

# Application of a Growth Curve Approach to Modeling the Progression of Alzheimer's Disease

Yaakov Stern,<sup>1,2,3</sup> Xinhua Liu,<sup>3</sup> Marilyn Albert,<sup>5</sup> Jason Brandt,<sup>4</sup> Diane M. Jacobs,<sup>1,3</sup>  
Caridad Del Castillo-Castaneda,<sup>3</sup> Karen Marder,<sup>1,3</sup> Karen Bell,<sup>1</sup> Mary Sano,<sup>1,3</sup>  
Fred Bylsma,<sup>4</sup> Ginette Lafleche,<sup>5</sup> and Wei-Yann Tsai<sup>6</sup>

The Departments of <sup>1</sup>Neurology and <sup>2</sup>Psychiatry, <sup>3</sup>the Gertrude H. Sergievsky Center, and <sup>4</sup>the School of Public Health, Columbia University College of Physicians and Surgeons.

<sup>5</sup>Department of Psychiatry and Behavioral Sciences, Johns Hopkins University.

<sup>6</sup>Departments of Psychiatry and Neurology, Massachusetts General Hospital, Harvard Medical School.

**Background.** Studies using clinical measures to track AD progression often assume linear declines over the entire course of the disease, which may not be justified. The objective of this study was to model change in measures of the clinical severity of Alzheimer's disease (AD) over time.

**Methods.** We developed a method to apply growth curve models to prospective data and characterize AD patients' functional change over time. Data from the modified Mini-Mental State Examination (mMMSE) and measures of basic and instrumental ADL, administered semiannually for up to 5 years to 236 patients with probable AD, were modeled.

**Results.** The rate of decline in mMMS scores per 6-month interval gradually increased as scores dropped from the maximum of 57 to 20. The rate of decline then decreased as scores approached 0, resulting in an inverse "S" curve. The rate of increase in instrumental ADL scores per interval attenuated as the scores increased, while that for basic ADL scores across intervals was constant.

**Conclusions.** Differences in the pattern of progression of the three measures is in part a function of their psychometric properties. The progression curves may also reflect content-specific features of the instruments. Superimposition of the modeled decline in these three content areas suggests a hypothetical model of the relative timing of cognitive and functional changes in AD.

THE Predictors Study was designed to develop models for predicting the course of an individual patient's Alzheimer's disease (AD) (1). Much of our effort has been devoted to examining the predictive utility of specific clinical variables such as extrapyramidal signs (2), psychosis (2), and age at onset (3) in an attempt to explain heterogeneity in disease course.

Important for prediction is an adequate description of the natural history of AD. The standard approach is to quantify disease progression by administering global measures of cognitive or functional disease severity at regular intervals over the course of the disease. The Mini-Mental State Examination (MMSE) (4), which assesses cognition, and the Blessed Dementia Rating Scale (BDRS) (5), which assesses instrumental and basic activities of daily living, are commonly used for this purpose, and several studies have estimated expected rates of change (6-9). Decline on these scales has been viewed as linear, with constant change expected over any particular time interval. However, this is not the case. Annual change in MMSE scores for participants in CERAD (the consortium to establish a registry for Alzheimer's disease) differed as a function of the score itself; more marked change occurred in the moderate range of scores (10). This observation was simply based on inspection of annual changes associated with each score and was

not based on any formal model of the decline process. A "trilinear model" of decline has been proposed, in which rapid change occurs in the midrange of disease severity with relative plateaus early and late in the disease (11). However, there is no basis for assuming that this model of decline applies equally to all measures of disease severity.

The observed pattern of decline in scores may also be a function of the psychometric properties of each scale. Thus, they may not actually reflect differences in the rate of progression of the disease itself. For example, some tests tend to be less sensitive to changes at their scoring extremes than in their midrange. These ceiling and floor effects can influence observed rates of change, yet the disease continues to progress once a patient has reached minimum scores. Also, both the MMSE and BDRS are made up of heterogeneous items that reflect different cognitive abilities or functional activities, and these domains are unequally represented. Patterns of progression in a test score may therefore be a function both of the relative weight of the component items and of potential differences in the point of the disease at which specific domains are affected.

We developed a method to extend nonlinear growth curve models (12) to characterize changes in prospectively collected data (13). This modeling approach is flexible in that it allows changes in the "shape" of the curve in order to best fit the

data. In addition, this approach allows the incorporation of subgroups or time-dependent covariates. In the explication of the statistical procedures, we applied them the progression of modified Mini-Mental State (mMMS) scores in AD, and also evaluated differences in the pattern of mMMS score changes in patients with young and old age at onset. We now use this modeling approach to compare disease progression as measured by the mMMS and assessments of instrumental and basic activities of daily living.

