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Modelling Mini Mental State Examination changes in Alzheimer's disease

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SUMMARY

The Mini Mental State Examination (MMSE) is widely used to measure dementia severity in Alzheimer's disease patients. While changes over time in the MMSE due to dementia have been studied, the relationship between MMSE scores and the duration of disease course is less well understood. Using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) data, we modelled change in MMSE as a function of time for this population. For this purpose we used the interval between consecutive MMSE assessments as the time factor. We also investigated the impact of sex, education and age at testing on the resulting model. Analyses showed that Alzheimer's disease progression over time (ADP) can be modelled using a cubic or a logarithmic function of MMSE score. From these curves ADP can be obtained as a function of MMSE. These models demonstrate that there are different rates of change for various ranges of the MMSE. Additional analyses suggest that patient factors affect rates of ADP, younger patients and more educated patients progress more rapidly, while sex has little impact on ADP. Such estimations of disease course are useful when comparing different populations for both clinical and research purposes. Copyright © 2000 John Wiley & Sons, Ltd.

INTRODUCTION

Assessment of illness severity is critical to the diagnosis, treatment and research of Alzheimer's disease (AD). Several clinical staging methods have been developed for estimating dementia severity in AD patients. However, these broad categorical approaches can suffer from observer bias. Consequently, structured mental status measures are often used in conjunction with clinical ratings for more objective measurement of dementia severity. One of the original efforts in this regard indicated that scales incorporating cognitive and descriptive items correlate with the underlying

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neuropathology of AD [1]. The most popular of these brief cognitive scales, the Mini Mental State Examination (MMSE) [2], has been widely used because of its brevity and applicability across the mild and moderate stages of AD [3–5].

In general, the values that are obtained from different cognitive and descriptive scales for the same group of AD patients tend to correlate highly with each other [6, 7]. The relationships between diverse assessments of AD suggests that these scales, evaluating different AD symptoms, including daily function, cognitive impairment, or global impression of severity and change, all reflect the same underlying pathological process. Consequently, these scales warrant further analysis of their dynamic relationship with the course of the disease.

Many studies have examined the temporal course of measures of dementia severity. There is a clear indication that these measurements show a worsening of AD symptoms over time [7–9]. Several models have been applied to understand the dynamics of the change associated with disease progression. For example, a tri-linear model has been used to estimate at which point decline begins and ends [10]. However, ceiling and floor effects of the measures used to estimate severity limit the usefulness of most scales in the earliest and latest phases of the illness [11, 12] and may impact on such estimates of decline. Other methods including 'growth curve' approaches have also been useful for representing the change that occurs in cognitive test performance over time [13–15]. Further, another analytic approach using non-parametric smoothing has shown that scores from several measures can be combined and related to a 'time-index' estimation of dementia severity based on disease time course or duration [16]. Using the relationship between change scores and a population-based disease time-course, any scale can theoretically be referenced to the absolute measure of 'time' (in days, months or years of disease). This model can then be applied to study factors that could influence the rate of progression in a population.

Here we propose a method based on the concept of 'time-index' [16]. The present study applies this method to the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) [17] data set for modelling change in the MMSE. Rate of change of the MMSE in the CERAD data has been examined previously [7]. The present model extends these analyses to a time-based model that estimates the relationship between MMSE changes and AD progression (ADP). This model is then used to examine the influence of factors such as age, sex and education level on change over time.

POPULATION

The initial database consisted of all patients in the CERAD data archive (1986–1996, Documentation and Data, Archive Rev. 1.0, March 1996), all of whom were diagnosed as probable or possible AD. A complete description of the characteristics of these patients and collected data can be found in the paper by Heyman *et al.* [17]. From this database we selected all 1496 observed MMSE differences (MMSE scores between 29 and 1) that were obtained at least 180 days apart. The resulting data set included MMSE scores from 719 patients followed between 6 months and 7 years (mean = 2.3 years, median = 2 years). The number of MMSE differences per patient ranged between 1 and 7, with time between sequential assessments ranging from 182 days to 2298 days (mean = 402 ± 139 days, median = 371 days). For these patients followed up to 7 years, 91.1 per cent of the sequential differences were less than 550 days apart. The mean age for the 719 patients at entry was 71.9 ± 7.8 years (median 72.47 years). The distributions of these patients' gender, education and age at entry into the protocol are shown in Table I.

