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Taking Account of Between-Patient Variability When Modeling Decline in Alzheimer's Disease

L. Joseph,[1,2] D. B. Wolfson,[3] P. Bélisle,[1] J. O. Brooks, III,[4] J. A. Mortimer,[5] J. R. Tinklenberg,[6] and J. A. Yesavage[6]

The pattern of deterioration in patients with Alzheimer's disease is highly variable within a given population. With recent speculation that the apolipoprotein E allele may influence rate of decline and claims that certain drugs may slow the course of the disease, there is a compelling need for sound statistical methodology to address these questions. Current statistical methods for describing decline do not adequately take into account between-patient variability and possible floor and/or ceiling effects in the scale measuring decline, and they fail to allow for uncertainty in disease onset. In this paper, the authors analyze longitudinal Mini-Mental State Examination scores from two groups of Alzheimer's disease subjects from Palo Alto, California, and Minneapolis, Minnesota, in 1981–1993 and 1986–1988, respectively. A Bayesian hierarchical model is introduced as an elegant means of simultaneously overcoming all of the difficulties referred to above. *Am J Epidemiol* 1999;149:963–73.

Alzheimer's disease; Gibbs sampler; hierarchical model; natural history; models, statistical; random effects model

With increasing life expectancy, Alzheimer's disease has become a health issue of major concern, prompting much research on different aspects of this disease. In particular, Yesavage and Brooks (1) discuss the importance of longitudinal studies in Alzheimer's disease. Recently, the discovery of the apolipoprotein E (apoE) ε4 allele as a possible risk factor for Alzheimer's disease, as well as its promise as a prognostic indicator of disease course, has provided further motivation for carefully collected longitudinal data on disease progression and sound methods of analysis of these data (2, 3).

There have been many articles on the assessment of decline in Alzheimer's disease (4–9). By introducing statistical models, researchers have attempted to describe the natural history of Alzheimer's disease and to ascertain which factors influence the disease course. Carefully constructed models that describe decline are indispensable for several reasons. First, by anticipating how a group of subjects might be expected to decline, one may better design clinical trials to evaluate the effect of treatments for Alzheimer's disease. For example, models provide the framework for deciding how many and which patients should participate in a study, how often they should be evaluated, and how long a study should continue. Once the data are collected, such models must then be used to evaluate any effect, for "effect" may only meaningfully be interpreted as a model characteristic. Even ad hoc comparisons have hidden model assumptions. Models can also be used to examine the role of covariates, such as age of onset, gender, years of education, and the apoE gene profile, on decline (5, 9). Finally, prediction by means of some form of regression model, say, may not only be useful for anticipating the disease course of individual patients and, consequently, future care that may be needed, but also for planning on a larger scale. In Canada, for example, roughly 50 percent of demented individuals live in the community (10).

Since progressive cognitive impairment is the hallmark of Alzheimer's disease, the natural history has often been studied by following patients longitudinally while noting their scores on one or more scales of cognitive impairment. These examinations are usually administered at regular time intervals. Examples of commonly used scales are the Brief Cognitive Rating Scale (11), the Global Deterioration Scale (12), the

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Abbreviations: apoE, apolipoprotein E; MMSE, Mini-Mental State Examination.

[1] Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada.
[2] Division of Clinical Epidemiology, Department of Medicine, Montreal General Hospital, Montreal, Quebec, Canada.
[3] Department of Mathematics and Statistics, McGill University, Montreal, Quebec, Canada.
[4] Department of Psychiatry, Stanford University School of Medicine, Stanford CA.
[5] Institute on Aging, University of South Florida, Tampa, FL.
[6] Veterans Affairs Health Care System, Palo Alto Division, Stanford University School of Medicine, Stanford, CA.

Dementia Rating Scale (13), and the Mini-Mental State Examination (MMSE) (14).

A review of the literature reveals both a wide variety of methods of modeling decline and inconsistency in the findings on the role played by different covariates on disease course. The disparate statistical methods applied to different data sets make comparisons difficult. For instance, Yesavage et al. (4) and Katzman et al. (5) use the difference between first and last scores divided by the time between these evaluations to estimate the rate of decline. On the other hand, Haxby et al. (6) take a more sophisticated approach by considering three different regression models with MMSE scores regressed on time. In the first, a simple linear regression is fit to each patient, and in the second, a common regression is assumed for all patients, while the third allows for an initial plateau in the regression line followed by a period of decline. A similar, stepwise weighted least-squares regression with several covariates (in addition to time) is fitted by Mortimer et al. (7). Brooks et al. (8) also propose a model with plateaus, specifically the model of Haxby et al., by introducing a trilinear regression with plateaus at disease onset and in the final stages. Teri et al. (9) and Growdon et al. (15) model disease progression by regressing rate of decline on several demographic variables and on level of dementia, but not on time, while Stern at al. (16) take a similar route by using a growth curve model. The latter investigators model the expected change in score over a 6-month time period, given the score at the beginning of the time period, and also examine the effect of the appearance of extra pyramidal signs on the rate of decline by introducing a time-dependent covariate. In assessing the effect of ApoE on cognitive change, Hyman et al. (17) are forced, by their limited data, to quantify decline as the difference between scores taken at two different points in time. Maltby et al. (18) examine the efficacy of tacrine on slowing the disease course by using a repeated-measures analysis of variance, allowing the treatment effects to vary randomly. Jacqmin-Gadda et al. (19) also used a random effects linear model to quantify decline in MMSE scores in nondemented elderly subjects, but their model did not include the plateau in MMSE scores that is expected to be present in more rapidly declining Alzheimer's disease patients. As will be detailed below, we also pursue the general idea of a random effects model, but add several new features.

