Estimation and Validation of a Multiattribute Model of Alzheimer Disease Progression

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Objectives. *To estimate and validate a multiattribute model of the clinical course of Alzheimer disease (AD) from mild AD to death in a high-quality prospective cohort study, and to estimate the impact of hypothetical modifications to AD progression rates on costs associated with Medicare and Medicaid services.* ***Data and Methods.*** *The authors estimated sex-specific longitudinal Grade of Membership (GoM) models for AD patients (103 men, 149 women) in the initial cohort of the Predictors Study (1989–2001) based on 80 individual measures obtained every 6 mo for 10 y. These models were replicated for AD patients (106 men, 148 women) in the 2nd Predictors Study cohort (1997–2007). Model validation required that the disease-specific transition parameters be identical for both Predictors Study cohorts. Medicare costs were estimated from the National Long Term Care Survey.* ***Results.*** *Sex-specific models were validated using the 2nd Predictors Study cohort with the GoM transition parameters constrained to the values estimated for the 1st Predictors Study cohort; 57 to 61 of the 80 individual measures contributed significantly to the GoM models. Simulated, cost-free interventions in the rate of progression of AD indicated that large potential cost offsets could occur for patients at the earliest stages of AD.* ***Conclusions.*** *AD progression is characterized by a small number of parameters governing changes in large numbers of correlated indicators of AD severity. The analysis confirmed that the progression of AD represents a complex multidimensional physiological process that is similar across different study cohorts. The estimates suggested that there could be large cost offsets to Medicare and Medicaid from the slowing of AD progression among patients with mild AD. The methodology appears generally applicable in AD modeling.* ***Key words:*** *clinical assessment; outcomes; staging of dementia.* ***(Med Decis Making 2010;30:625–638)***

Modeling the clinical course of Alzheimer disease (AD) is essential for accurate, reliable, and valid medical decisions for the care and treatment of AD patients and for estimating cost offsets for proposed medical and pharmaceutical interventions. In addressing these issues, decision makers have increasingly relied on Markov transition models to form the core components of their decision analyses.[1]

Markov transition models are typically based on 3 assumptions: (A1) that each patient is always in one of a small number of discrete health states, (A2) that the transitions from one health state to the next are independent of the prior states and timings of prior transitions, and (A3) that the patient population in each state is homogeneous with respect to the risk of subsequent transitions. Although such assumptions are often used in modeling the clinical course of AD,[2] it is recognized that each assumption is only an approximation that is violated to some degree.[3,4]

Analyses based on the Cox proportional hazards model have demonstrated that individual variability in transition rates is substantial for AD patients, which violates assumption A3.[3,5] Caro and colleagues[6] dealt with this violation in their Assessment of Health Economics in Alzheimer's Disease (AHEAD) model by conducting long-term forecasts for a 3-state Markov model at the individual-patient level and by basing transitions on Cox regression parameters for extrapyramidal signs, psychotic symptoms, cognitive function, duration of illness, current age, age at onset of disease, and gender that

A supplemental appendix to this article is published electronically only at http://mdm.sagepub.com/supplemental.

Web Tables A1–A7 are supplementary tables with detailed statistical tests and extensive sets of parameter estimates that are provided online in a Web-only format for interested readers

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were derived from the Predictors Study.[5] This approach allowed the transitions to depend on the time in the current state, thereby resolving potential violations of assumption A2. This model was used to develop cholinesterase inhibitor guidance for the National Health Service (United Kingdom), although Caro and colleagues[7] disagreed with this application of their model.

Although Caro's specification of the model transitions at the individual patient level resolved some important violations of the assumptions of the Markov model, it was not fully satisfactory for generating long-term forecasts. Two issues remain to be resolved.

First, the Cox regression model implicitly assumes that the predictors are fixed for individual patients. Actually, 5 of the 7 predictors (i.e., extrapyramidal signs, psychotic symptoms, cognitive function, duration of illness, and current age) change over the course of the disease, with the first 3 being significant markers of the stage of the disease. These changes are not addressed by using the Cox regression model, nor are they addressed elsewhere in Caro's model. Adequate resolution of this issue must also deal with the right-censoring problems typically encountered in survival analysis.

Second, it is not clear that the Caro model's use of 3 states—1) not needing full-time care (FTC); 2) needing FTC, operationalized as nursing home (NH) institutionalization; and 3) death—are adequate for characterizing the progression of AD. There are several options for defining the number and nature of such states, which can be based on any of several instruments for the staging of the disease, including the 7-state Global Deterioration Scale (GDS)[8] or the 3-state Clinical Dementia Rating (CDR) scale,[9] with extensions to 4, 5, or 6 states to represent ''questionable,'' ''profound,'' and ''terminal'' stages.[10]

Eisdorfer and colleagues[11] found that the GDS incorrectly predicted the timing of psychiatric symptoms and functional impairments. They recommended separate measures for cognitive, clinical, and functional status and the development of multidimensional scales.

Bolstering Eisdorfer's recommendations, Stern and colleagues[12] used longitudinal data from the Predictors Study to establish that the progression of AD occurs in 3 dimensions, with different and distinct nonlinear changes on measures of cognition, activities of daily living, and instrumental activities of daily living.

These results invalidate assumption A1 of the Markov model: It is not true that each patient is always in one of a small number of discrete health states. The health states are multidimensional; the multiplicity of available scales indicates that the states are not discrete. The outcome categories of the multiple attributes used to inform the staging models are discrete, but they are so numerous that any attempt to represent them as a single dimensional scale with 3 to 7 stages necessarily involves substantial simplification and distortion of the underlying process.

This article takes up Eisdorfer's challenge to develop a multidimensional, multiattribute approach for modeling the progression of AD, thereby resolving the limitations of the Markov transition model identified above. The approach responds to Caro and colleagues' recent critique of the AHEAD model and calls for the development of models that ''incorporate individual patient characteristics and history'' and ''allow proper handling of competing risks and treatment persistence and compliance.''[7] The approach also responds to Green's recent call for ''more appropriate methods for the modeling of AD progression'' using ''multi-attribute health states using a combination of cognitive function, functional ability, and behavior and mood.''[13]

The fundamental assumption is that the multiple measures of individual patient attributes are symptoms of AD, not direct measures of the biological characteristics of AD itself. The latter are currently unavailable and hence unobserved; they are assumed to be the underlying drivers of the disease and are the missing factors that account for the

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observed symptoms, as evidenced by ongoing research targeted on discovery of AD biomarkers.[14] Moreover, the observed symptoms are assumed to be only probabilistically determined by the unobserved biological characteristics of the disease. This allows patients with the same unobserved biological characteristics to exhibit different patterns of symptoms, including occasional reversals in symptoms even as disease progression continues.