Table I. Distribution of gender, age and education.

Gender		Age		Education	
Male	42.4%	<72 years at entry	44.1%	$\leqslant 12$ years	58.4%
Female	57.6%	$\geqslant 72$ years at entry	55.9%	>12 years	41.6%

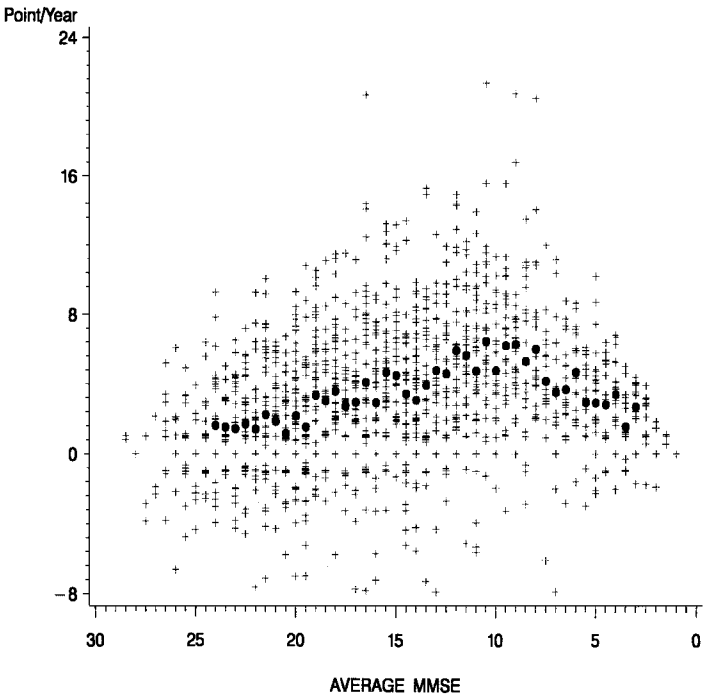


Figure 1. Change in MMSE scores over time as a function of average MMSE score for 1496 measurement intervals (+). Mean rates of change denoted by •.

METHODS

For each pair of MMSE scores we calculated the rate of change, in points per year, defined as

$$\text{Change} = \frac{\text{MMSEscore1} - \text{MMSEscore2}}{\text{Time2} - \text{Time1}} = \frac{\Delta\text{MMSE}}{\Delta t}$$

as a function of the average MMSE score ((MMSEscore1 + MMSEscore2)/2) over a given measurement interval. Then for each resulting average MMSE severity score we calculated the mean change (Figure 1 and Table II).

These mean changes, over the range of 24 to 3, were then inverted to obtain an estimate (in years per point) of the time needed for the MMSE score to decrease by one point as a function of each averaged interval MMSE value. Because of a lack of fit of a linear model ($p<0.001$), two curves, a quadratic polynomial and an 'inverse' function, were then fitted to the inverted mean values using weighted (by number of data points available for each MMSE) linear regression.

Table II. Mean MMSE change/year (± standard error) for different values of MMSE.

MMSE	MMSE change/year	MMSE	MMSE change/year
3	2.19 ± 0.34	14	3.36 ± 0.45
4	2.83 ± 0.27	15	4.28 ± 0.44
5	2.90 ± 0.40	16	3.69 ± 0.49
6	4.00 ± 0.44	17	3.22 ± 0.44
7	3.75 ± 0.62	18	3.29 ± 0.27
8	5.42 ± 0.64	19	2.77 ± 0.40
9	6.06 ± 0.54	20	1.81 ± 0.35
10	5.56 ± 0.53	21	1.77 ± 0.32
11	5.30 ± 0.51	22	1.72 ± 0.41
12	5.58 ± 0.49	23	1.52 ± 0.35
13	4.46 ± 0.52	24	1.45 ± 0.38

Figures 2(a) and 2(b) show the mean values, the fitted curves, and the 95 per cent pointwise confidence curves and Figure 2(c) shows both fitted curves superimposed.