An additional difficulty with Alzheimer's disease is that since initial symptoms are often nonspecific, age of onset has been avoided as a time origin. Consequently, authors have used other assorted time origins for their models, making interpretation and cross-comparisons difficult. Despite the range of models used on a diversity of data sets, there are some points of agreement. There is marked between-patient variability in the rate of decline of cognitive scores. MMSE (and other) scores show little change early on, fall in an approximately linear fashion, and then level off late in the disease. These plateaus are probably due to the insensitivity of these scales to small changes that might occur very early or very late in the disease rather than to true periods of no change.

In this paper, we introduce a method, new to Alzheimer's disease research, that allows for precise description of the pattern of decline in patients with Alzheimer's disease. Our model simultaneously allows for between-patient variability via a random effects model, while also including plateau effects and adjusting for imperfect age of onset estimates. Estimation of the effects of covariates on the decline rates can be accomplished through a simple extension of the model. We next apply our model to longitudinal MMSE data from patients with Alzheimer's disease recruited for prognostic studies in Palo Alto, California, and Minneapolis, Minnesota.

MATERIALS AND METHODS

Two independently collected data sets from different parts of the United States were analyzed in this study. These will be referred to as the Minneapolis data set and Palo Alto data set, respectively. Although subjects in the Palo Alto data set were followed for a longer period of time, table 1 shows that the patient characteristics were similar.

The Minneapolis data set

The Minneapolis data set consists of subjects who were recruited between August 1986 and December 1988 from the Minneapolis Veterans Affairs Medical Center and from the community to participate in a prospective longitudinal study of primary degenerative dementia (7). Ninety-three subjects were initially screened for primary degenerative dementia using the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (20) criteria. Of these, 76 were retrospectively found to satisfy the National Institute of Neurological and Communicative Disorders and Stroke criteria (21), which were published after the Minneapolis study had started. Family histories were also recorded. Those subjects who were deemed to have primary degenerative dementia were included in the cohort. Patients with a possible cerebrovascular etiology for their dementia were excluded. Eleven patients were retrospectively excluded either because it was ascertained that they probably did not

TABLE 1. Demographic characteristics for study subjects

	No. of subjects	Age at entry into study		Age at AD* onset		Males		Family history of dementia		Length of follow-up (years)		MMSE* score at entry	
		Mean	(SD)*	Mean	(SD)	No.	%	No.	%	Mean	(SD)	Mean	(SD)
Palo Alto, California	55	64.1†	(9.0)	60.3†	(9.7)	32	65	NA‡		5.1	(2.7)	18.4	(7.7)
Minneapolis, Minnesota	65	67.6	(8.7)	63.7§	(8.5)	47	72	26¶	41	2.3	(0.85)	17.3	(4.66)

* AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; SD, standard deviation.
† Four subjects had missing information.
‡ Family history data not available for the Palo Alto data.
§ Six subjects had missing information.
¶ One subject had missing information.

have Alzheimer's disease or because they had contributed fewer than three data points by the end of the study. Sixty-five subjects remained for the analysis. Detailed inclusion and exclusion criteria are given by Mortimer et al. (7).

After acceptance into the study, subjects were assessed at 6-month intervals until death or loss due to other reasons. No subject contributed more than eight data points. That is, there was a maximum of a baseline measurement and three and one-half years of follow-up. Data used for this analysis included the approximate age of onset, age at entry into the study, gender, and years of education. Age of onset was provided by the family and, as such, is probably interval censored because of the vague initial symptoms of Alzheimer's disease. Other data not relevant to the present analysis were also collected (7).

Figure 1 provides the trajectories of the MMSE histories (as a function of time) of a sample of three subjects from the Minneapolis data set. Note that not all subjects were followed for the full eight periods.

The Palo Alto data set

Subjects for the Palo Alto data set were identified and followed between January 1981 and April 1993 at the Stanford Alzheimer's Disease Diagnostic and Treatment Center to participate in a longitudinal study of dementia (22). As with the Minneapolis data, subjects were carefully evaluated at entry and were excluded if it was suspected that their cognitive impairment was not caused by Alzheimer's disease. Subjects were included if they satisfied National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association criteria (21) for definite or probable Alzheimer's disease. Patients with fewer than three MMSE data points were excluded from the analysis but continued to be followed as part of the study. Data on 55 subjects were available. Figure 2 provides the trajectories of the MMSE histories of a representative sample of subjects from the Palo Alto data set. The time axis is, again, in units of 6-month periods from the initial MMSE score.