## METHODS

### Subjects

All subjects were participants in the Predictors Study, a multi-site, longitudinal study of disease course in AD. Two hundred thirty-six patients with probable Alzheimer's disease were recruited into the study at three sites: Columbia-Presbyterian Medical Center, New York; Johns Hopkins Hospital, Baltimore; and Massachusetts General Hospital, Boston. Details of inclusion and exclusion criteria, and recruitment methods have been previously described (1). Briefly, all patients were required to meet NINCDS-ADRDA criteria (14) for probable Alzheimer's disease (pAD). To ensure that severity of dementia was mild at study entry, all patients were required to have an mMMS score of 30 or above (corresponding to approximately 16 on the standard MMSE). Patients with small subcortical lesions that were clinically and historically silent were included. However, patients with cortical lesions of any size or location, or with focal cortical atrophy in a specific vascular distribution were excluded.

### Procedures

All patients were seen at 6-month intervals and underwent the following evaluations.

*Cognitive assessment.* — Cognitive function was examined using the modified Mini-Mental State Examination (15). This instrument includes all items from the standard Mini-Mental State Examination (4) and also includes the Wechsler Adult Intelligence Scale Digit Span subtest (16), and additional attention/calculation, general knowledge, language, and construction items. The maximum score on this test is 57. This is a valid and reliable instrument (17) that is brief yet informative.

*Functional assessment.* — Functional capacity was rated using the BDRS (Part 1) (5) using a structured interview to guide and standardize BDRS administration. A previous factor analysis of the BDRS items in 187 patients with pAD demonstrated four factors, and prospective data from a separate cohort of 67 patients suggested that the factors' pattern of progression differs (18). In the current analyses, we concentrated on two factors which reflect two specific types of ADL measured by the BDRS.

Instrumental ADL (IADL) was assessed by items 1–7, which address functions such as orientation, performing chores, and remembering lists. These items are traditionally scored on a 3-point scale as absent (score = 0), partially (0.5), or fully impaired (1). To simplify analysis, this 3-

point scale was recoded, and ranged from 0 to 2. Thus, the maximum score for IADL was 14. Basic ADL (BADL) was measured by 3 items: eating, dressing, and toileting. These are rated on a 4-point scale ranging from 0 to 3. Thus, the maximum BADL score was 9. For both ADL domains, a higher score denotes more impairment.

### Statistical Analysis

The mathematical properties of the modeling approach have been described (13). This approach applies the principles of growth models, which can be specified by an equation that assumes that the growth rate, or change in a test score, is a function of the present score. The modeling procedure begins by calculating changes in test scores between all adjacent 6-month visits for each subject. Thus, only patients with at least two consecutive scores on a measure can be included in the calculations. The goal is to characterize the conditional average change in a score based on the current score,  $E(Y_{k+1} - Y_k | Y_k)$ , where  $Y_k$  represents a test score at time  $k$ ,  $Y_{k+1} - Y_k$  is the change in the next interval, and  $E$  denotes the expectation operation. We model the conditional average change with a function in a form similar to Von Bertalanffy's growth curve model (12), which unifies monomolecular, logistic, Gompertz, and other models. The values of the model parameters determine the "shape" of the model and the point of maximal change in scores (if one exists). A quasi-likelihood approach is used to estimate model parameters to best fit the data. The procedure minimizes the mean square error of prediction of changes in test scores; 95% confidence intervals can be calculated for the various model parameters as well.

We applied the model in two complementary ways. First, we used the model to predict change in a score from one visit to the next as a function of the current score. Second, we simulated the progression of test scores over time, given a specific starting score. In this case, the starting score generates a prediction of the score at the next time interval, and this process is repeated until the score reaches its upper or lower bound. The generated curve is therefore a generalized representation of the progression of the test score over time. The modeling procedure was applied separately to the mMMS total score and the two BDRS factors.

## RESULTS

### Demographics

Mean patient age at intake into the study was 73.1 ( $SD = \pm 8.9$ ) yrs. There were 96 men and 140 women, and mean years of education was 13.10 ( $\pm 3.66$ ). At the initial visit, mean estimated duration of illness was 3.9 ( $\pm 2.4$ ) yrs; mMMS, 37.9 ( $\pm 5.6$ ) (by design, no patient's mMMS score was below 30); IADL, 6.01 ( $\pm 2.6$ ); and BADL, 0.52 ( $\pm 0.91$ ).