To model relative duration of illness we then integrated the fitted curves to obtain a measure of Alzheimer's disease progress (ADP) in years as a function of MMSE score. An MMSE value of 24 was used for normalization because it is an accepted cutpoint for presence of AD [5]. The fitted curves and the numerically integrated raw means are shown in Figure 3.

RESULTS

Means of the raw data obtained from Figure 1 are listed in Table II. The rates of progression ranged between 1 and 2 points per year for MMSE scores between 20 and 24. Rates exceeded 5.3 points per year for scores between 8 and 12.

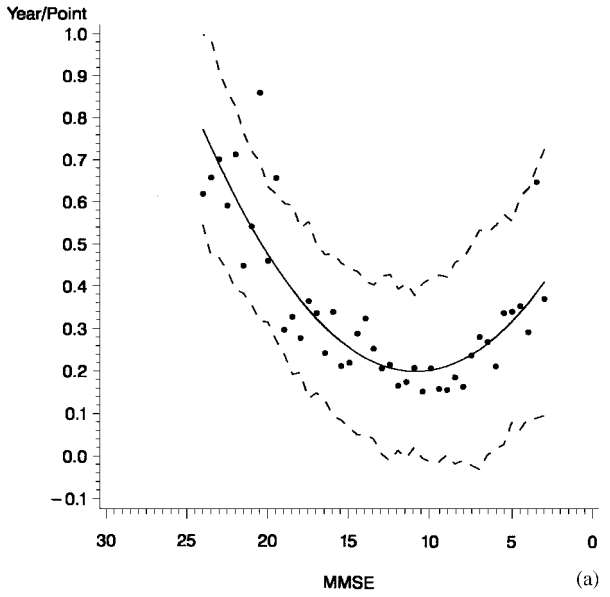
The equations for the integrals (normalized to zero for MMSE = 24) of the fitted quadratic and 'inverse' curves shown in Figure 3 are

$$\mathrm{ADP} = -0.0011\mathrm{MMSE}^3 + 0.0364\mathrm{MMSE}^2 - 0.6012\mathrm{MMSE} + 8.669$$

$$\mathrm{ADP} = -0.5157\log(\mathrm{MMSE}) + 4.2109\log(30 - \mathrm{MMSE}) - 5.906$$

It should be noted that we only used the values between 24 and 3 to fit these curves, since we had few data points below this range and annualized change was essentially zero for higher values.

To determine if age, gender or education affected these curves, we applied the extra sums of squares principle from regression analysis to the quadratic curve for the rate of change. We found that age is a significant factor ($p < 0.05$), education is a marginally significant factor ($p < 0.10$), and gender is not a significant factor ($p > 0.10$). The numerically obtained ADP (integrated inverse mean MMSE scores) are depicted in Figure 4(a) for both genders, in Figure 4(b) for educational level (those who attained at the most a high school degree and those that continued further) and in Figure 4(c) for age group using the cut-off 72 years. The effects of gender, age and education on the duration of the decline from 24 to 4 points on the MMSE are shown in Table III.