Under this approach, we achieve parsimony and transparency by using a large number of factors to identify a low-dimensional process that describes AD progression. In the remainder of this article, we describe and report results from such a model.

METHODS

Model

The analyses used a longitudinal form of the Grade of Membership (GoM) model.[15,16] GoM provides a statistically optimized summarization of large amounts of data on individual AD patients by use of a small number of distinct variables that represent the most salient characteristics of the AD process as it develops over time.[17,18]

Longitudinal GoM is a multidimensional state-space model that is based on 3 assumptions:

A1. That each patient is always located at some point (the state vector) in an unobserved low-dimensional continuous bounded state space that accurately represents the biological characteristics of AD
A2. That the changes in the state vector during the interval from one observation time to the next can be completely determined by an upper-triangular transition matrix that characterizes the progression of AD for that observation interval, with the axes of the coordinate system ordered by increasing AD severity
A3. That the observed symptoms are random variables that are conditionally independent, given the state vector, with the symptom probabilities being functionally dependent on the elements of the state vector; there is no explicit upper limit to the number of such symptoms.

To specify this model mathematically, we denote the categorical data array[a] for the observable variables as $\{x_{ijt}\}$, where

i = index for I individual AD patients
j = index for J discrete variables in the study
l = index for L_j symptom indicators (response levels) within variable j
m = index for M combinations (j, l)
t = index for time since intake examination.

The fundamental equation expresses the probability of each possible outcome as a time-varying linear function of the GoM scores:

$$Prob(x_{ijt} = l) = \mathbf{g}'_i \left\{ \prod_{\alpha=0}^{t-1} \mathbf{U}_\alpha \right\} \lambda_{m_{jl}} = \mathbf{g}'_i \mathbf{V}_t \lambda_{m_{jl}}, \qquad (1)$$

where $\mathbf{g}'_i$ denotes the transpose of $\mathbf{g}_i$, the K-element column vector of GoM scores for individual i indicating his or her initial location in the postulated state space of dimensionality $D = K - 1$; the elements are nonnegative and sum to 1 over the range of the index k, $k = 1, \ldots, K$. The K elements define a set of K latent states, classes, or ''pure types.'' $\mathbf{U}_t$ is the upper-triangular $K \times K$ state-space transition matrix governing the AD progression over the interval $(t, t + 1)$; the elements in each row are nonnegative and sum to 1. $\mathbf{V}_t$ is the $K \times K$ matrix containing the cumulative product of the t state-space transition matrices governing the AD progression over the interval $(0, t)$. By convention, $\mathbf{V}_0 = \mathbf{I}$, a $K \times K$ identity matrix. $\lambda_{m_{jl}}$ is the K-element column vector of probabilities for symptom (response) m; the elements are nonnegative and, for fixed indexes (j, k), the elements $\lambda_{km_{jl}}$ sum to 1 over the range of the index l, $l = 1, \ldots, L_j$.

It follows from assumption A3 that the likelihood is the product over i, j, l, and t of the probabilities in equation 1:

$$LIK = \prod_i \prod_j \prod_l \prod_t \left(\mathbf{g}'_i \left\{ \prod_{\alpha=0}^{t-1} \mathbf{U}_\alpha \right\} \lambda_{m_{jl}} \right)^{y_{ijlt}}, \qquad (2)$$

where $y_{ijlt} = 1$ if $x_{ijt} = l$, and $y_{ijlt} = 0$ if $x_{ijt} \neq l$. The maximum likelihood estimation (MLE) of the parameters is described by Stallard.[16]

For the special case of $K = 1$, defining a 0-dimensional (0-D) state space, the right side of equation 1 is a scalar quantity that is independent of i and t; the right side of equation 2 is a composite function formed from the product of J multinomial likelihood functions with MLE values equal, respectively, to the

[a] For simplicity, all continuous variables are assumed to be recoded to discrete categorical variables prior to the analysis.

observed relative frequencies of each response to each of the J variables. The 0-D model is the null model for statistical model selection.

For any specified value of K, the representation of the right side of equation 2 as a product over J variables implies that the J variables are assumed to be statistically independent. For the 0-D model, this condition implies marginal independence. For all other cases, the independence is conditioned on the state vector (assumption A3).

Equation 2 readily accommodates planned missing data due to death and various forms of questionnaire ''skip patterns'' and unplanned randomly missing data due to dropout and sporadic missing items.[16]

Erosheva[19] used a geometric approach to establish the connections between the basic nonlongitudinal GoM model and the Rasch model, demonstrating that the GoM model may be viewed as a specific form of item response theory (IRT) model. Erosheva[19] further demonstrated that GoM scores differ from Rasch ability parameters in that only the former are intrinsic to the response probability manifold, a characterization that allows GoM scores to be described as natural measures of latent traits with certain invariance properties defined by Ramsay.[20] Thus, the 1-D GoM model can describe multivariate dichotomous categorical data within an IRT framework with extensions to polytomous categorical data and to 2-D, 3-D, or higher dimensional models readily implemented.

Selection of the best model from among several competing (e.g., 1-D, 2-D, 3-D) models is based on identifying the model with the smallest value of the Bayesian information criterion (BIC),[21,22] computed for each model as follows:

$$BIC = -2 \times \ln(LIK) + df \times \ln(N), \tag{3}$$

where df is the number of independently adjusted parameters in the model and N is the effective sample size.

N can be calculated in 2 ways: 1) $N = N^*$, the weighted geometric mean number of responses for the J variables, with the weight for each variable equal to the df (denoted df_j) for the corresponding λ parameters (BIC1), and 2) $N = N^{**}$, the geometric mean number of additive terms in the formulas for the diagonal elements of the $df \times df$ Hessian matrix of the log-likelihood function (BIC2).