### mMMS Progression

Two hundred eighteen subjects completed the mMMS at two or more consecutive visits and were followed for 6 to 54 months. Observed scores ranged from 0 to 57. The change between two consecutive visits ranged from a decline of 29 points to an 8-point improvement. We applied a basic

growth model to the mMMS scores. The derived growth curve function was as follows:

$$E(Y_{k+1}-Y_k) | Y_k = -.18Y_k * \ln(57/Y_k) \quad 0 \leq Y_k < 57$$

Substituting a current mMMS score for  $Y_k$  in the equation generates a prediction of the amount of decline in the score over the subsequent 6-month interval. The standard deviation of this estimate is 4.88. The value  $-.18$ , which is  $\beta$  in the formally described modeling procedure (13), is an estimated value that, in effect, determines the dynamic change in scores. The standard error of the estimate of  $\beta$  is  $.01$ . The mMMS score at which change was maximal was 19 (95% CI: 13-26). Ninety-five percent of the residual scores (predicted minus observed change) were within 2 standard deviations of 0 and there was no specific pattern to the residual/score plot, indicating that the model fits the data well.

For each given score, we calculated the associated conditional average change over a 6-month period. For purposes of comparison, we also calculated the mean of the empirically observed changes for each mMMS score. Figure 1 demonstrates that the smooth curve generated from the model's prediction fits the empirically observed average changes. The observed average changes across 6-month intervals fluctuate markedly for low and high scores because there were few observations available in these score ranges. It is apparent from Figure 1 that the decline in mMMS scores over a 6-month period gradually increases as scores drop from 57 to 19; the rate of decline then decreases as the score approaches 0.

We also used the model to generate a curve representing the decline in mMMS scores for a patient with an initial mMMS value of 56 (Figure 2). This curve again demonstrates that the most rapid decline in mMMS scores is in the midrange of the disease, with less rapid decline in scores early and late in the disease. From the curve we may roughly estimate that the total period of decline in mMMS scores is about 15 years.

*Instrumental ADL*

Two hundred twenty-one subjects completed the BDRS at two or more consecutive visits and were followed for 6 to 54

months. Observed scores ranged from 0 to 14. The change between two consecutive visits ranged from  $-7$  to  $8$ . We applied a growth model to the instrumental ADL scores. The derived function was as follows:

$$E(Y_{k+1}-Y_k) | Y_k = .145(14-Y_k) \quad 0 < Y_k \leq 14$$

Substituting a current instrumental ADL score for  $Y_k$  in the equation generates a prediction of the amount of increase in the score over the subsequent 6-month interval. The standard deviation of this estimate is 1.95. In this case,  $\beta = .145$  with a standard error of  $.01$ . Ninety-five percent of the residual scores (predicted minus observed change) were within 2 standard deviations of 0 and there was no specific pattern to the residual/score plot, indicating that the model fit the data well.

Figure 3 displays the predicted conditional average change over a 6-month period for each given score, as well as the mean of the empirically observed changes. The smooth curve generated from the model fits the empirically observed (actual) changes.

Taking an initial IADL value of 1, we used the model to generate a curve for increase in IADL scores (Figure 4). From the curve we may roughly estimate the period of decline in IADL scores as about 12 years.

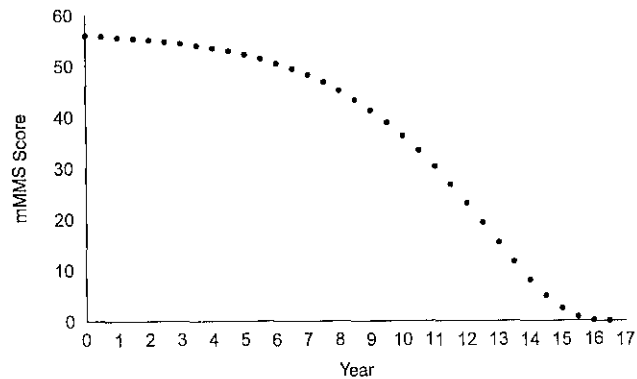


Figure 2. A time series of mMMS scores generated by the growth curve model with the initial score of 56.

