of the subject-specific slopes was 3.37, essentially unchanged from model 1. The correlation between the subject-specific intercept and slope estimates was 0.35, indicating a tendency for patients who entered with higher MMSE scores to have less decline during the observation period.

Although the MMSE is valid during a 1-month interval, suggesting that repeated observations over time are not confounded by a practice effect, our analysis of data collected during an observation period of up to 6 years indicated that, because of high measurement error and wide variability in individual rates of change, the MMSE had limited value as a method to mark cognitive changes in individuals with AD who are followed up for less than 3 years. Even after 4 years of follow-up, 15.8% of the remaining 82 patients had no clinically meaningful decline in MMSE score. Until factors affecting clinical or biological heterogeneity are identified, the MMSE will con-

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time trend slope term (years in study). These were subject-

We estimated only 2 random effects: an intercept and a

viations for each subject from the population averages.
in study) should provide a reasonable estimate of how a
tia) or protocol entry selection factors. Thus, under the

assumption of a constant rate of MMSE score change over

ted. Information was restricted by the willingness and abil-
y of patients to provide in-person follow-up data. This lim-
its the ability to apply our conclusions to the larger universe
of patients with AD, particularly those at the very high and
very low ends of the MMSE score range. Nevertheless, the
large number of carefully evaluated patients enrolled in this
CERAD study and the multiple participating sites provide
an excellent opportunity to explore questions that cannot
be addressed easily using smaller, single-site cohorts.

At entry into CERAD, patients were at different stages
of disease. We presumed that the rate of MMSE change
was constant over time and minimally affected by the point
of entry into CERAD (relative to age at onset of demen-
tia) or protocol entry selection factors. Thus, under the
assumption of a constant rate of MMSE score change over
time, the effect-specific slope estimates (eg, age by years
in study) should provide a reasonable estimate of how a
given effect affected the rate of change.

In the model, the random effects represented de-

viations for each subject from the population averages.
We estimated only 2 random effects: an intercept and a
time trend slope term (years in study). These were subject-
specific terms that essentially fit a simple linear regres-
sion for MMSE on time for each case. The estimates were
an individual’s estimated deviation from the fixed-effect
intercept and slope of the sample. Variations in subject-
specific parameters and their correlation were of par-
ticular interest. The heterogeneity in rate of change in
the AD cohort was given by variance in subject-specific
slope estimates. Consistent with previous observations
large heterogeneity in individual rates of change is striking, relative to the low variation in popu-
lation average estimates, and sheds light on the diffi-
culty of using individual patient MMSE scores as a clini-
cal prognosis tool. Correlation of the slope with the
intercept estimated the (linear) association between the
rate of MMSE score change and MMSE score level at en-
try. The weak correlation of 0.33 provided reassurance
that CERAD selection criteria had little impact on our
rate-of-change estimates.

From an individual patient management stand-
point, this study highlights a number of clinically rel-

vant points. First, to be clinically meaningful, a change
in MMSE score during any period must exceed 3 points.
This threshold makes it more likely that the difference
reflects an actual change in cognitive abilities rather than
testing imprecision. Second, the MMSE, when used as
the sole measure of cognitive change for an individual
patient, may not be a reliable measure for intervals of less
than 3 years. Procedures that might enhance the utility
of the MMSE as a measure of change are not obvious.
Other structured instruments for measuring cognitive
change in patients with dementia have similar limita-
tions. From a practical standpoint, a clinician may want
to continue to use the MMSE, particularly if the assess-
ment can be done often enough to allow averaging of the
changes that may be due to random variation. Although
not assessed in this study, clinicians should always con-
sider other factors that may affect individual MMSE scores,
such as changes in the patient’s living environment, medi-
cations, and the presence of problem behaviors. In addition,
changes in a patient’s functional abilities and the observa-
tions of a knowledgeable caregiver are impor-

<table>
<thead>
<tr>
<th>Table 3. Linear Mixed Models to Assess Mini-Mental State Examination Change Over Time for Patients With Alzheimer Disease*</th>
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<tbody>
<tr>
<td><strong>Table 3. Linear Mixed Models to Assess Mini-Mental State Examination Change Over Time for Patients With Alzheimer Disease</strong>*</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
</tr>
<tr>
<td><strong>Parameter (β)</strong></td>
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<tr>
<td>Fixed effects</td>
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<tr>
<td>Years in study</td>
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<tr>
<td>Sex by years in study</td>
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<tr>
<td>Age of 71 y by years in study</td>
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<tr>
<td>Disease duration of 4 y by years in study</td>
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<td>Thyroid disease by years in study</td>
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<tr>
<td>Random effects</td>
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<tr>
<td>Intercept</td>
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<tr>
<td>Years in study</td>
</tr>
<tr>
<td>Error</td>
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<tr>
<td>Correlation</td>
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<tr>
<td>Model 1 Variances</td>
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<tr>
<td>Intercept, years in study</td>
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</table>
| * Variables found to be nonsignificant and therefore excluded from the final model included age at onset of dementia symptoms and hypertension as a comorbidity. Ellipses indicate data not applicable.
tant components in reaching an overall conclusion about changes in dementia severity. Third, the rate of change in MMSE score is not influenced to a clinically meaningful extent by the age at onset of dementia symptoms or the presence of relatively mild medical comorbidity. Furthermore, in this cohort, neither age at the time of assessment nor sex contributed to (or predicted) either the annual rate of MMSE score change or the variability associated with that annual change. Fourth, although the hallmark of AD is progressive cognitive impairment, the rate of change for individual patients varies, and it is not uncommon for patients to have a stable or even an improved score during a 1-year interval. Although we have found that the degree of variation narrows with increasing length of follow-up, this may simply reflect a self-censoring process associated with drop out as patients are admitted to a nursing home, become too severely impaired to return for follow-up evaluations, or die.

Thus, although the MMSE remains a convenient instrument for the rapid assessment of cognitive status, its ability to document changes over time in individual patients with AD is limited. The most important limitations are the high measurement error, which almost equals the average annual score change, and the highly variable individual annual change. As a consequence, improvement in the MMSE score during 1 year and/or stability in the score for periods up to 4 years may still be consistent with a clinical diagnosis of AD.

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