An Improved Model for Disease Progression in Patients From the Alzheimer's Disease Neuroimaging Initiative

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The objective of this analysis was to develop a semi-mechanistic nonlinear disease progression model using an expanded set of covariates that captures the longitudinal change of Alzheimer's Disease Assessment Scale (ADAS-cog) scores from the Alzheimer's Disease Neuroimaging Initiative study that consisted of 191 Alzheimer disease patients who were followed for 2 years. The model describes the rate of progression and baseline disease severity as a function of influential covariates. The covariates that were tested fell into 4 categories: (1) imaging volumetric measures, (2) serum biomarkers, (3) demographic and genetic factors, and (4) baseline cognitive tests. Covariates found to affect baseline disease status were years since disease onset, hippocampal volume, and ventricular volume. Disease progression rate in the model was influenced by age, total cholesterol, APOE ε4 genotype, Trail Making Test (part B) score, and current levels of impairment as measured by ADAS-cog. Rate of progression was slower for mild and severe Alzheimer patients compared with moderate Alzheimer patients who exhibited faster rates of deterioration. In conclusion, this model describes disease progression in Alzheimer patients using novel covariates that are important for understanding the worsening of ADAS-cog scores over time and may be useful in the future for optimizing study designs through clinical trial simulations.

Keywords: *ADAS-cog; disease progression; Alzheimer disease; NONMEM; population modeling*

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Alzheimer disease (AD) is a progressive neurodegenerative disease associated with accumulation of amyloid plaques and neurofibrillary tangles in specific brain regions of AD patients. These pathologic markers are produced because of the aggregation of amyloid β peptide in the brain and tau hyper-phosphorylation within neurons. These pathologic phenomena are the cause of neuronal death and structural changes in the brain, which lead to the clinical syndrome of AD characterized by cognitive deficit, neuropsychiatric symptoms, and impaired activities of daily living. Current treatments for AD treat the cognitive manifestations of AD, but none of them delay the progression of the disease. AD is characterized by reduced cholinergic activity in the brain, and 3 acetylcholinesterase inhibitors (AChEIs), donepezil, galantamine, and rivastigmine, are approved as symptomatic treatments for AD. Similarly, neuronal excitotoxicity related to the glutamatergic neurotransmission is thought to be associated with AD pathogenesis. Memantine is another approved agent that acts by blocking glutamate overstimulation and has been shown to be moderately effective for the treatment of moderate to severe AD.

An improved understanding of cognitive decline in AD is clinically important for individuals and their families for prognosis and planning and is critically needed for clinical research to measure drug effects, particularly for dugs aimed at disease modification. A key measure of cognition in AD is the cognitive component of the Alzheimer's Disease Assessment Scale (ADAS-cog), which is considered the gold-standard primary outcome instrument for AD registration trials.[1,2]

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Modeling the longitudinal changes in ADAS-cog is the primary goal of this analysis, and it offers several potential benefits. It may allow for a more precise understanding of the natural history of cognitive decline in the disease and thereby allow optimization of trial designs to detect disease-modifying effects of drugs. In addition, it may allow for more precise correlation of cognitive states with structural or chemical biomarkers that also change with disease. An adequate ADAS-cog model may facilitate identification of risk factors, demographics, and other covariates that affect baseline disease status and the rate of disease progression, which may serve as stratification variables in future clinical trials. Finally, the model can estimate the between-subject variability and residual variability associated with disease progression in AD, which is a critical factor in determining adequate sample size for clinical trials.

Historically, AD progression rate has been modeled as a linear process.[3-5] Availability of long-term data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) public database from https://www.loni.ucla.edu/ADNI now allows assessment of the linear disease progression assumption for AD. In ADNI, as of November 7, 2009, 129 AD patients have ADAS-cog measurements available at baseline, year 1, and year 2. Initial screening of the data indicated that the mean difference in progression rate between years 1 and 2 is 1.74 points (95% confidence interval, 0.31-3.17), which is statistically significant ($P < .05$). This suggests that the rate of decline is nonlinear and incorporation of nonlinear effects would provide an improved model of AD progression.