N^{**} approximates the df^{th} root of the ratio of 1) the determinant of the expected Fisher information matrix for all observations to 2) the determinant of the expected Fisher information matrix for 1 observation: the approximation recommended by Raftery as most accurate.[22] N^* is equivalent to the geometric mean number of additive terms in the formulas for the diagonal elements of the partition of the Hessian matrix corresponding to the λ parameters, which excludes the diagonal elements corresponding to the g and u parameters; hence, $N = N^*$ is expected to be less accurate.[b]

For comparison, we also calculated Akaike's information criterion (AIC)[23] and Bozdogan's asymptotically consistent form of AIC (CAIC) using $N = N^*$.[24] For $\ln(N^*) > 2$ (i.e., for 8 or more observations), the following inequality holds: AIC < BIC1 < CAIC, indicating that model selection decisions based on BIC1 will be intermediate to those based on AIC and CAIC.

We hypothesized that the transition matrices $\{\mathbf{V}_t\}$ governing the changes in the state vectors are fundamental parameters of the disease process that are constant from one patient to the next, within sex, implying that the transition matrices estimated from any one database should fit any other. Application of these matrices to the initial vector of GoM scores, $\mathbf{g}_i$, yields the vectors of time-varying GoM scores, $\mathbf{g}_{it}$, as follows:

$$\mathbf{g}'_{it} = \mathbf{g}'_i \mathbf{V}_t. \tag{4}$$

We tested this hypothesis by applying the BIC selection procedures to the 2nd Predictors Study cohort with the transition matrices constrained to the values estimated for the 1st Predictors Study cohort.

Data

The Predictors Study was specifically designed to investigate the natural history of AD to develop improved models for the management of the disease.[25] Case selection was based on the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders criteria for probable AD, criteria that were confirmed in up to 96% of postmortem diagnostic evaluations.[26] The study comprises 2 distinct cohorts, designated Predictors 1 and Predictors 2, respectively.

Predictors 1 consists of longitudinal follow-up of 103 men and 149 women; Predictors 2 consists of longitudinal follow-up of 106 men and 148 women. All cases were determined to have probable AD at the time of recruitment into the study, with the

[b] In fact, BIC1 and BIC2 yielded identical model selection decisions for all analyses in this article.

severity of dementia determined to be mild at that time (generally based on a modified Mini-Mental Status (mMMS)[27] score of 30 or above in Predictors 1 or 16+ on the standard Mini-Mental Status Examination in Predictors 2).[c]

The analyses of Predictors 1 were based on the first 21 waves of follow-up, which occurred approximately every 6 mo over the period 1989 to 2001. The use of exactly 21 waves was motivated, in part, by the fact that the total resulting follow-up time was 10 y. Beyond the 21st wave, the sample sizes became too small.

The analyses of Predictors 2 were based on the first 16 waves of follow-up, occurring approximately every 6 mo beginning in 1997, continuing through early 2007. Beyond the 16th wave (7.5 y follow-up), the sample sizes became too small.

The longitudinal GoM model was estimated using 79 (women) or 80 (men) variables from Predictors 1 (myocardial infarction was deleted for women due to no events) and was validated using a closely matched set of variables from Predictors 2. The variables were representative of measures likely to be collected in many AD databases, but they were not an exhaustive compilation of all variables available in one or the other of the Predictor Study cohorts. They included cognition (mMMS, 6 items and total score), functional capacity (part 1 of the Blessed Dementia Rating Scale [BDRS],[28] 11 items and total score; Dependence Scale,[29] 13 items, total score, and equivalent institutional care[30] levels), behaviors (5 items), psychopathological symptoms (3 items), motor signs (1 item), seizures (3 items), vision, cardiovascular disease risk factors/signs (6 items), alcohol use (4 items), occupation, citizenship, education, spoken language, demographic factors, neurologist's estimation of AD duration, and 6-mo survival.

The average age (standard deviation) at intake examination was 71.4 (9.4) y for men and 74.5 (9.0) y for women in Predictors 1. The corresponding ages were 75.4 (7.5) y and 77.3 (8.2) y, respectively, in Predictors 2. The estimated average duration (standard deviation) of AD at intake was 4.8 (2.7) y for men and 4.3 (2.4) y for women in Predictors 1. The corresponding average durations were 4.6 (2.3) y and 4.3 (2.3) y, respectively, in Predictors 2. On average, the Predictors 2 cohort was 3 to 4 y older at intake. The average AD durations in the 2 cohorts ranged from 4.3 to 4.8 y at intake.

We used the National Long Term Care Survey (NLTCS) data in supplementary analyses to generate Medicare cost parameters for each of the GoM pure types in the NLTCS model in a form that was matched to each of the GoM pure types in the Predictors 1 model.

Predictors 2 introduced measures of the cost of medical care that were not available in Predictors 1 and that were used in the supplementary analyses to validate the relative cost differentials for Medicare costs among the GoM pure types in the NLTCS model.

Medicaid NH costs were obtained from Grabowski et al.[31] These costs were assumed to depend only on the fact of institutionalization, independent of the individual GoM scores.

All costs were converted to 2007 dollars using the CPI-U Medical Care series.

RESULTS

Sex-specific 1-D, 2-D, and 3-D models of AD progression were estimated from Predictors 1 for 103 men and 149 women. Predictors 2 was used in subsequent analyses to validate the results obtained from Predictors 1. Predictors 2 and the NLTCS were further used in supplementary analyses to estimate the costs associated with Medicare-reimbursed medical interventions and Medicaid-reimbursed NH stays and the cost offsets associated with hypothetical modifications to AD progression rates.

The 1-D and 3-D models were chosen to reflect plausible alternative models of AD progression consistent with the review of the literature provided above. Briefly, standard specifications of both the Markov transition model and the existing global assessment scales (e.g., GDS, CDR) imply a 1-D model of AD progression. Alternatively, analyses by Eisdorfer, Stern, and others indicated that AD progression may be better modeled as a 3-D process.[11,12] However, these prior reports did not indicate how this might be done nor how to compare the results of such a 3-D model with 1-D models.

The analyses were stratified by sex because prior GoM analyses reported substantial differences between men and women with respect to the estimated AD pure types and AD-related care measures.[15,18]

Predictors 1 Estimation

For each sex-specific model, a total of 79 or 80 variables (female; male) were employed in estimation.