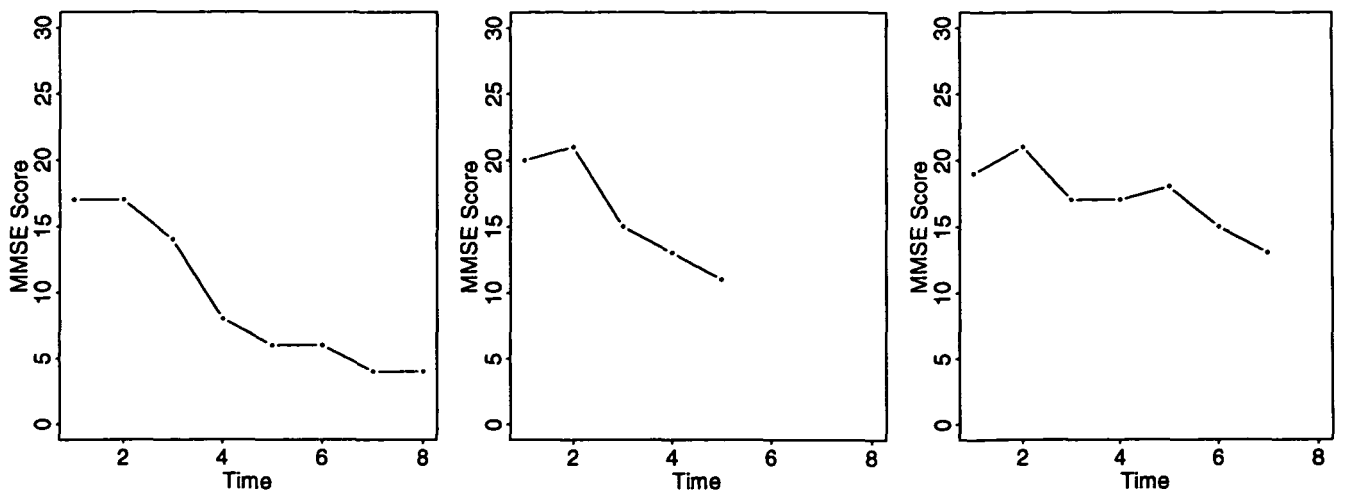

FIGURE 1. MMSE scores over time for three subjects from the Minneapolis data set, Minneapolis Veterans Affairs Medical Center, 1986–1988. The time axis is in units of 6-month periods.

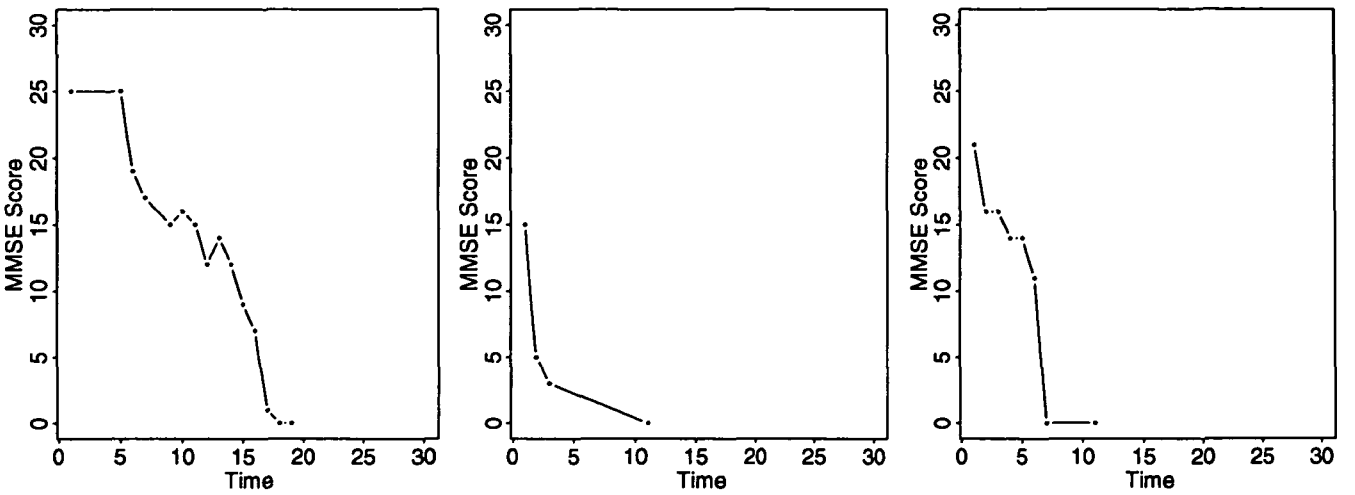

FIGURE 2. MMSE scores over time for three subjects from the Palo Alto data set, Stanford Alzheimer's Disease Diagnostic and Treatment Center, 1981–1993. The time axis is in units of 6-month periods.

Statistical methods

Overview. Longitudinal MMSE scores may be regarded as repeated measures data with highly variable paths. Frequently, as is pointed out by Crowder and Hand (23), large between-subject variability is best dealt with by random effects models. While our model allows for random effects, we use a flexible Bayesian hierarchical approach that is quite different from the methods commonly described under the heading "random effects models" (23, pp. 98, 105, and 112). Figures 3–5 illustrate the advantages of including hierarchical random effects in a model that describes data with widely varying parameters.

In figure 3, all subjects are shown to have different "true" rates of decline, but there is no common statistical model assumed for these rates. Figure 3 represents the decline phases of patients from two populations. There are two problems with using simple (nonhierarchical) linear regressions to estimate each patient slope. First, if there are relatively few observations from each patient, as is common in Alzheimer's disease research, estimates of patient-specific regression parameters can be highly unreliable. Second, comparisons between the two populations are difficult to make, since no concise summary of the disparate slopes from each population is available, especially one that takes into account the uncertainty in the individually estimated slopes.

Figure 4 depicts the case in which all subjects within a population are assumed to have identical rates of decline. Estimates of parameters are reliable, since data from all patients contribute toward estimating a single slope, and comparison between populations is standard. The model is unrealistically restrictive, however, since it assumes a single rate of decline for all patients in a given population, known not to be the case for Alzheimer's disease patients.