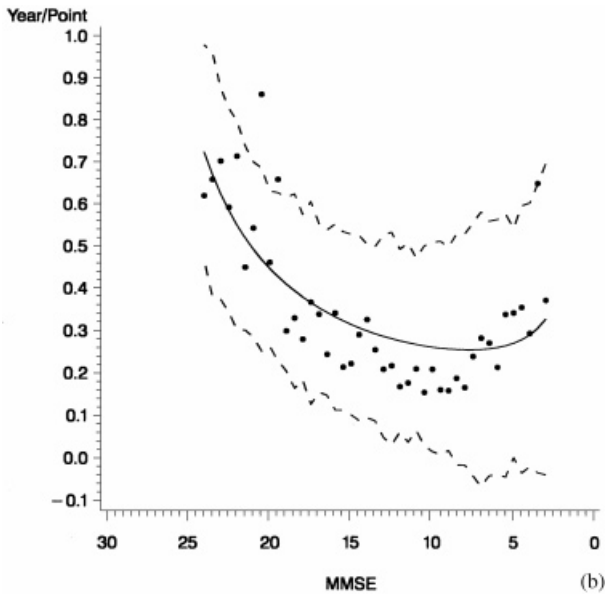
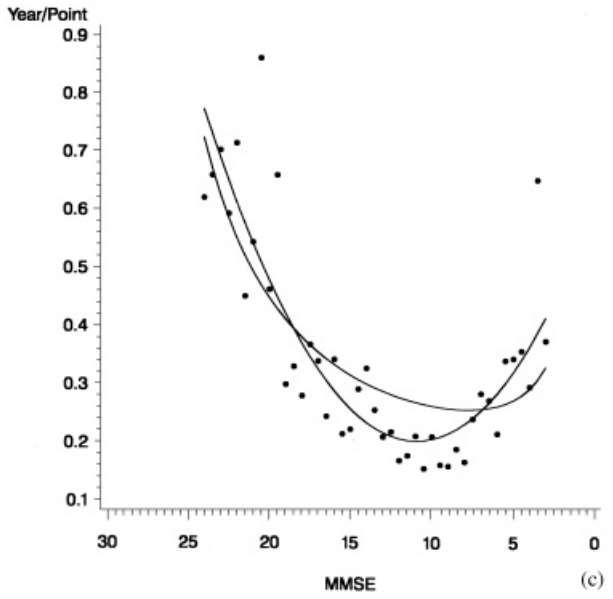


Figure 2. Inverted mean rates of change versus MMSE score yielding an estimate of the amount of time needed to have MMSE change by one point. Weighted least square fit of the quadratic regression model described below (solid line) and 95 per cent confidence limits for the mean (dashed line): (a) $\hat{y} = ax^2 + bx + c$, $a = 0.00334 \pm 0.00048$, $b = -0.0730 \pm 0.0136, c = 0.6013 \pm 0.0884$, $r^2 = 0.721$; (b) $\hat{y} = a/\ln x + b/\ln(30 - x)$, $a = 0.5157 \pm 0.2230$, $b = 4.2109 \pm 0.2774$, $r^2 = 0.921$; (c) both curves superimposed.



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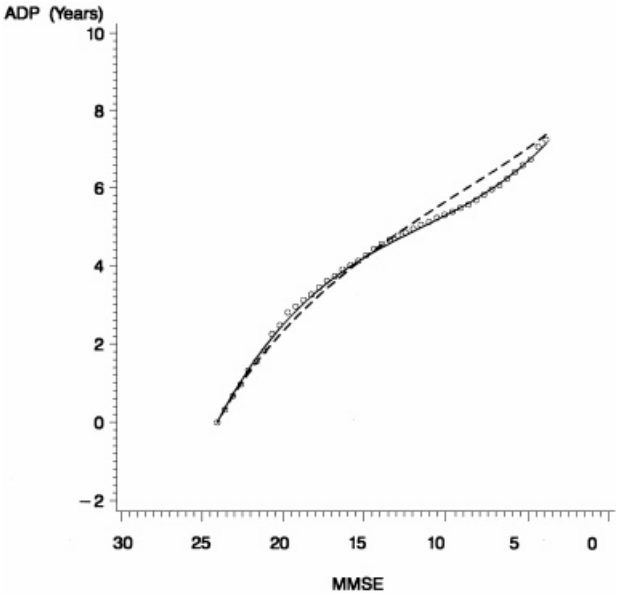

Figure 3. Average amount of time associated with a one point change in MMSE, as a function of MMSE score. Solid line is quadratic fit.