[c]Sixteen cases in Predictors 1 had an initial modified Mini Mental Status score in the range of 21 to 29; 10 cases in Predictors 2 had an initial Mini-Mental Status Examination score in the range of 9 to 15. These cases were retained in the analysis because Grade of Membership generates scores for each individual independently.

Under the Bayesian information criteria (both BIC1 and BIC2), the 3-D models provided better fits for both sexes to Predictors 1 than the 1-D and 2-D models; hence, the 3-D models were selected as the best models.[d]

Tables 1 and 2 display the sex-specific λ parameters (i.e., response/symptom probabilities) by pure type for the 1-D and 3-D models for 10 variables. Three of the 10 variables were summary scores for another 30 items not included in the 2 tables: *mMMS* (6 items), *Dependence Scale* (13 items), and *BDRS* (part 1; 11 items).

The remaining 7 variables were selected to display other important aspects of AD progression. *Residence Status* indicates the current place of residence of the patient; on average (under the heading ''Observed'' in column 4), 24.4% of men and 33.0% of women resided in an NH. *Equivalent Institutional Care* was derived as an adjunct to the *Dependence Scale*; on average, 38.5% of men and 53.6% of women needed FTC equivalent to that provided in a health-related facility. These differences are consistent with prior reports that rated FTC risk as greater than actual NH risk, which justifies keeping both sets of measures in the model.[6] *Overall mMMS Response* represents the probability that the *mMMS* questions would be attempted at the current examination; the average attempt rate was 64.2% for men and 62.5% for women. *Moderate Extrapyramidal Signs* indicate the presence/absence of non–drug-induced motor signs using a Parkinson's disease rating scale; 26.0% of men and 30.5% of women exhibited such signs. *Delusions* and *Hallucinations* separately indicate the presence/absence of 2 important psychopathological features of AD; 37.3% of men and 39.7% of women had delusions, but only 13.4% of men and 10.1% of women had hallucinations. *Prospective 6-Month Survival* represents the risk of death for individual patients from one examination to the next; the average death probability was 6.5% for men and 5.5% for women.

Columns 5 to 8 display the parameters, the ΔBIC_j statistics, and their rankings (among the full set of $J = 79$ or 80 variables) for the 1-D model; columns 9 to 14 display the corresponding parameters, ΔBIC_j statistics, and rankings for the 3-D model. The ΔBIC_j statistics in columns 8 and 14 are the differences between the BIC_j statistics for the 0-D model and the BIC_j statistics for the 1-D and 3-D models, respectively. The BIC_j statistics were computed by restricting equation 3 to the data for the jth variable with df_j set equal to the number of free parameters for that variable; that is, the initial GoM scores and transition parameters were assumed to be fixed for these calculations, and N_j was set equal to the corresponding number of observed responses.

Because the ΔBIC_j statistics account for differences in sample size and number of parameters, they can be used to assess the relative influence of the different variables. Positive values indicate that the 1-D or 3-D model is favored over the 0-D model, which is true for all comparisons except *Hallucinations* for the female 1-D model. Each ΔBIC_j statistic for the 3-D model is larger than the corresponding value for the 1-D model, indicating that the 3-D model is favored over the 1-D model for all 10 variables. Overall, the ΔBIC_j statistics were positive for 57 to 61 of the 79 or 80 variables in each sex-specific 1-D or 3-D GoM model.[e]

The predicted values in columns 5 and 9 are the marginal probabilities for the 1-D and 3-D models. They can be compared with the observed values in column 4 in which the differences were generally in the range ± 0.020, indicating that both models closely reproduced the observed distributions of outcomes in the sex-specific study data. For both sexes, the *Dependence Scale* exhibited the highest ranked ΔBIC_j statistics for both models. *Equivalent Institutional Care* ranked 2nd for 3 of the 4 comparisons, with the exception being the female comparison of 0-D with 1-D, with *BDRS (Part 1) Score* moving up to 2nd.

The pure type probabilities in columns 6 to 7 and 10 to 13 are the MLEs of the $\lambda_{m_{jl}}$ parameters for the 1-D and 3-D models, respectively. They can be compared across models and with the observed values for the 0-D model in column 4. These comparisons are the key to understanding the substantive meaning of the model.

Consider the pure-type probabilities for the 1-D model in columns 6 and 7. For both sexes, the estimates for the mild pure type (type I) generally indicated a higher than average (column 4) probability of a favorable response and a lower than average probability of an unfavorable response, whereas the reverse held for the severe pure type (type II).

For *Equivalent Institutional Care* for men, the average probability of FTC was 38.5%, which

[d] Supplementary tables with log-likelihood values from equation 2, corresponding Akaike's information criterion, BIC1, BIC2, and consistent form of AIC statistics, as well as extensive sets of parameter estimates are provided online in a Web-only format for interested readers. See http://mdm.sagepub.com/.

[e] See Table A2 in the supplementary online material.

Table 1 Response Probabilities by Pure Type for the 1- and 3-Dimensional Models of Alzheimer Disease Progression in the Predictors 1 Data, Men