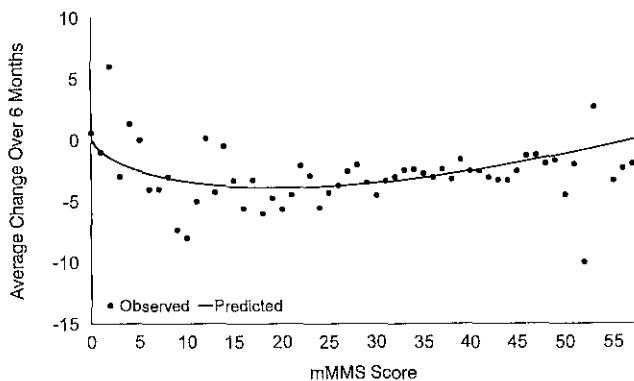


Figure 1. Based on the growth curve model, predicted average change of mMMS scores over a 6-month interval as a function of the current score. The average of empirically observed score changes is presented for comparison.

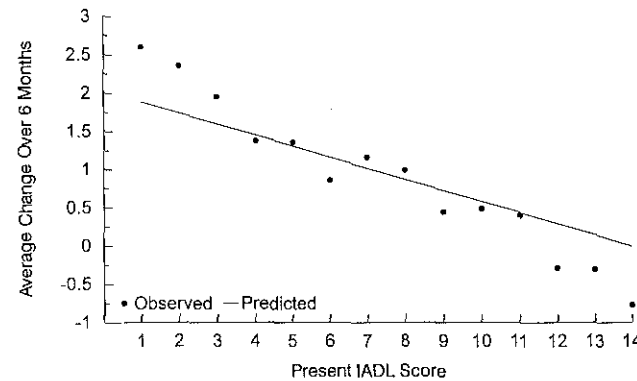


Figure 3. Based on the growth curve model, predicted average change of instrumental ADL scores over a 6-month interval as a function of the current score. The average of empirically observed score changes is presented for comparison.

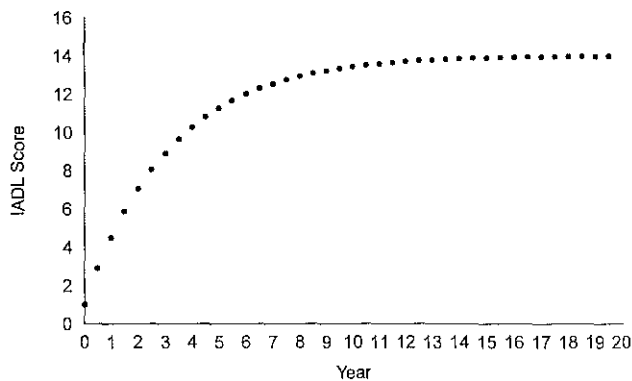


Figure 4. A time series of instrumental ADL scores generated by the growth curve model with the initial score of 1.

**Basic ADL**

Observed BADL scores ranged from 0 to 9. Note that 0 denotes no impairment and 9 denotes maximal impairment. The change between two consecutive visits ranged from -3 to 9. We applied a growth model to the basic self-care scores. The derived growth curve function was as follows:

$$E(Y_{k+1}-Y_k) | Y_k = .46 \quad 0 \leq Y_k < 9$$

There is no difference in the amount a score changes per 6-month interval as a function of the current score; in each case the score increases .46 points. The standard deviation of this estimate is 1.28. Of course, once the score reaches 9 it no longer increases. In this case  $\beta = .46$  with a standard error of .043. Ninety-five percent of the residual scores (predicted minus observed change) were within 2 standard deviations of 0, and there was no specific pattern to the residual/score plot, indicating that the model fit the data well.

Figure 5 displays the predicted associated conditional average change over a 6-month period for each given score, as well as the mean of the empirically observed changes. Taking an initial basic self-care score of 0, we used the model to generate a curve for increase in scores (Figure 6). From the curve we may roughly estimate the period of decline in BADL scores as about 10 years.