Two recent groups have published important disease progression models for naturalistic studies in AD. Ito et al[4] analyzed the ADNI data using a linear AD progression model based on a population-based mixed effects approach, whereas Ashford and Schmitt[6] applied a logistic model to characterize disease progression in AD. These analyses represent a significant advancement over previously published disease progression models. The study by Ito et al tested covariate effects on disease progression, whereas Ashford and Schmitt explored a model other than linear disease progression. Despite these advances, several opportunities offered by the richness of the ADNI data remain to be explored. ADNI allows for the testing of linear versus nonlinear rates of progression because of the relatively large number of well-characterized AD patients with longitudinal assessments. In addition, information on an expanded list of potential covariates of interest is available from the patients enrolled in ADNI, which will be explored further in this analysis.

In this analysis, we focused on the AD population within ADNI rather than build a model that incorporates information from mild cognitive impairment (MCI) patients, who represent a rather heterogeneous population.[7] In addition, recent reports have shown that elderly normal controls and patients with MCI in ADNI show bimodal distributions with respect to their biomarker profiles and disease progression characteristics (ie, converters vs nonconverters).[8] To accommodate bimodal distributions, disease progression analysis using mixture modeling approaches for the other ADNI populations could be the objective of future research.

The objectives of the current analysis are to develop a nonlinear mixed effects model for disease progression in AD, which allows estimation of the typical disease progression parameters in the target population along with their inter- and intraindividual variability and incorporates the effects of influential covariates on disease progression. Moreover, the present investigation expands the knowledge gained from previously published models and assesses previously untested assumptions about linear disease progression in AD. Finally, the present investigation also offers a differing perspective by evaluating an expanded set of previously untested covariates on disease progression parameters.

METHODS

Study Details

Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and participants have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90 years, to participate in the research—approximately 200 cognitively

Table I Summary of Structural Models

Model Description	Progression Rate	Inflection Point	Inflection Point Estimate	Number of θs	AIC Value
Linear	$\frac{dADAS_{cog}}{dt} = r$	NA	NA	2	−1085
Logistic 1	$\frac{dADAS_{cog}}{dt} = r.ADAS_{cog}\left[1-\frac{ADAS_{cog}}{70}\right]$	$\frac{70}{2}$	35	2	−1105
Logistic 2	$\frac{dADAS_{cog}}{dt} = r.ADAS_{cog}\left[1-\frac{ADAS_{cog}}{70}\right]^{\gamma}$	$\frac{70}{1+\gamma}$	65	3	−1113
Logistic 3	$\frac{dADAS_{cog}}{dt} = r.ADAS_{cog}\left[1-\left(\frac{ADAS_{cog}}{70}\right)^{\beta}\right]$	$\left(\frac{70^{\beta}}{1+\beta}\right)^{\frac{1}{\beta}}$	50	3	−1114
Logistic 4	$\frac{dADAS_{cog}}{dt} = r.ADAS_{cog}^{\alpha}\left[1-\frac{ADAS_{cog}}{70}\right]$	$\left(\frac{\alpha.70}{1+\alpha}\right)$	44	3	−1115

NA, not applicable

normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

All AD patients had clinical/neuropsychological assessments and 1.5T MRI measurements. AD patients were assessed at 0, 6, 12, and 24 months. ADNI allows public access to all accumulating data; the data set available on November 7, 2009, from the ADNI database (www.loni.ucla.edu/ADNI) consisted of 191 AD patients and was used in the current analysis. The availability of individual data makes it possible to evaluate covariate effects on disease progression in AD along with an assessment of between-subject variability in the disease progression parameters.

Population Analysis Software

Data set preparation, exploration, and visualization were performed using S-Plus 6.0 Professional Release 2 software (Insightful Corporation, Seattle, Washington). ADAS-cog data were used for nonlinear mixed effect modeling by extended least squares regression using NONMEM Version VI with an Intel FORTRAN 10 compiler.[9]

Selection of the Structural Model

The model-building exercise employed the first-order conditional estimation method (FOCE) in NONMEM while using log-transformed data (see Random Effects Model). A sequence of models was tested and the results compared to select the best model. The simplest linear progression model was chosen first for model fitting. This was followed by a series of logistic models[10] to characterize the inflection point characteristic of disease progression observed in AD. The disease progression is characterized by an initially increasing rate of progression with increasing scores followed by slowing of the disease progression rate as scores approach an asymptote of 70. The generalized logistic model[10] that represents the rate of disease progression (in the form of a differential equation) is as follows:

$$\frac{d\,ADAS_{cog}}{dt} = r \times ADAS_{cog}^{\alpha}\left[1-\left(\frac{ADAS_{cog}}{ADAS_{cog\,max}}\right)^{\beta}\right]^{\gamma}, \quad (1)$$
$$ADAS_{cog}(0) = ADAS_{cog0}$$