				1-Dimensional Model				3-Dimensional Model					
					Pure Type				Pure Type				
Variable	Response	No. of Observations	Observed	Predicted	I	II	ΔBIC_j 0–1 and Rank	Predicted	I	II	III	IV	ΔBIC_j 0–3 and Rank
Dependence scale	0: Independent	11	0.012	0.012	0.015	0.008	474.29	0.012	0.049	0.010	0.000	0.000	881.54
	1: Occasional reminders	12	0.013	0.013	0.024	0.000	3	0.013	0.051	0.012	0.000	0.000	1
	2: More frequent reminders	330	0.359	0.358	0.647	0.000		0.354	0.761	0.808	0.059	0.000	
	3: Needs supervision	227	0.247	0.247	0.304	0.176		0.233	0.136	0.169	0.615	0.000	
	4: Active ADL help	101	0.110	0.110	0.010	0.234		0.104	0.003	0.000	0.326	0.052	
	5: Physical dependence	238	0.259	0.260	0.000	0.582		0.283	0.000	0.000	0.000	0.948	
Equivalent institutional care	Limited home care	201	0.219	0.210	0.379	0.000	469.07	0.228	0.631	0.439	0.000	0.000	746.19
	Adult home care	364	0.396	0.384	0.621	0.091	4	0.420	0.365	0.561	0.803	0.000	3
	Health-related facility (FTC)	354	0.385	0.406	0.000	0.909		0.352	0.004	0.000	0.197	1.000	
BDRS (part 1) score	0–5	74	0.081	0.080	0.145	0.000	401.22	0.083	0.255	0.136	0.000	0.000	708.70
	6–10	256	0.280	0.278	0.500	0.000	10	0.288	0.676	0.549	0.092	0.000	5
	11–15	255	0.279	0.278	0.355	0.182		0.293	0.068	0.314	0.723	0.034	
	16–27	330	0.361	0.363	0.000	0.818		0.336	0.000	0.000	0.185	0.966	
Overall mMMS response	No answers	410	0.358	0.365	0.091	0.680	182.09	0.362	0.113	0.124	0.171	0.810	270.92
	Any answers	736	0.642	0.635	0.909	0.320	26	0.638	0.887	0.876	0.829	0.190	28
mMMS score	0–19	215	0.294	0.280	0.000	0.761	266.02	0.277	0.000	0.000	0.295	0.971	528.27
	20–29	132	0.180	0.181	0.203	0.144	19	0.190	0.000	0.221	0.439	0.000	16
	30–39	203	0.277	0.283	0.392	0.096		0.285	0.251	0.508	0.267	0.029	
	40–57	182	0.249	0.256	0.405	0.000		0.248	0.749	0.270	0.000	0.000	
Residence status	Home	650	0.707	0.680	0.983	0.305	312.81	0.703	0.924	0.994	0.984	0.078	469.04
	Retirement home	8	0.009	0.008	0.013	0.003	17	0.009	0.018	0.006	0.014	0.000	19
	Nursing home	224	0.244	0.268	0.000	0.599		0.248	0.000	0.000	0.000	0.827	
	Hospital	5	0.005	0.006	0.000	0.013		0.006	0.001	0.000	0.002	0.015	
	Rehabilitation center	18	0.020	0.022	0.000	0.048		0.020	0.000	0.000	0.000	0.066	
	Other	14	0.015	0.016	0.004	0.031		0.015	0.057	0.000	0.000	0.013	
Moderate extra pyramidal signs	Absent	436	0.740	0.736	0.949	0.301	109.37	0.740	0.980	0.879	0.775	0.040	151.61
	Present	153	0.260	0.264	0.051	0.699	31	0.260	0.020	0.121	0.225	0.960	32
Delusions	Absent	574	0.627	0.630	0.511	0.781	18.90	0.634	0.910	0.528	0.159	0.966	175.80
	Present	341	0.373	0.370	0.489	0.219	41	0.366	0.090	0.472	0.841	0.034	31
Hallucinations	Absent	792	0.866	0.866	0.916	0.803	1.04	0.865	1.000	0.894	0.718	0.885	35.13
	Present	123	0.134	0.134	0.084	0.197	57	0.135	0.000	0.106	0.282	0.115	42
Prospective 6-mo survival	Died	70	0.065	0.064	0.017	0.121	12.95	0.064	0.009	0.018	0.038	0.152	17.04
	Survived	1015	0.935	0.936	0.983	0.879	46	0.936	0.991	0.982	0.962	0.848	52

Note: ADL = activities of daily living; FTC = full-time care; BDRS = Blessed Dementia Rating Scale; mMMS = modified Mini-Mental Status.

Table 2 Response Probabilities by Pure Type for the 1- and 3-Dimensional Models of Alzheimer Disease Progression in the Predictors 1 Data, Women

				1-Dimensional Model				3-Dimensional Model					
					Pure Type				Pure Type				
Variable	Response	No. of Observations	Observed	Predicted	I	II	ΔBIC_j 0–1 and Rank	Predicted	I	II	III	IV	ΔBIC_j 0–3 and Rank
Dependence scale	0: Independent	14	0.010	0.010	0.014	0.006	871.21	0.010	0.032	0.010	0.000	0.005	1342.45
	1: Occasional reminders	12	0.008	0.008	0.017	0.000	3	0.009	0.044	0.003	0.000	0.000	1
	2: More frequent reminders	271	0.191	0.189	0.390	0.000		0.195	0.854	0.169	0.000	0.000	
	3: Needs supervision	420	0.296	0.293	0.556	0.047		0.303	0.070	0.662	0.645	0.000	
	4: Active ADL help	260	0.183	0.185	0.022	0.338		0.183	0.000	0.155	0.355	0.210	
	5: Physical dependence	442	0.311	0.315	0.000	0.610		0.301	0.000	0.000	0.000	0.786	
Equivalent institutional care	Limited home care	215	0.152	0.167	0.346	0.000	658.93	0.147	0.699	0.091	0.000	0.000	1070.89
	Adult home care	442	0.312	0.337	0.630	0.063	12	0.320	0.301	0.874	0.125	0.012	3
	Health-related facility (FTC)	758	0.536	0.495	0.024	0.937		0.533	0.000	0.035	0.875	0.988	
BDRS (Part 1) score	0–5	108	0.076	0.077	0.158	0.000	696.28	0.077	0.348	0.058	0.000	0.000	973.40
	6–10	358	0.253	0.254	0.512	0.012	9	0.258	0.609	0.318	0.380	0.000	8
	11–15	410	0.290	0.290	0.329	0.253		0.296	0.044	0.590	0.511	0.105	
	16–27	538	0.380	0.379	0.000	0.735		0.369	0.000	0.034	0.109	0.895	
Overall mMMS response	No answers	660	0.375	0.387	0.095	0.645	304.21	0.384	0.170	0.114	0.091	0.769	416.21
	Any answers	1098	0.625	0.613	0.905	0.355	26	0.616	0.830	0.886	0.909	0.231	29
mMMS score	0–19	331	0.304	0.303	0.000	0.728	490.86	0.273	0.000	0.042	0.000	1.000	825.18
	20–29	275	0.253	0.253	0.261	0.242	16	0.267	0.067	0.591	0.322	0.000	14
	30–39	353	0.324	0.325	0.536	0.030		0.338	0.465	0.351	0.619	0.000	
	40–57	129	0.119	0.119	0.204	0.000		0.122	0.468	0.017	0.059	0.000	
Residence status	Home	841	0.593	0.586	0.937	0.257	387.50	0.573	0.999	0.934	0.180	0.289	549.49
	Retirement home	30	0.021	0.021	0.029	0.013	20	0.020	0.000	0.055	0.022	0.004	23
	Nursing home	468	0.330	0.337	0.016	0.638		0.348	0.000	0.000	0.663	0.622	
	Hospital	2	0.001	0.001	0.001	0.002		0.001	0.001	0.000	0.000	0.003	
	Rehabilitation center	44	0.031	0.032	0.000	0.061		0.033	0.000	0.000	0.036	0.070	
	Other	33	0.023	0.023	0.017	0.029		0.024	0.000	0.011	0.099	0.013	
Moderate extra-pyramidal signs	Absent	648	0.695	0.695	0.915	0.360	133.97	0.693	1.000	0.858	0.564	0.240	189.81
	Present	285	0.305	0.305	0.085	0.640	31	0.307	0.000	0.142	0.436	0.760	34
Delusions	Absent	841	0.603	0.607	0.463	0.745	44.39	0.607	0.736	0.277	0.498	0.839	119.70
	Present	554	0.397	0.393	0.537	0.255	40	0.393	0.264	0.723	0.502	0.161	37
Hallucinations	Absent	1,254	0.899	0.899	0.909	0.890	–6.87	0.899	0.998	0.757	0.949	0.934	36.68
	Present	141	0.101	0.101	0.091	0.110	71	0.101	0.002	0.243	0.051	0.066	47
Prospective 6-mo survival	Died	92	0.055	0.055	0.012	0.094	20.60	0.055	0.004	0.001	0.094	0.099	27.83
	Survived	1581	0.945	0.945	0.988	0.906	48	0.945	0.996	0.999	0.906	0.901	51