**DISCUSSION**

We used a growth curve modeling procedure to examine the progression of three different measures of the severity of AD. The pattern of change in scores over time differed across the three measures. For the mMMS there was a period of rapid decline in scores with markedly slower progression early and late in disease course. The slow progression early in the disease may occur because the earliest cognitive changes of AD might not be detectable by the mMMS. If this were the case, more sensitive or challenging tests might show more rapid decline even early in the disease. Alternately, the earliest changes in the mMMS may be occurring before the clinical signs of AD have emerged and may truly indicate relatively slower progression in the earliest portions of the disease process. Late in the disease, the rate of change in the mMMS score again slows, and the score plateaus close to its minimum score. One possible explanation for this is that cognitive decline is still occurring, but cannot be de-

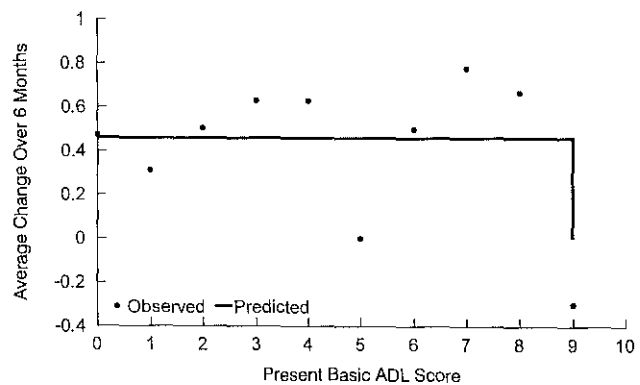


Figure 5. Based on the growth curve model, predicted average change of basic ADL scores over a 6-month interval as a function of the current score. The average of empirically observed score changes is presented for comparison.

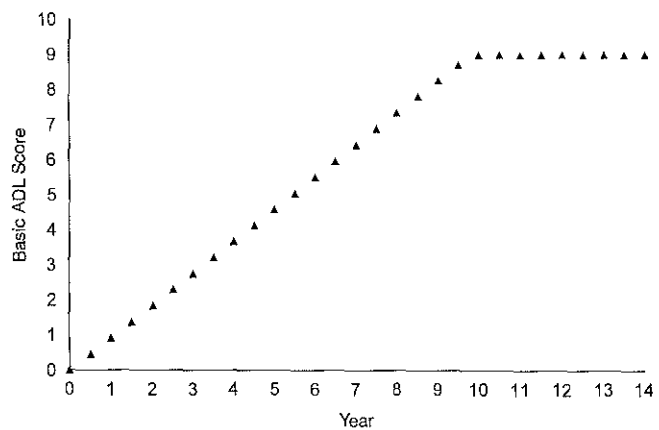


Figure 6. A time series of basic ADL scores generated by the growth curve model with the initial score of 1.

tected by the mMMS items, since at this point patients are not capable of performing accurately on most of them. To this end, some investigators have proposed alternate mental status tests for severely impaired patients, in order to capture additional information about cognitive status after the mMMS scores reach bottom (19-21). We do not feel that this is the case with the mMMS, because many patients continued to answer a few mMMS questions correctly even during this second plateau period. It would be of value to apply the growth curve modeling technique to data from a "severe impairment" battery in order to determine whether there is further progression of cognitive impairment that the mMMS cannot detect or whether a true endpoint of depleted cognitive capacity has been reached.

The BDRS measures IADL and BADL as different domains (18) and, as we demonstrate, these two aspects of ADL progress at different rates and in different patterns. Difficulties with IADL increase more rapidly earlier in the disease, while BADL difficulties have a slow, linear increase. One practical implication of these findings is that prospective analyses cannot assume that different measures of AD severity are interchangeable; there are differences in

how measures change over time. There are probably several reasons for these differences in progression including the psychometric properties of the measures as discussed above. It is intriguing to speculate that our results also reflect some differences in the neuroanatomic substrate for the measured deficits, but there is no direct support for this idea from the present data.

The formulas derived for each model may be used to calculate a rough estimate of the amount of time it will take for a patient to move from one score to another. However, the modeling procedure does not provide techniques for calculating confidence intervals for individual estimates. The procedure is simply to enter the starting score into the appropriate formula. This yields the estimated change in the score over a 6-month period. This process can be repeated until the target score is reached. Figures 2, 4, and 6 can be used as rough guides for this estimation.