where r is a rate parameter to adjust for each individual's progression velocity, $ADAS_{cogmax}$ is fixed at the maximum possible score of 70, $ADAS_{cog0}$ is the baseline score, and α, β, and γ represent the shape/steepness factors that also control the inflection point. To test a series of logistic models, first α, β, and γ were all set to 1, which represents logistic model 1 with an inflection point at half-maximal score.[10] For logistic models 2, 3, and 4, γ, β, and α were not set to 1; they represented 1 additional estimated parameter in their respective models (see Table I). Ashford and Schmitt[6] have used a 2-power coefficient model with α and γ for modeling disease progression with MMSE scores. However, attempts to fit more than 1 power coefficient in the

current analysis led to model instability or lack of convergence. It should be noted that there are insufficient data from patients with severe AD (only 5% of the data are above an ADAS-cog score of 40), and this may prevent estimation of 2 shape parameters from the current data. Thus, estimation of more than 1 power coefficient was not investigated further. The mathematical relationships tested for the structural model were often nonnested and sometimes had the same number of parameters. The selection of the best structural model was therefore guided by the Akaike information criterion (AIC), which is equal to the NONMEM objective function value plus twice the number of parameters in a given model. Another important criterion for selection of the structural model was its ability to capture the inflection point. The linear model does not have an inflection point, but the inflection point for logistic models 1 to 4 is described by explicit functions provided in Table I.[10] The model that gave an inflection point closest to the literature reported value[5,6,11] of 40 to 42 was given a preference. A few other criteria that were used to compare different candidate models were (1) decrease in the residual error, (2) more random distribution in the weighted residuals against the predicted score and time, (3) more random distribution of the observed versus predicted scores across the identity line, and (4) precision of the parameter estimates. The model selected based on these criteria is referred to as the base structural model.

Random Effects Model

Between-subject variability on $ADAS_{cog0}$ was evaluated using an exponential error model:

$$ADAS_{cog0j} = ADAS^{*}_{cog0} \times e^{\eta j}, \quad (2)$$

where $ADAS_{cog0j}$ is the true value of the baseline parameter for the jth subject, $ADAS^{*}_{cog0}$ is the population typical value (TV) for the parameter, and η_j is an intersubject random effect that distinguishes the jth subject's true value from the population TV and is assumed to follow a Gaussian distribution. The model for between-subject variability on $ADAS_{cog0}$ assumes that the variance is constant with respect to the log of the TV of the parameter, and this parameterization is needed to prevent baseline scores from becoming negative. Furthermore, the observed baseline score ranges from 7 to 43, and an exponential error model helps to capture the long right tail of the distribution.

Between-subject variability on parameter r was evaluated using a proportional error model:

$$r_j = r^{*} \cdot (1 + \eta j), \quad (3)$$

where r_j is the true value of the rate parameter for the jth subject, r* is the population TV for the parameter, and η_j is an intersubject random effect that distinguishes the jth subject's true value from the population TV and is assumed to follow a Gaussian distribution. The model for between-subject variability on the r parameter assumes that the variance is proportional to the TV of the parameter. Rate of disease progression may be either positive or negative (disease may worsen and improve over time) in an individual patient, and it is therefore important to use a proportional error model for this random effect so that both types of progression can be captured.[12]

Residual variability in ADAS-cog was evaluated using an additive error model after natural logarithmic transformation of the observed scores and model predictions as follows:

$$\ln \text{ADAS-cog}_{obs} = \ln \text{ADAS–cog}_{ipred} + \varepsilon, \quad (4)$$

where ADAS-cog_{obs} is the observed score, ADAS-cog_{ipred} is the corresponding model-predicted individual value, and ε is an independent normally distributed random variable with zero mean and variance, σ^2. Based on visual inspection, the scores are more variable as the absolute value of the scores increases (see Results section), and naturally ADAS-cog scores are nonnegative. Both these characteristics of the data (heteroscedasticity and nonnegative values) are appropriately captured using the log-transform both-sides approach for the residual error.

Building a Covariate Model

An initial list of 34 covariates was considered in this analysis (for covariate description and abbreviations, see Table II). These covariates fell into the following 4 categories: (1) MRI volumetric measures, (2) serum biomarkers, (3) demographic and genetic factors, and (4) cognitive tests at baseline/screening.