Note: ADL = activities of daily living; FTC = full-time care; BDRS = Blessed Dementia Rating Scale; mMMS = modified Mini-Mental Status.

dropped to 0.0% for type I and increased to 90.9% for type II. For *Residence Status*, the average probability of residing in an NH was 24.4% for men, which dropped to 0.0% for type I and increased to 59.9% for type II.

For the *Dependence Scale* for men, the average probability of a rating within levels 4 to 5 was 36.9%, which dropped to 1.0% for type I and increased to 81.6% for type II. Level 4 included persons who had to be dressed, washed, and groomed; taken to the toilet regularly; or fed. Level 5 included persons who had to be turned, moved, or transferred; assisted with a diaper or catheter; or tube fed.

An important exception to the above generalization was the higher than average occurrence of *Delusions* for type I, with probabilities of 48.9% for men and 53.7% for women, compared with the respective average probabilities of 37.3% and 39.7%. This pattern is consistent with prior reports from the Predictors Study that the prevalence of delusions peaked at the 2nd year and then dropped.[32] Note, however, that the 1-D model provides no mechanism for delusions to be predictive of a faster rate of progression of AD, despite reports of such effects,[33] since the rate of progression for all patients is constrained to that shown in Web Figures 1 to 3.

Two other observations can be made with respect to differences between the sex-specific estimates for type I in the 1-D model. For the *Dependence Scale*, the mode occurred at level 2 for men and level 3 for women, indicating that type I women were more likely to need supervision. For the *mMMS Score*, the mode occurred at 40 to 57 for men and 30 to 39 for women, indicating that type I women had poorer cognitive functioning.

The pure-type probabilities for the 3-D model in columns 10 to 13 indicate, for both sexes, that the mildest pure type (type I) generally had a higher than average (column 4) probability of a favorable response and a lower than average probability of an unfavorable response, whereas the reverse held for the severest pure type (type IV).

The response probabilities for types II and III were less extreme than for types I and IV, consistent with the assumption that higher numbered pure types exhibited greater AD severity.

Comparisons with the corresponding results from the 1-D model in columns 6 and 7 show that the type I results from the 3-D model were generally more favorable than the type I results from the 1-D model; conversely, the type IV results from the 3-D model were generally less favorable than the type II results from the 1-D model. Thus, the 3-D model had a broader range of possible outcomes between the mildest and severest states than the 1-D model. This was important because it provided room in the state space to better represent the individual differences among individuals who were classified as mild in the 1-D model.

Trajectories of AD Progression

Web Figure 1 displays the estimated deterioration in AD health status as a function of time for the 1-D model, for persons who were initially at the highest level of health status among the Predictors 1 cohort (i.e., with a GoM score of 1 on type I). The points on the plots are the leading diagonal elements of the $\mathbf{V}_t$ matrices, which quantify the cumulative progression of AD at each 6-mo observation time. Women deteriorate more rapidly than men, but the timing of the start and end of the decline in AD health status is similar. At 5 y, the AD health status score for women is less than half that for men.

Web Figures 2 and 3 present the individual trajectories of AD progression for the 1-D model, where each point is the 1st element of the corresponding GoM score vector, $\mathbf{g}_{it}$ (see equation 4). The plots in Web Figures 2 and 3 are bounded above by the sex-specific plots shown in Web Figure 1. The plots show that there was substantial heterogeneity in each study cohort at intake to the study (year 0), even though all of the participants were determined to have mild severity of AD at that time. The individual trajectories maintain constant proportionality with respect to each other over the entire duration of the process. This is the primary constraint imposed by the 1-D model.

Web Figures 4 and 5 present the individual trajectories of AD progression for the 3-D model, where each point is the sum of the first 3 elements of the corresponding GoM score vector, $\mathbf{g}_{it}$. The plots show that there was less heterogeneity in each study cohort at intake to the study (year 0) in the 3-D than in the 1-D model (Web Figures 2 and 3). The individual trajectories no longer maintain constant proportionality with respect to each other over the entire duration of the process. Instead, there is substantial heterogeneity in the rates of progression, with some individuals reaching the most severe state in 2.5 y whereas others take as many as 10 years or more.

Predictors 2 Validation

The $\mathbf{V}_t$ matrices estimated from Predictors 1 were preferable to the $\mathbf{V}_t$ matrices estimated from

Predictors 2 for both sexes for the 3-D model under the BIC criteria, using the following model forms:

F1. Fix the λ and *u* parameters at the values estimated from Predictors 1; GoM scores were estimated from Predictors 2
F2. Fix the *u* parameters at the values estimated from Predictors 1; GoM scores and λ parameters were estimated from Predictors 2 (this is the preferred model form)
F3. All parameters were independently estimated from Predictors 2

The differences in log-likelihood function values between Model Forms 2 and 3 were 96.75 for men and 65.00 for women (90 *df* each). Based on these differences, both sets of BIC statistics strongly favored fixing the transition matrices at the values estimated from Predictors 1 for both sexes.[f]

The BIC comparisons between Model Forms 1 and 2 indicated that Form 2 was preferable. This means that the λ parameters from Predictors 1 cannot be used for Predictors 2. Nonetheless, the ΔBIC_j statistics for 32 of 80 variables for men and 44 of 79 variables for women were negative in value, indicating that the Predictors 1 values would be acceptable for Predictors 2 in these cases.