While some studies have treated prospective decline in scales that assess AD as linear, the present study and several others (10,11) emphasize the need for alternate approaches to modeling AD progression. Brooks et al. (11) have suggested a trilinear model for decline in AD. This model posits three periods in the course of AD, a period during which decline occurs, preceded and followed by periods in which no perceptible decline occurs. Their procedure focuses on identifying the beginning and end of the period of decline for each patient as well as calculating the rate of decline during the decline period. This trilinear approach differs from the modeling approach we use (12) in several substantial ways. First, our approach makes no initial assumption regarding the "shape" of the decline process. Rather, it derives it empirically. We see no reason for the a priori assumption that differing aspects of disease progression can be characterized by a single model. The published application of the trilinear model has analyzed the progression of MMSE scores. In this case the trilinear model would appear to roughly capture progression in a fashion similar to the function we describe here for mMMS progression. However, the trilinear approach would ignore the more subtle changes in scores occurring earlier and later in the disease and would treat the period of maximal decline as linear. In one analysis (11) they calculated that prior to the period of rapid decline there is a period of no perceptible decline in which the MMSE score is 20.7. The maximum MMSE score is 30, so it is likely that some decline is actually taking place during this period, albeit at a slower rate. Thus, we find that the estimated 6-month change in mMMS scores is much smaller when scores are close to the maximum. Further, since the trilinear approach assumes that progression, when it occurs, is constant, it would be less successful in characterizing the period of rapid progression of mMMS scores, which is not linear.

On a more technical level, the approach to deriving the two types of models differs as well. The modeling approach we use utilizes changes in scores over consistent time intervals. This represents an adaptation of standard growth curve models, which utilize actual scores. Standard growth curve models are functions of time and require knowledge of the absolute start of the period of progression. In diseases such as AD it is difficult to accurately estimate the time of onset.

On a mathematical basis, utilizing change scores eliminates the requirement for an absolute startpoint and allows estimation of a function that characterizes change in the scores. For a patient to be included in the estimation process, at least two consecutive visits are required, because a change score over a fixed interval must be calculated. Beyond that requirement, all data from all patients are included in the analysis, with the assumption that observed progression in each patient represents a piece, or partial realization, of a typical pattern of progression. The trilinear approach utilizes observed data points, requires a minimum of 5 points for its application, and eliminates patients whose data do not fit a particular component of the model from the estimation process.

A final advantage of the modeling approach we utilize is that it allows the incorporation of covariates. There is increasing evidence that specific clinical features of AD are associated with differential rates of decline. The ability to incorporate these features into a model would bring us closer to the point of making accurate predictions of rate of decline for individual patients. Application of covariates is beyond the scope of the present study, but our original description of the modeling approach demonstrates how the model of mMMS progression can be refined to reflect differences in patients with early and late disease onset (13).

The modeling procedure itself does not address the issue of the relative timing of the changes in cognition, IADL and BADL. In Figure 7, we have superimposed the three progression curves in a manner which we believe is representative of their relative decline. The decisions about relative placement of the 3 curves were guided by inspection of the data set at different point in disease progression. For example, we determined the typical IADL and BADL scores for patients with specific mMMS scores. We include this figure in the Discussion section because the relative placement of the curves is not derived from our statistical modeling procedures. Inspection of the figure indicates that cognitive decline may begin much earlier than functional decline. Thus, AD might not be noticed or diagnosed until 5 or 6 years into the progression of the mMMS scores, about the time when IADL problems begin. Relatively rapid decline of cognitive and IADL functions follows, with slowly increasing BADL difficulties beginning some time afterward. Sev-

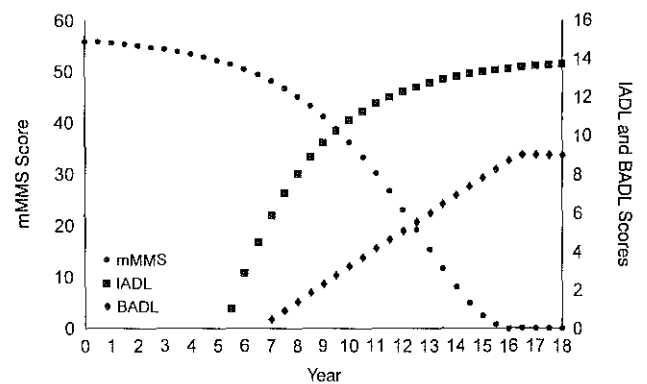


Figure 7. Proposed model for the relative decline in cognition, instrumental ADL, and basic ADL in Alzheimer's disease.

eral recent reports suggesting that cognitive change may begin well before dementia is diagnosed (22,23) are consistent with this proposed model.

Our results have clear implications for both the prediction of disease course in AD and the planning of clinical trials. The fact that rates of progression vary as a function of current severity means that careful consideration of baseline severity is important when planning studies that have a prospective component. Further validation and development of this approach, particularly with the addition of relevant covariates, may contribute to the development of predictor models for individual patients.

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Address correspondence and reprint requests to Dr. Yaakov Stern, Sergievsky Center, 630 West 168th Street, New York, NY 10032.

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