Consider again the situation in figure 3, in which the rates of decline for individual patients differ. Focus on a single group, say that of figure 3a. Instead of regarding the patient slopes simply as a collection of different numbers, think of them as having been randomly selected from some population of slopes (i.e., from randomly selected patients with Alzheimer's disease, each of whom is associated with a decline slope). This population of slopes is described by means of a probability density function, for example, a normal density in which the mean represents the average slope in the population and where the between-subject variability in that population is represented by the normal variance. The two probability density functions in figure 5 may be thought of as being the densities that generated the slopes of figures 3a and 3b, respectively, and may be compared. Each possible value for the MMSE slope is associated with its relative likelihood (height of the probability density curve), so that the two curves in figure 5 present the ranges and relative likelihoods of each possible decline rate in the two populations. Not only do we then have a convenient summarization of the slopes of any single group (through the group density), but we also have a convenient means of comparing two or more groups by comparing their probability density functions. Further, reliable estimation of all patient slopes is made possible by the "borrowing of strength" from the ensemble of slopes to aid in the estimation of each individual slope; these slopes are linked through the hierarchical distribution.

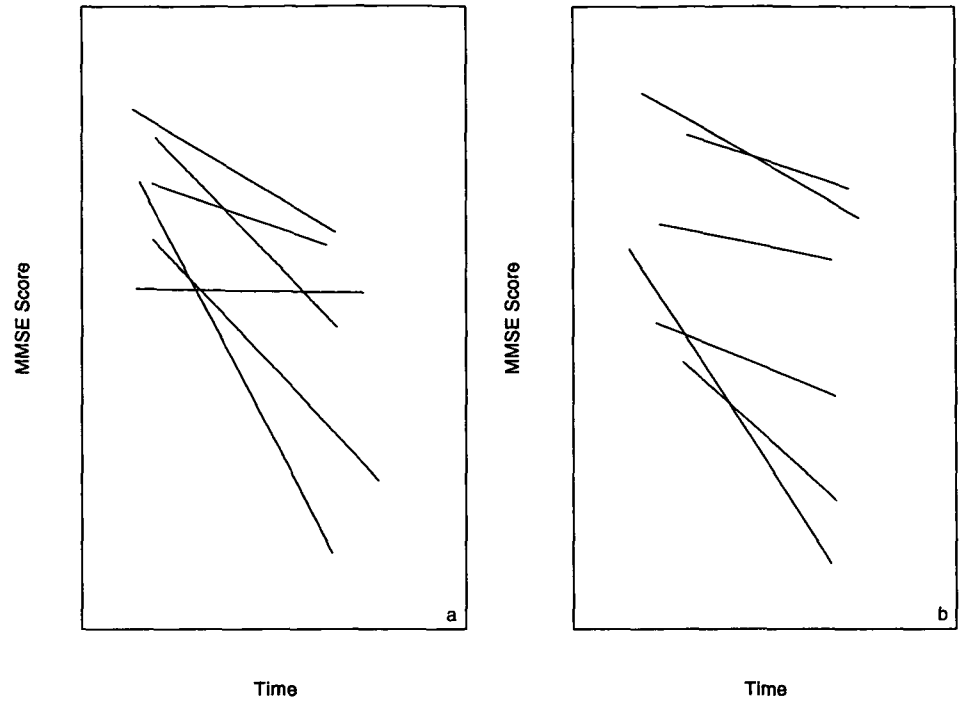

FIGURE 3. Prototypic decline slopes from two hypothetical populations when each patient may have different rates of decline within each population.

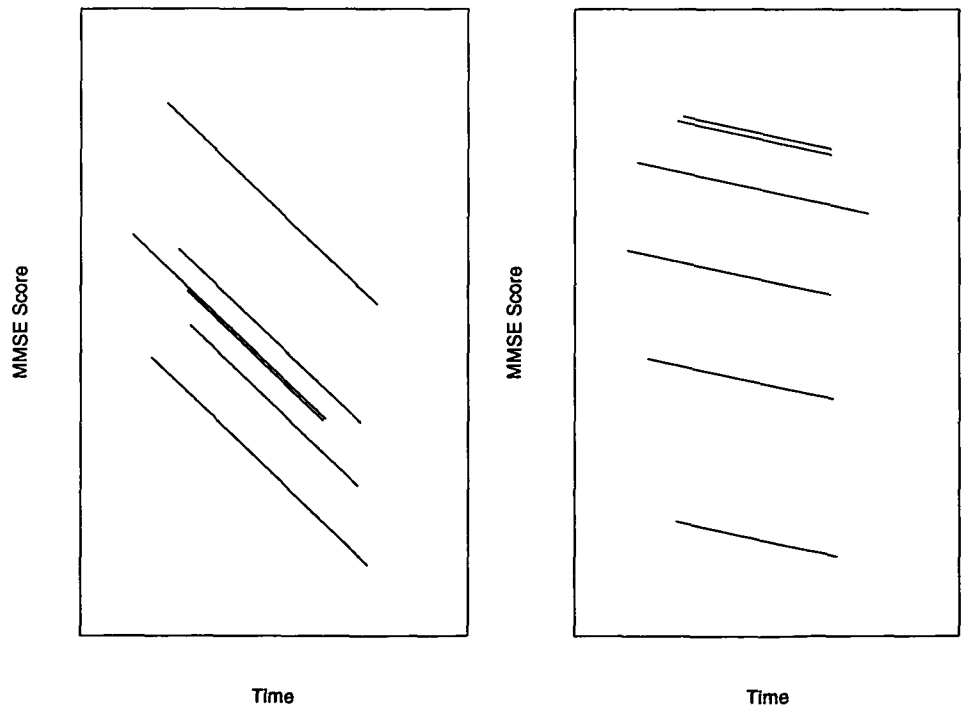

FIGURE 4. Prototypic decline slopes from two hypothetical populations when all patients are assumed to have identical rates of decline within each population.