CONCLUSIONS

Following the clinical axiom that the dementia associated with AD progresses over time, the analyses in this paper show a mathematical representation of that decline. Analyses of the rates of progression showed that the rate of change of MMSE scores depends on the average MMSE score for the time interval examined. These differing rates of progression may reflect the item characteristics (10 points for orientation, 6 points for memory, 5 points for attention, 8 points for language, and 1 point for praxis) of the MMSE [11, 16], suggesting that the scale is more sensitive to changes in the middle to late stages of AD (for example, a shift on the three memory recall items early in disease to language tasks in later stages). Alternatively, the increased rate may reflect accumulating impact of AD pathology on cognition at later disease stages. Regardless, numerical integration of the inverse of these mean values results in the mean time-course of the illness as a function of the MMSE. Further, both cubic and logarithmic functions adequately characterize AD progression.

There is considerable heterogeneity in the raw observations of the rate of change, and rates of change vary by observed MMSE score. Interrater comparisons and test–retest assessments of the MMSE show that there is variability in measurement which is unrelated to disease progression [2, 18] and may therefore influence estimates of progression. Also, environmental and patient factors may contribute to this variability. It is therefore likely that disease progression, day-to-day fluctuations in patient performance, different individual rates of progression, and disease heterogeneity (including such factors as genes, head injury etc.) contribute to the variation in MMSE changes over time. Since shorter time intervals between measurements increase the effect of non-specific variability on the estimated rate of progression [13], we selected only those assessments that were at least 180 days apart.

Analyses incorporating patients' age, sex and education revealed different rates of progression. The data suggest that the disease mechanism is more rapid when it affects younger individuals. Participants' sex had a minimal effect on AD progression, with females having a slightly slower course than males. However, education had a substantial impact on AD progression. While other studies have shown that education appears to reduce the risk of developing AD [19, 20], the present analysis found that more education is associated with a more rapid course (Table III). These results can be interpreted in a variety of ways, for example, better initial performance on mental status tests in more educated individuals may delay diagnosis, and thus make the course appear more rapid once AD is diagnosed. Examination of the influence which such factors have on the rate of progression of AD can further our understanding of the disease process.

One issue that was considered in developing these analyses was whether or not to evaluate the rate of change as a function of the initial MMSE score [19] or as a function of the mean MMSE score [16]. The use of the initial or baseline MMSE score would be of interest if scores were examined for change over a single short time interval using techniques such as ANOVA possible with the baseline score as covariate. However, when assessment times are variable and longer intervals are examined, estimated intermediate MMSE values become relevant and the mean score over that time interval provides the critical reference point. Since we were interested in the mean rate of change as a function of the MMSE score, we chose to model the data in this fashion.

This study shows that the CERAD data set can be used to establish a simple and straightforward model of change as a function of the MMSE score. This same method could be used to model relationships between the time course of AD and any other psychometric test or rating scale as well as to estimate progression as a function of a combination of measures for different populations. The