Medicare Cost Estimates

Table 3 compares the direct medical care cost estimates derived from the Predictors 2 data with the Medicare cost estimates derived from the NLTCS using the transition parameters from Predictors 1. Predictors 1 provided no cost data, necessitating the use of some set of auxiliary procedures to obtain cost estimates like those in Table 3.

The Predictors 2 estimates with and without use of the transition parameters from Predictors 1 were highly correlated ($r = 0.99$) across the 4 pure types, supporting the use of the Predictors 1 transitions to characterize the AD process in the NLTCS cost estimates.

The NLTCS costs for men were highly correlated ($r = 0.96$ each) with the Predictors 2 costs, but the costs for women were substantially less highly correlated ($r = 0.76$ and 0.80). For men, type I had the lowest costs among the 4 pure types. For women, type I had the lowest costs for the Medicare estimates but the 2nd lowest for the direct medical care estimates obtained from the Predictors 2 data. This difference accounts for the lower female correlations between Medicare and Predictors 2 costs.

Applications

Our 2nd objective was to employ the clinical model to estimate the impact of hypothetical modifications to progression rates on costs associated with Medicare and Medicaid services. This was done in 2 steps:

S1. The transition parameters,[g] probabilities of death (Tables 1 and 2), and cost estimates (Table 3) were used to project survival and costs over a 10-y period corresponding to the 10-y follow-up in Predictors 1. Table 4 displays the summary results for the 4 pure types.
S2. The modifications to the AD progression rates were specified as delays in the start of the deterioration process. A delay was reasonably consistent with the patterns of deterioration shown in Web Figures 4 and 5. Two delays were considered:
- a 3-y delay to approximate the largest gaps between the plots in Web Figures 4 and 5 and
- a 9-mo delay to approximate the size of delays that could be clinically significant.

Tables 5 and 6 display the simulated interventions by sex.

The results indicated that large potential offsets for Medicare costs could occur for patients at the earliest stages of AD (type I):

- A 3-y delay in initial disease progression produced 10-y cumulative (discounted at 3%) Medicare cost offsets of $10,015 for men and $11,543 for women and corresponding average annual offsets of $1526 (men) and $2110 (women).
- A 9-mo delay produced 10-y cost offsets of $2560 (men) and $2173 (women) and annual offsets of $471 (men) and $566 (women).

The results also indicated that large potential offsets for Medicaid NH costs could occur for patients at several stages of AD (types I–III for men; types I–II for women). For type I:

- A 3-y delay produced 10-y NH cost reductions of $36,165 (men) and $45,644 (women) and annual reductions of $4271 (men) and $5873 (women).

[f] See Table A5 in the supplementary online material.

[g] The transition matrices for the sex-specific 3-D models are reported in Tables A6 and A7 in the supplementary online material, where they were combined with the probabilities of death to generate 10-y life tables for type I. Life tables for the other pure types were computed similarly.

Table 3 Cost Estimates (Average Cost per Year in Constant 2007 Dollars) from Predictors 2 and National Long Term Care Survey (NLTCS) Based on Alternative Models Using Predictors 1 and/or Predictors 2 Transition Parameters

					Pure Type						Correlations of Cost Vectors		
Cost Item/Type	Data and Transition Parameters	n	Observed	Predicted	I	II	III	IV	χ^2	df	1	2	3
Men													
1. Direct medical care	Predictors 2 Alone: Form 3	265	12,083	12,105	7471	10,681	14,985	17,380	22.50	15	1.000	0.989	0.957
2. Direct medical care	Predictors 2 with Predictors 1 Transitions: Form 2	265	12,083	12,115	7432	10,228	14,472	18,797	23.16	15	0.989	1.000	0.969
3. Medicare payments	NLTCS with Predictors 1 Transitions	583	11,387	11,451	5674	10,832	12,269	17,549	119.58	51	0.957	0.969	1.000
Women													
1. Direct medical care	Predictors 2 Alone: Form 3	349	10,662	10,660	6641	6308	12,483	20,589	45.49	15	1.000	0.999	0.795
2. Direct medical care	Predictors 2 with Predictors 1 Transitions: Form 2	349	10,662	10,645	6929	6024	12,331	21,545	46.12	15	0.999	1.000	0.764
3. Medicare payments	NLTCS with Predictors 1 Transitions	1595	10,569	10,593	4275	8749	13,258	13,572	111.12	51	0.795	0.764	1.000

Note: Direct medical care included hospitalization, outpatient treatment and procedures, assistive devices, and medications. Costs were based on units of direct medical care services using nationally representative average payment rates for the various services, originally expressed in constant 2004 dollars using the medical care component of the Consumer Price Index (CPI) and converted to constant 2007 dollars using the same CPI series. Medicare services included home health care, hospice care, skilled nursing facility care, acute care, and other services provided under Parts A and B of Medicare. Costs include the Medicare program payments and exclude deductibles and copayments.

Table 4 Sex-Specific Baseline Projections of 10-Y Medicare Costs and Nursing Home (NH) Utilization Rates and Costs (in 2007 Dollars), 3-Dimensional Grade of Membership Model

Initial Pure Type	Total Years Lived	Years Lived in NH	Discounted Medicare Costs	Discounted Medicare Cost per Year Lived	Discounted NH Costs	Discounted NH Cost per Year Lived
Men						
I	8.54	0.99	58,199	6817	40,971	4799
II	6.23	1.70	76,906	12,351	74,679	11,993
III	4.33	2.15	63,752	14,737	100,682	23,275
IV	2.93	2.42	51,949	17,724	119,027	40,610
Women						
I	8.38	1.79	65,001	7760	76,587	9143
II	6.05	2.53	66,392	10,970	116,206	19,201
III	4.36	2.87	55,446	12,725	137,806	31,626
IV	4.20	2.61	54,845	13,055	125,584	29,893

Nursing home costs are fixed at the average Medicaid daily rate of $145 in 2007 dollars; costs are discounted at 3% per year.