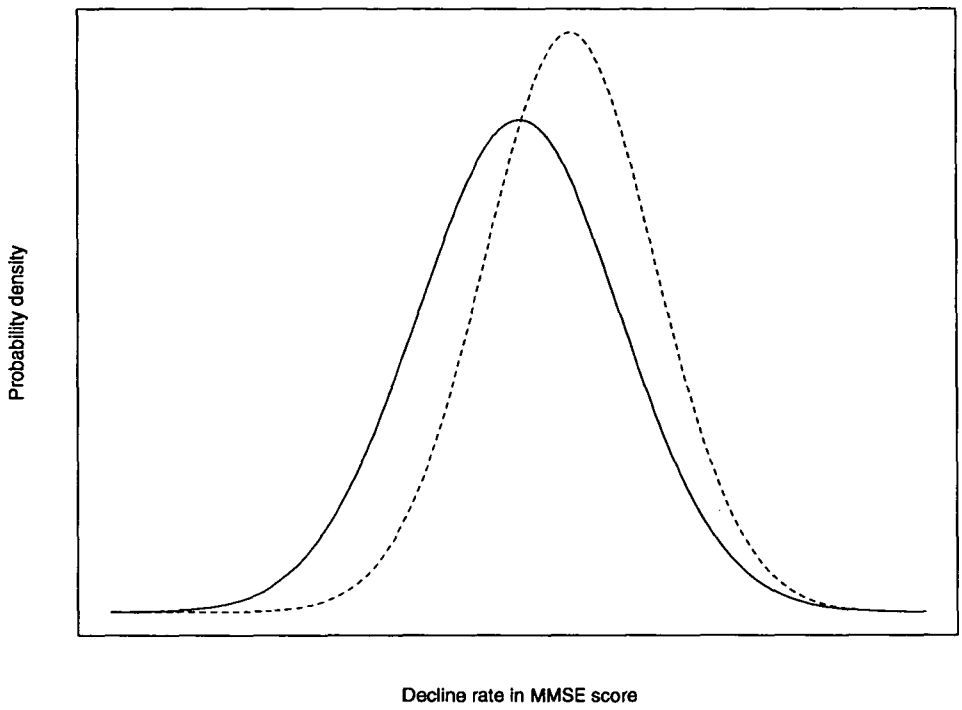

FIGURE 5. Distributions that summarize the decline rates in each of two populations.

For the MMSE data analyzed here, a modification of the situation depicted in figure 3 is made to accommodate the plateau expected in the observed MMSE scores, so that only data from the decline period contribute to the estimates of the slopes. The allowance we make for the inclusion of plateaus that vary randomly among subjects precludes the application of mixed linear models (24); our mixture model is nonlinear. Nevertheless, the basic analytic strategy as presented above remains unchanged.

The model. In view of the discussion in the introduction to this paper, one may expect that at least two distinct periods could be identified in MMSE trajectories for dementia patients, from disease onset to the final plateau. These are a period of relatively steady decline, which ends in a final stable period, most often with an MMSE score below 10, where either decline truly stops or, more likely, the MMSE becomes insensitive to further decline.

Although Brooks et al. (8) fitted a trilinear model to the Palo Alto data, after careful reexamination of the two data sets, it was decided to fit only linear and bilinear models because of the lack of sufficient data from the early stages of the disease. Bilinear models were also considered by Brooks and Yesavage (25). A linear model was considered since it was a priori believed that by the end of the respective studies some subjects may not have reached the final plateau stage. The bilinear model presented here was ascertained through the use of Bayes factors (26) to have by far the best fit among five models that were considered. Included among these models were linear models with a single residual variance parameter across all subjects, a similar linear model with individual residual variance parameters across patients, and bilinear models with various different combinations of individual and common variance parameters for the decline and plateau phases. The model presented below was independently selected as the best for both data sets. Full details are contained in the report by Bélisle et al. (27).

The model has three levels specified in a hierarchy. At the first level is the joint density of the data, commonly called the likelihood function. The bilinear model is depicted in figure 6, where it is seen that for each patient, five parameters are needed to determine the sloping regression line that changes at some point to become horizontal in the plateau stage. Ignoring the patient label, for convenience, these parameters are: b, the slope of the regression line; v_1, the variance of the MMSE scores during the decline period; v_2, the variance of the MMSE scores during the plateau period; h, the value of the regression line at entry into the plateau phase; and c, the time at which the regression line enters the plateau stage. At the second level, each of the first-level parameters, b, v_1, v_2, h, and c, is assigned a probability distribution on the basis of experience and past studies, but not on the current data. In our analysis, we used "low-information" prior distribu-