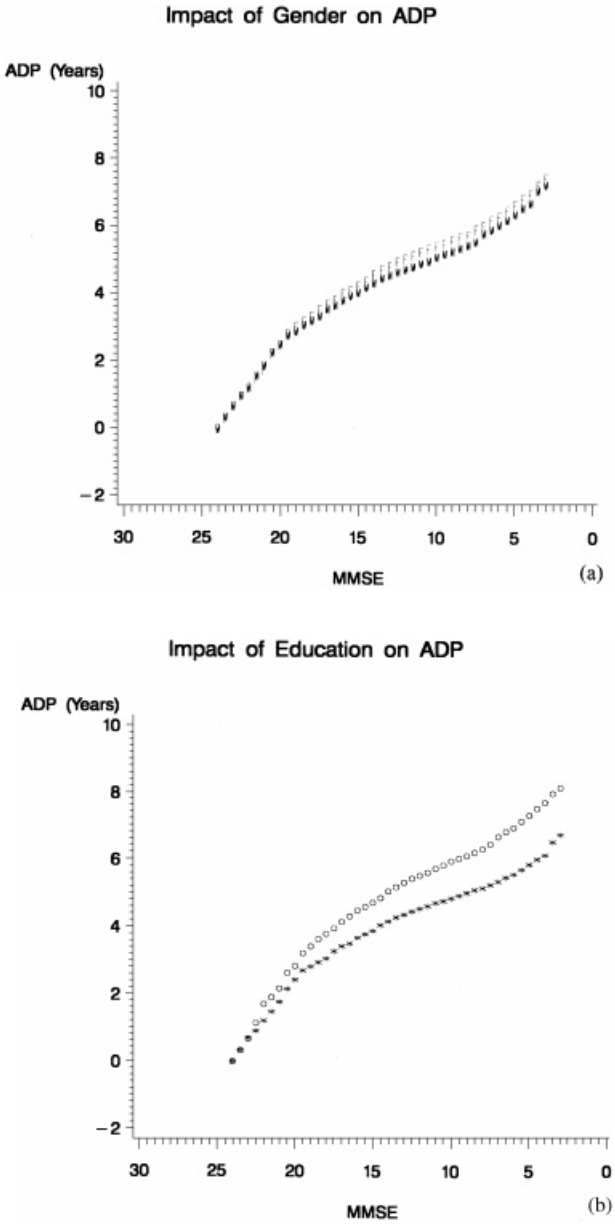

Figure 4. Comparison of numerical integration for patients grouped by: (a) gender, F, female and M, male; (b) education, ○, < 12 years of education, *, 12 or more years of education; (c) age, ○, < 72 years, *, 72 years or older, the solid line represents the integral of the quadratic fit for each group. The individual values of the inverse of change is infinite when two consecutive MMSE are the same.

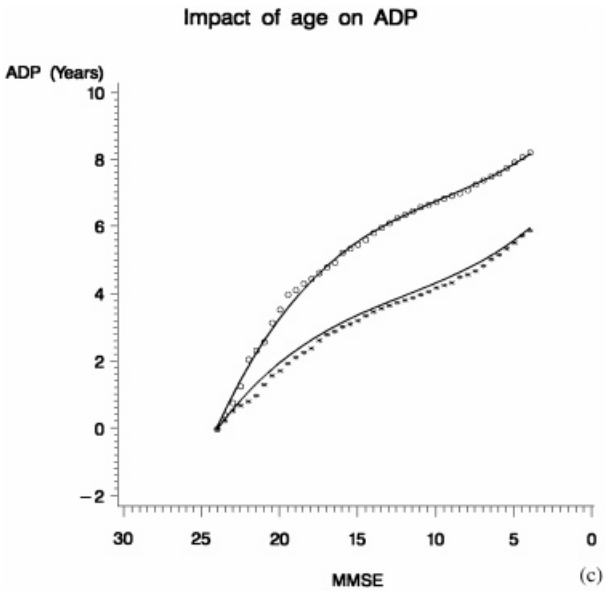

Figure 4. Continued.

Table III. Duration of decline (years) from 24 to 4 points.

Gender	Decline	Age	Decline	Education	Decline
Male	6.67	<72 years	5.90	$\leqslant 12$ years	7.69
Female	6.95	$\geqslant 72$ years	8.23	>12 years	6.12

different rates of progression due to age, education, and mean MMSE suggest that caution should be used when interpreting changes in mental status measures (for example, therapeutic trials) since, as this study indicates, a simple mean population change of 2 or 4 points on a measure such as the MMSE does not always translate into an equivalent course of 9 to 12 months of the disease. Rather, the degree of change seen on a given mental status test should be referenced to the mean interval score before discussing the measures of point change in terms of disease course.

We are presently working on how ratings can be combined across different functional measures in order to give a more precise estimate of disease severity, for clinical or research purposes, across the duration of the Alzheimer's disease process.

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