Covariate search was guided by the following principles. Only relatively uncorrelated covariates were assessed in this analysis to avoid the detrimental effects of collinearity on the precision and accuracy of the model parameter estimates.[13,14] To assess and confirm correlation between the predictors, an absolute correlation coefficient value $|r| > 0.3$ was used as the cutoff criterion.[13,14] If important covariates were correlated, then a single summary variable was created to represent correlated predictors (see the following).[13] Cognitive

Table II Summary of Covariate Characteristics

Variable Name (Abbreviation), Units	Mean or %	SD
Magnetic resonance imaging volumetric measures		
Brain volume (BVOL), mL	998	107
Ventricular volume (VVOL), mL	54.3	28
Hippocampal volume[a] (HVOL), mm^3	2895	525
Serum biomarkers		
Fasting serum glucose (FSG), mg/dL	99	22
Mean corpuscular volume (MCV), fL	91	5
Serum cholesterol (CHOL), mg/dL	198	39
Serum triglycerides (TG), mg/dL	154	93
Vitamin B_{12} (B12), pg/mL	545	348
Demographic and genetic factors		
Age at Alzheimer disease diagnosis (AAGE), y	72	8
Age (AGE), y	76	7
Apolipoprotein E genotype status (APOE4), %		
0 Alleles	34.0	NA
1 Allele	47.1	NA
2 Alleles	18.8	NA
Body mass index (BMI), kg/m^2	25.6	4
Diastolic blood pressure (BP), mm Hg	73	9
Family history of dementia (FHD), %		
None	58.1	NA
Father	7.3	NA
Mother	29.3	NA
Both	5.2	NA
Gender (SEX), %		
Male	52.9	NA
Female	47.1	NA
Years of education (EDU)	15	3
Baseline/screening cognitive tests		
Baseline Alzheimer's Disease Assessment Scale (ADAS-cog)	18.6	6
Activities of daily living score (ADL)	13.0	7
American National Adult Reading Test (ANAR)	15.8	10
Auditory verbal learning delayed recall (AVD)	0.744	1.6
Boston Naming Test (BNT)	22.5	6
Category Fluency Test: animal names (CATA)	12.4	5
Category Fluency Test: vegetable names (CATV)	7.83	3.3
Clinical dementia rating global score (CDR), %		
0.5 Score	51.8	NA
1 Score	48.2	NA
Clock drawing test (CDT)	3.39	1.3
Digit symbol substitution test (DSST)	27.0	13
Digit span backwards test (DSB)	4.97	1.8
Global depression total score (GDT), %		
0 Score	22.5	NA
1 Score	32.5	NA
2 Score	19.9	NA
3 Score	13.1	NA
4 Score	8.9	NA
5 Score	2.6	NA
6 Score	0.5	NA
Logical memory: delayed (LDEL)	1.26	1.9
Logical memory: immediate (LIMM)	4.08	2.9
Mini-Mental State Exam (MMSE)	23.4	2
Neuropsychiatric Inventory (NPI)	3.47	3.3
Number cancellation (NOC)	1.78	1.3
Trail Making Test: part A (TRAA), s	66.9	36
Trail Making Test: part B (TRAB), s	196	84
Derived covariate		
Years since AD onset (YSO = AGE – AAGE)	4	2

NA, not applicable
a. Average of left and right hippocampal volume.

test scores were not tested as covariates on baseline ADAS-cog score because the objective of this analysis was not to find if ADAS-cog is correlated with other scores. However, baseline cognitive test scores that were not strongly correlated ($|r| < 0.3$) with the baseline ADAS-cog score were tested as covariates on the progression rate parameter.

The covariate analysis proceeded via 3 steps. The first step of the analysis was driven by prior knowledge about covariate effects on AD progression parameters r and $ADAS_{cog0}$.[15] Based on prior knowledge, APOE ε4 genotype, serum cholesterol, and age influence r, whereas 2 other factors (age and age at AD diagnosis) affect $ADAS_{cog0}$.[4,16,17] However, age and age at AD onset (AAGE) were highly correlated, and a new summary variable, YSO (AGE – AAGE), was created to represent years since onset of the disease. These prior covariates were introduced on the typical values of the parameters in the base structural model to produce the base reference model:

$$ADAScog_0^* = \theta_{ADAScog0} \cdot e^{\theta_{YSO} \cdot YSO}, \quad (5)$$

$$r^* = \theta_r \cdot \left(\frac{AGE}{76}\right)^{\theta_{AGE}} \cdot \theta_{APOE}^{Apoe} \cdot \theta_{CHOL}^{Chol}, \quad (6)$$