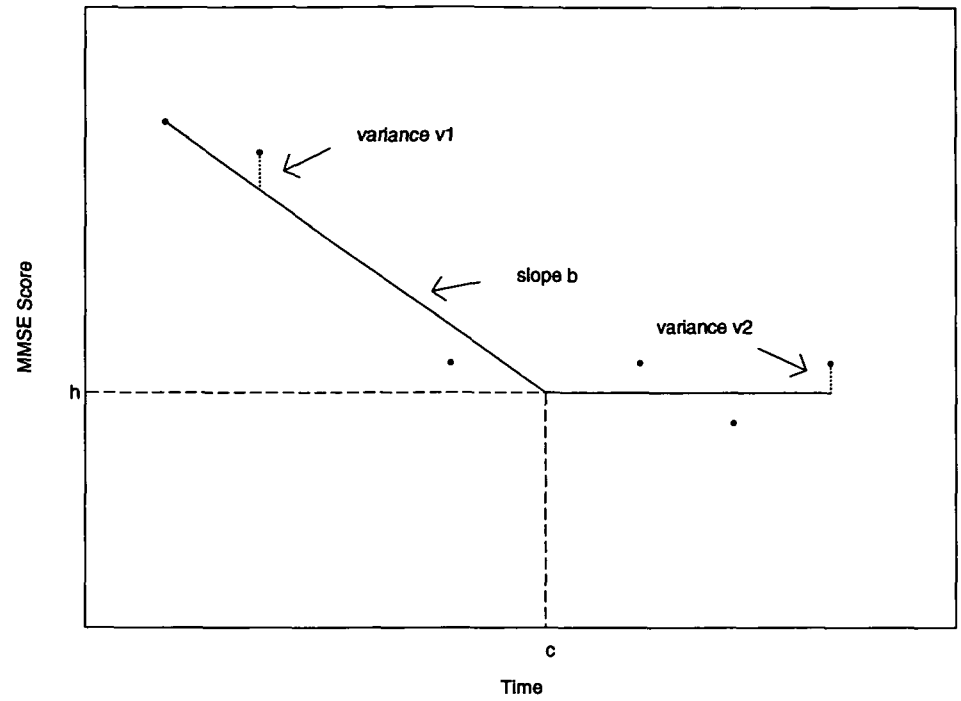

FIGURE 6. The bilinear model with parameters of the model.

tions, where the entire range of plausible values is covered by a roughly "flat" prior distribution over the range of most likely values. Therefore, all likely values are approximately equally likely a priori. This allowed the data to dominate the prior distributions. Therefore, while the prior distributions retain their importance as a starting point in the modeling process, they contribute little (compared with the data) to the final numerical estimates of the parameters of the model. Future use of the model may, of course, include less diffuse prior distributions that reflect greater experience with longitudinal Alzheimer's disease data. At this level, all of the prior distributions are specified exactly except for b, which is assumed to have a normal distribution with unspecified mean and standard deviation, m and s, respectively. A third level in the hierarchy is therefore required, where prior probability distributions for m and s are specified. The prior distribution for m was taken to be a normal distribution, while the prior distribution for s^2 was the inverse chi-square distribution (so that $1/s^2$, often called the precision, would be chi-square).

Note that since interest here is focused primarily on the rate of decline, the inclusion of a third level was restricted to describing the variation in the slope parameter b (via m and s). This third level is needed to summarize the distribution of the rates of decline in a population, given the observed MMSE scores, as in figure 5.

The essence of the model is that the widely varying rates of decline in a given population may initially be summarized by their prior probability distribution, given by information at level 2 when there are no hierarchical random effects and by levels 2 and 3 when there are hierarchical random effects. The data of the current study, represented by the likelihood function (first level), are used to update this distribution via Bayes' theorem to give a posterior distribution from which all inferences are made. The posterior distribution summarizes the knowledge about the parameter values contributed by both past studies and the present trial. Technically, the updating is carried out through the Gibbs sampler, the use of which is becoming increasingly popular for complex medical modeling (28).

RESULTS

In a preliminary analysis, we verified the appropriateness of using normal distributions to summarize the ensemble of slopes from each data set by plotting histograms of the individual decline rates given by crude linear regressions. A separate hierarchical model was then fitted to the Minneapolis and Palo Alto data sets, respectively. The summarization achieved by these models facilitated a comparison between the two locations. The two populations from which the Minneapolis and Palo Alto data sets were obtained

seem to have similar, although not identical, rates of decline, plateau heights when decline ceases, and intervals from disease onset to the end of decline. The observed differences were not substantial from a clinical point of view. For example, there is little clinical difference between MMSE values that fall below about 8 points on the scale. Nevertheless, the observed variation between centers could be true differences or could be due to sampling variation from relatively small sample sizes. They could also result from the slightly different entry criteria of the Minneapolis data compared with the Palo Alto data set.

We assumed, in the absence of contradictory evidence from past studies, that the prior distributions for the different parameters were unaffected by group membership (i.e., Palo Alto or Minneapolis). Figure 7 displays the common prior density for a "randomly selected" slope along with the posterior densities of this slope computed from Minneapolis and Palo Alto data sets. The prior density in figure 7 reflects our assessment, prior to seeing the current data, that the slopes would be normally distributed with mean –2, indicative of an average drop of two points per 6-month period, but that individual slopes as low as –7 or as high as +3 were not impossible. We allowed for the possibility of positive scores since, over a short period of time, it is plausible that the scores of a few patients might slightly increase. By updating the prior density using the information contained in each of the two data sets, we obtained the two posterior densities. The Minneapolis and Palo Alto posterior slopes are each again approximately centered around –2 (the mean for Palo Alto was –1.9, and the mean for Minneapolis was –2.4), but with smaller variances than that of the prior density. For example, the slopes for the vast majority of Palo Alto subjects are expected to be in the range from –4 to 0, in contrast to the prior range of –7 to +3. To assess the sensitivity of the results to the choice of –2 for the prior mean slope, we repeated the analysis with a prior mean slope of –1. The results were almost identical and are also similar to those previously reported in the literature (4, 7, 29).

To quantify this comparison further, we estimated the probability that a randomly selected rate of decline from the Minneapolis population is greater than that from the Palo Alto population. If the two populations were identical, the probability would be 0.5. This probability was estimated to be 0.618, which is not substantially different from 0.5, although it suggests the possibility that slopes from Minneapolis may be slightly higher.