Table 5 Simulated Cost-Free Intervention Effects on 10-Y Medicare Costs and Nursing Home (NH) Utilization Rates and Costs (in 2007 Dollars), 3-Dimensional Grade of Membership Model, 9-Mo and 36-Mo Delays, Men

Initial Pure Type	Total Years Lived	Years Lived in NH	Discounted Medicare Costs	Discounted Medicare Cost per Year Lived	Discounted NH Costs	Discounted NH Cost per Year Lived
9-mo delay						
I	0.23	−0.29	−2560	−471	−12,145	−1511
II	0.45	−0.15	2612	−440	−7562	−1940
III	0.43	−0.16	3395	−618	−9430	−4086
IV	0.00	0.00	0	0	0	0
36-mo delay						
I	0.57	−0.87	−10,015	−1526	−36,165	−4271
II	1.53	−0.74	6940	−1537	−34,640	−6829
III	1.51	−0.66	11,189	−1906	−35,866	−12,177
IV	0.00	0.00	0	0	0	0

Nursing home costs are fixed at the average Medicaid daily rate of $145 in 2007 dollars; costs are discounted at 3% per year.

Table 6 Simulated Cost-Free Intervention Effects on 10-Y Medicare Costs and Nursing Home (NH) Utilization Rates and Costs (in 2007 Dollars), 3-Dimensional Grade of Membership Model, 9- Mo and 36-Mo Delays, Women

Initial Pure Type	Total Years Lived	Years Lived in NH	Discounted Medicare Costs	Discounted Medicare Cost per Year Lived	Discounted NH Costs	Discounted NH Cost per Year Lived
9-mo delay						
I	0.36	−0.22	−2173	−566	−10,184	−1540
II	0.58	−0.10	3252	−465	−6655	−2676
III	0.00	0.01	−1	−10	330	52
IV	0.00	0.00	0	0	0	0
36-mo delay						
I	1.09	−1.03	−11,543	−2,110	−45,644	−5873
II	2.13	−0.53	10,758	−1540	−29,871	−8648
III	0.01	0.02	−10	−27	908	147
IV	0.00	0.00	0	0	0	0

Nursing home costs are fixed at the average Medicaid daily rate of $145 in 2007 dollars; costs are discounted at 3% per year.

- A 9-mo delay produced 10-y NH cost reductions of $12,145 (men) and $10,184 (women) and annual reductions of $1511 (men) and $1540 (women).

The actual federal Medicaid NH cost offsets would be smaller, because of the following:

- Approximately 50% of AD patients rely on Medicaid to pay all or part of their NH costs[34]; the federal government (Centers for Medicare & Medicaid Services) pays about 60% of these costs, with individual states paying varying balances in the range of 24% to 50%[35] and average costs within individual states ranging from 30% below to 40% above the national average cost.[31]

Thus, no more than 60% of the NH cost reductions could offset federal Medicaid payments for AD patients on Medicaid, assuming that all such reductions would first apply to the Medicaid share of the NH payments. In this case, the marginal offsets for all AD patients would be close to 30% of the NH cost reductions in Tables 5 and 6.

Even with these downward adjustments, the federal Medicaid NH cost offsets would still be comparable to the Medicare cost offsets (type I).

DISCUSSION AND CONCLUSIONS

The analysis has both substantive and methodological implications.

Substantively, the analysis provided new estimates of the clinical course of AD that accounted for initial heterogeneity of the patient population at the start of follow-up and differential patterns of deterioration of health status over the course of follow-up.

The analysis successfully incorporated multiattribute measures of cognition, function, and behavior in a low-dimensional representation of AD progression.

The analysis ranked the top predictors in the following order: *Dependence Scale*, *Equivalent Institutional Care*, *Blessed Dementia Rating Scale* (*Part 1*), *Residence Status*, and *mMMS*.

The estimates suggested that there could be large cost offsets to Medicare from the slowing of disease progression among patients with mild AD and substantial cost offsets to federal Medicaid payments for NH care from the slowing of disease progression among patients with both mild and moderate AD.

Methodologically, the longitudinal GoM model meets Eisdorfer's[11] and Green's[13] criteria that the model can represent combinations of multiple attributes including measures of cognitive functioning, functional ability, behavior, and mood and that it does so in a transparent way.

The approach represents a viable alternative to the standard Markov transition model, with simpler assumptions that are more closely satisfied. It differs from prior applications of the GoM model to cross-sectional AD data[18] in that the longitudinal changes among individual AD patients are fully integrated into the model. Rather than representing individual AD patients as (random) points in a high-dimensional state space, the approach represents them as (random) trajectories in a low-dimensional state space.

The use of a low-dimensional state space in GoM was recommended by Wachter.[36] Our innovation extended Wachter's recommendation to the low-dimensional state-space trajectories of longitudinal GoM with the 3-D dimensionality validated using 2 forms of the Bayesian information criterion and with the transition parameters validated using a 2nd, independent data set (Predictors 2). The methodology appears applicable to the modeling of existing AD data sets. It may be sufficiently flexible to incorporate future AD progression predictors, such as biomarkers and brain-imaging technologies.

Our study had several limitations. The 506 cases in Predictors 1 and 2 were recruited at 3 sites in the northeastern United States using specific inclusion/exclusion criteria[25] that may influence the generalizability of the results to other AD patients. Sex differences in the transition matrices and outcome probabilities were identified but not modeled further. For example, the use of nursing homes and other paid LTC services was higher for women than men, in part because of the higher probability of lack of a spouse to provide care for widowed women. There are other important fixed variables that are already in (e.g., demographics) or could be added to (e.g., APOE genotype) the model that need to be further evaluated. The transition matrices in the current application were estimated separately for each observation interval, creating jumps in the trajectories that could be eliminated by smoothing the trajectories or graduating the transition matrices.

Our study was both exploratory and confirmatory. We successfully described AD progression as a 3-D process, validated that description on an independent data set, and provided strong evidence that AD is not a 1-D or 2-D process, but we did not prove that AD is truly a 3-D process. Although the biological mechanisms underlying AD progression should be consistent with a 3-D process, better understanding of those mechanisms may reveal a substantially more complex process.

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