where the exponent Apoe is 0 for APOE ε4 noncarriers and 1 for APOE ε4 carriers, the exponent Chol is 0 if cholesterol (CHOL) is less than 200 mg/dL and 1 if CHOL ≥200 mg/dL, and the various thetas (θ) reflect fixed effect parameters. There were not sufficient subjects with 0, 1, and 2 APOE ε4 alleles, and therefore APOE ε4 was dichotomized into carrier (1 or 2 alleles) and noncarrier status. With the exception of YSO and CHOL, the continuous covariates were introduced through a power equation after centering on the median, whereas categorical covariates were represented as fractional shifts for risk factors being investigated. YSO can assume a value of 0 at which the power equation for a continuous covariate would be undefined, and therefore an exponential function was used. Estimation of the cholesterol effect as a continuous covariate led to poor precision of the parameter estimate and model instability. This may suggest that only hypercholesterolemic patients exhibit faster disease progression. CHOL was categorized into a dichotomous variable based on the high cholesterol cutoff value of ≥200 mg/dL, and this parameterization stabilized the model.

The second step of the covariate search involved a screening procedure.[18] Screening was performed by general additive modeling (GAM) with the statistical package R-2.10.1 for Windows (http://www.r-project .org). The R version of the script has been incorporated into version 4 of the software package Xpose.[19] The empirical Bayes ("*post-hoc*") estimates of ηs for each parameter generated from the previous step and the individual covariates were used as input for the GAM analysis.

Only the independent covariates were tested during the screening procedure as indicated previously. Brain volume (BVOL) was correlated with both ventricular volume (VVOL; $|r| = 0.29$, $P < .001$) and hippocampal volume (HVOL; $|r| = 0.53$, $P < .001$), and therefore BVOL was not considered further. Similarly, serum triglycerides (TG) were correlated with CHOL ($|r| = 0.38$, $P < .001$), and AGE-related variables were already incorporated on the 2 key parameters (AGE on r and YSO on ADAS-cog_0). Thus, TG and AAGE were not considered further. Finally, only 6 cognitive tests at baseline/screening were not strongly correlated with ADAS-cog_0, and these 6 tests (ANAR, AVD, DSB, LDEL, NPI, and TRAB; see Table II for abbreviations) were tested as covariates on the r parameter. SEX, FHD, APOE4, VVOL, HVOL, BP, EDU, B12, MCV, FSG, BMI, and CHOL were tested on ADAS-cog_0 using GAM. Similarly, SEX, FHD, VVOL, HVOL, BP, EDU, B12, MCV, FSG, BMI, ANAR, AVD, DSB, LDEL, NPI, and TRAB were tested on the r parameter using GAM. The 2 covariates that could not be assessed in this analysis were race and global depression total score (GDT) because too few subjects were available in the database for these variables (>92% of the ADNI AD population was white, and depressed patients [GDT ≥6] were excluded from the study).

In the final and third step, NONMEM was used to optimize and finalize the population model[18] using a step-up procedure involving the likelihood ratio test. Covariates identified by GAM were tested one by one on top of the base reference model. Continuous covariates were introduced through a power equation after centering on the median, categorical covariates were represented as fractional shifts, and continuous covariates with possible 0 values were parameterized as exponential relationships (see equations (5) and (6)). A covariate was included in the model if it were significant ($P < .01$; decrease of >6.6 points in the objective function value) and led to the greatest drop in the objection function value. The process was repeated until no significant covariates could be found.

Model Evaluation

To verify the precision and stability of the models, the final parameter estimates were subjected to internal model evaluation. The evaluation consisted of a nonparametric bootstrap and a predictive check. Bootstrap analysis was performed using the package Perl Speaks NONMEM (Version PsN-3.1.0).[20] For that purpose, 1000 bootstrap replicates of the data set were obtained. Each bootstrap data set consisted of N random draws of individual subject data (with replacement) from the original data set, and the final model was refitted to each new data set. Bootstrap methodology has been implemented in PsN, which automatically creates the bootstrap data sets, runs that model in NONMEM using these bootstrap data sets, and then computes the percentiles of the bootstrap parameter estimates. The stability of the final model was evaluated by visual inspection of the distribution of parameter estimates from the new data sets and by comparison with the parameter estimates obtained from the fit of the original data set. Bootstrap runs with unsuccessful minimization were excluded from further analysis. The final model parameter estimates were compared with the median and 90% confidence intervals of the nonparametric bootstrap replicates.