A histogram of the estimated intervals between onset and the end of decline is shown in figure 8. Most of the intervals in both data sets were less than 10 years,

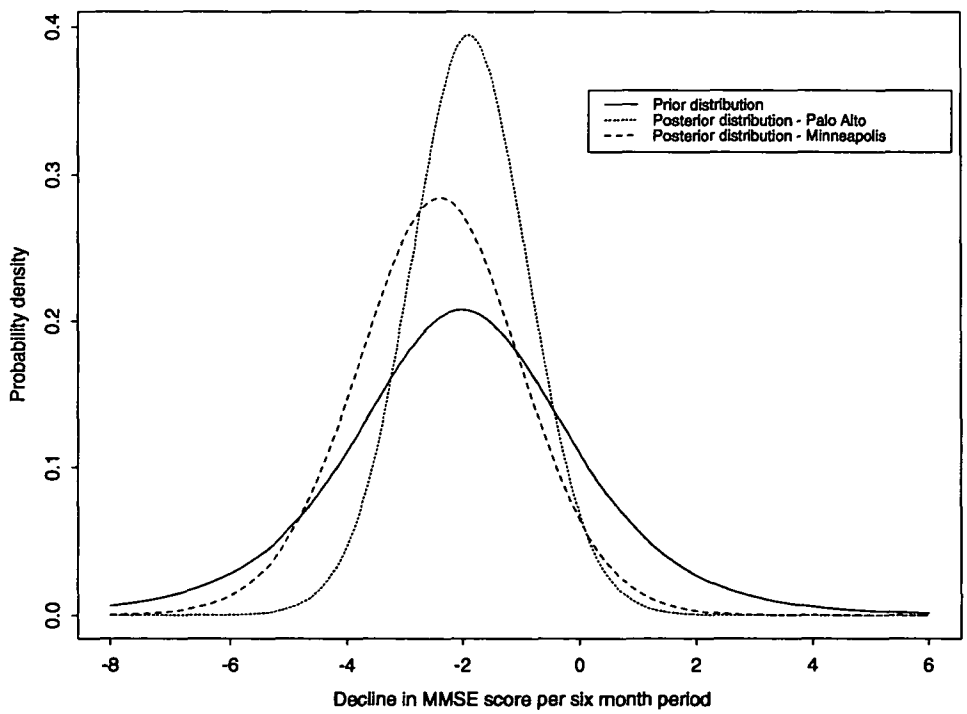

FIGURE 7. Prior and posterior distributions for the decline slopes in the Palo Alto and Minneapolis data sets, Stanford Alzheimer's Disease Diagnostic and Treatment Center, 1981–1993, and the Minneapolis Veterans Affairs Medical Center, 1986–1988.

although they were somewhat higher in the Palo Alto data set. Again, these differences may be an artefact of the different lengths of follow-up in the two data sets or may arise from inherent differences in the two populations. For example, the Palo Alto patients had somewhat higher education levels and socioeconomic statuses on average than did patients from Minneapolis.

Figure 9 displays histograms of the plateau heights, h, for the two locations. Essentially all MMSE scores level off at 10 points or lower. The plateau heights for Palo Alto are slightly more concentrated around lower values, which might be explained by sampling variability and differences in follow-up times between the two data sets.

Results from goodness-of-fit criteria were examined for each of the two data sets studied, and the model was found to fit the data well (27).

CONCLUSION

The work presented in this paper provides an elegant means to model Alzheimer's disease by accounting for the well-documented wide variability in patterns of decline among Alzheimer's disease patients. Our model goes beyond a linear random (mixed) effects regression model to include a slope that changes at some fixed, but unknown, time point, commonly called two-phase regression. A drawback of standard two-phase regression models is that they do not allow for the inclusion, as part of the modeling process, of prior knowledge one might have about the parameters. They also do not allow for the change to vary randomly in the population. Our Bayesian approach explicitly allows for the combination of prior knowledge from past studies with the information in the current trial or trials and also accommodates the random change points.

Our model is ideally suited to the comparison of other populations of Alzheimer's disease patients, such as those defined by their apoE status or treatment regimen. Inspecting curves such as those presented in figure 7 in treated and untreated groups can graphically demonstrate treatment effects and lead directly to the probability that a randomly selected slope from the treatment group will show less decline than one randomly selected from the control group. Similarly, our method should be broadly applicable to the study of the natural histories and comparison of treatment groups in other chronic diseases. Indeed, as part of a recent review of the status of current research in amyotrophic lateral sclerosis, Brooks emphasizes the importance of describing progression by referring to the World Federation of Neurology Research Group in Neuromuscular Disease

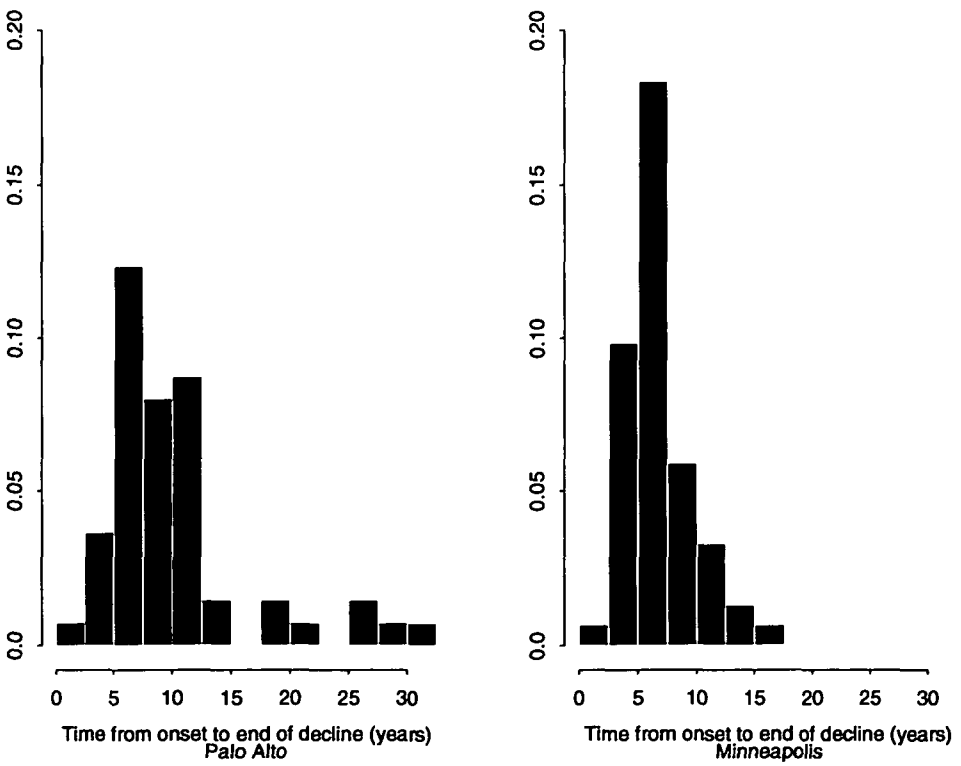

FIGURE 8. Histograms of the time from disease onset to end of the decline period in the Palo Alto and Minneapolis data sets, Stanford Alzheimer's Disease Diagnostic and Treatment Center, 1981–1993, and the Minneapolis Veterans Affairs Medical Center, 1986–1988.

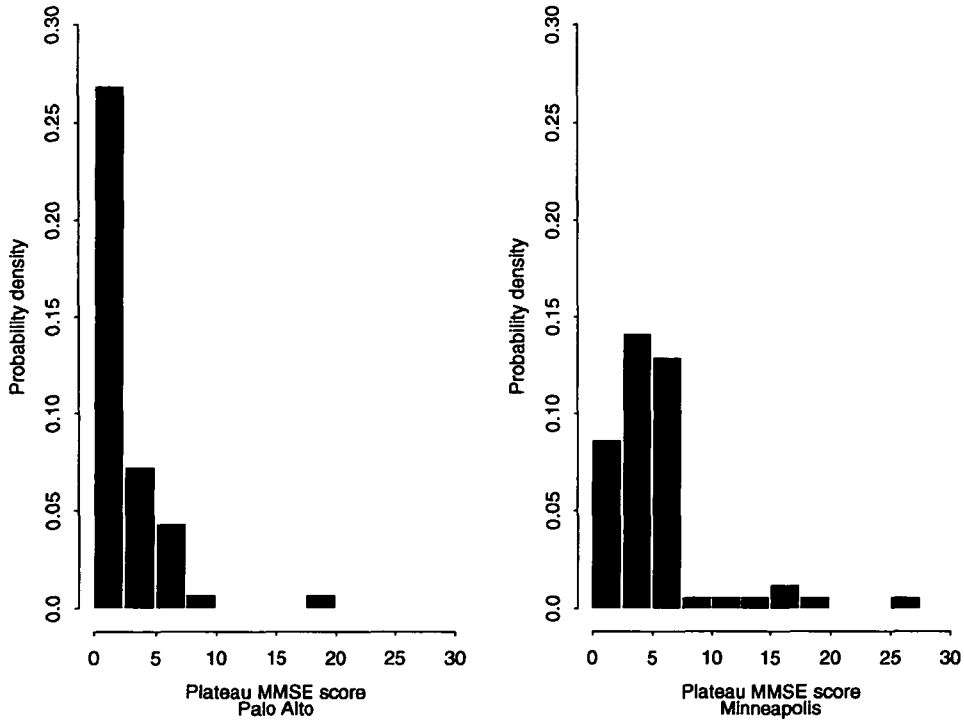

FIGURE 9. Histograms of the final plateau heights in the Palo Alto and Minneapolis data sets, Stanford Alzheimer's Disease Diagnostic and Treatment Center, 1981–1993, and Minneapolis Veterans Affairs Medical Center, 1986–1988.

Subcommittee on Motor Neuron Diseases, one of whose main areas of concern is ". . . to describe the course of the disease in individual patients, which would allow for statistical simplicity..." (30, p. S27).

Although the main purpose of this study was not to investigate the effect of covariates, by stratifying, we carried out a preliminary examination of the influence of age at onset and gender on rate of decline. Scatterplots of estimated slopes and decline durations showed neither gender nor age at onset effects, and with relatively small numbers of subjects, a full investigation of covariates appeared unwarranted. Our model, however, could easily be extended to include covariates. For example, the second-level hierarchical slope could be allowed to depend on one or more regression parameters (27). Further, accommodating the first plateau, to which Brooks et al. (8) refer, is also straightforward, although for accurate estimation there is a need to collect data from the early stages of Alzheimer's disease. Our model can also be extended to accommodate multivariate outcomes, although at the expense of additional complexity that may be caused by the correlations among the different measures. The model could also easily be adapted to estimate decline rates in other measures of cognitive ability that may have ceiling and floor effects.

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