To assess the predictive performance of the obtained model, data sets were simulated based on the fixed and random effect estimates of the final model. Visual predictive check was performed using the parameter estimates and variability parameters from the original data as the simulation template as described previously.[21] The 5th, 50th, and 95th percentiles were calculated from the simulated profiles for the predictive checks and were superimposed on the raw data to allow assessment of model predictability.

The following measures were defined a priori as model verification and evaluation criteria: (1) parameter estimates should have biological plausibility, (2) comparison of the overlap of the simulated distribution (ie, predictive checks) with the observations should show considerable similarity without significant over- or underprediction, and (3) model stability is evaluated by inspection of the distribution of the model parameters obtained through bootstrapping. The estimates from the original data set were expected to lie within the 90% confidence interval obtained from the bootstrap replicates. The model can be considered precise if the parameters from the original data set are similar to the median of the parameter distribution from the bootstrap replicates.

RESULTS

Patient Characteristics

The characteristics of the ADNI AD patients are shown in Table II. Patients (n = 191) were between ages 55 and 91 years (mean ± standard deviation [SD], 76 ± 7 years) and had AD for an average duration of 4 ± 2 years. The patients were well educated, with an average of 15 ± 3 years of education. Eighty (42%) patients had a family history of dementia with at least 1 parent having the disease. There was an apparent pattern for maternal transmission of the disease because 66 of the 80 patients with a family history had mothers with dementia. Compared with women, the decreased longevity in men could lead to disproportionately fewer paternal cases of dementia in the ADNI AD population, and this could give rise to the apparent pattern for maternal AD transmission. However, this observation of maternal transmission of the disease is consistent with earlier reports in the AD literature.[22,23] Of the AD patients, 66% were APOE ε4 carriers, and this confirms that APOE ε4 is a significant risk factor for AD (0 alleles: 34%; 1 allele: 47%; 2 alleles: 19%). AD patients also had relatively high cholesterol, with the mean cholesterol level in this population being 198 ± 39 mg/dL, which is very close to the high cholesterol cutoff of ≥200 mg/dL.

Development of Disease Progression Model

The results of the structural model search are provided in Table I. AIC monitoring for structural models indicated that the logistic model 4 with the alpha exponent had the lowest AIC value. This base structural model also yielded an inflection point of 44, which is very close to the literature reported value of 40 to 42.[5,6,11] This model was taken forward for the development of the submodel consisting of covariate effects on progression rate parameter and baseline disease status. Covariate model building began with incorporation of prior knowledge into the base structural model. Addition of 4 parameters (θ_{YSO}, θ_{AGE}, θ_{APOE}, θ_{CHOL}) led to an improvement in the NONMEM objective function value by 27 points. A likelihood ratio test was performed where the difference in objective function was compared with the chi-square distribution, with the number of degrees of freedom (*df*) equal to the number of additional parameters in the updated model ($P = .00002$; $df = 4$). The *P* value is highly significant, indicating that incorporation of prior knowledge improved the base structural model.

The empirical Bayes ("*post-hoc*") estimates of ηs for the parameters from the updated model (base reference model) were used as the basis for GAM analysis. The GAM screening procedure indicated that HVOL and VVOL could be potential covariates on $ADAS_{cog0}$. Similarly, digit span backward test, delayed logical memory, and part B of the Trail Making Test (Trails B test) could be potential covariates on the r parameter. This was followed by a step-up procedure in NONMEM: (1) in the first step, HVOL was selected as a covariate on $ADAS_{cog0}$ and led to a decrease in objective function value of 14 points. (2) The second step led to an improvement of 8 objective function points by incorporation of the Trails B test as a covariate on the r parameter. (3) In the final step, VVOL was the chosen covariate on $ADAS_{cog0}$, which was associated with an objective function improvement of 8 points. Addition of more covariates did not lead to a further improvement in the model.

As an alternative, instead of testing covariates individually in NONMEM, all of the influential covariates from the GAM procedure were added to the base reference model using the appropriate functional forms (see Methods section). Covariates introduced into the full covariate model were then tested formally using backward elimination, a procedure described by Wählby et al.[24] This method produced the same covariate model as produced by the step-up method, which further supported the suitability of the final covariate model. Figure 1 shows the goodness-of-fit plots for the

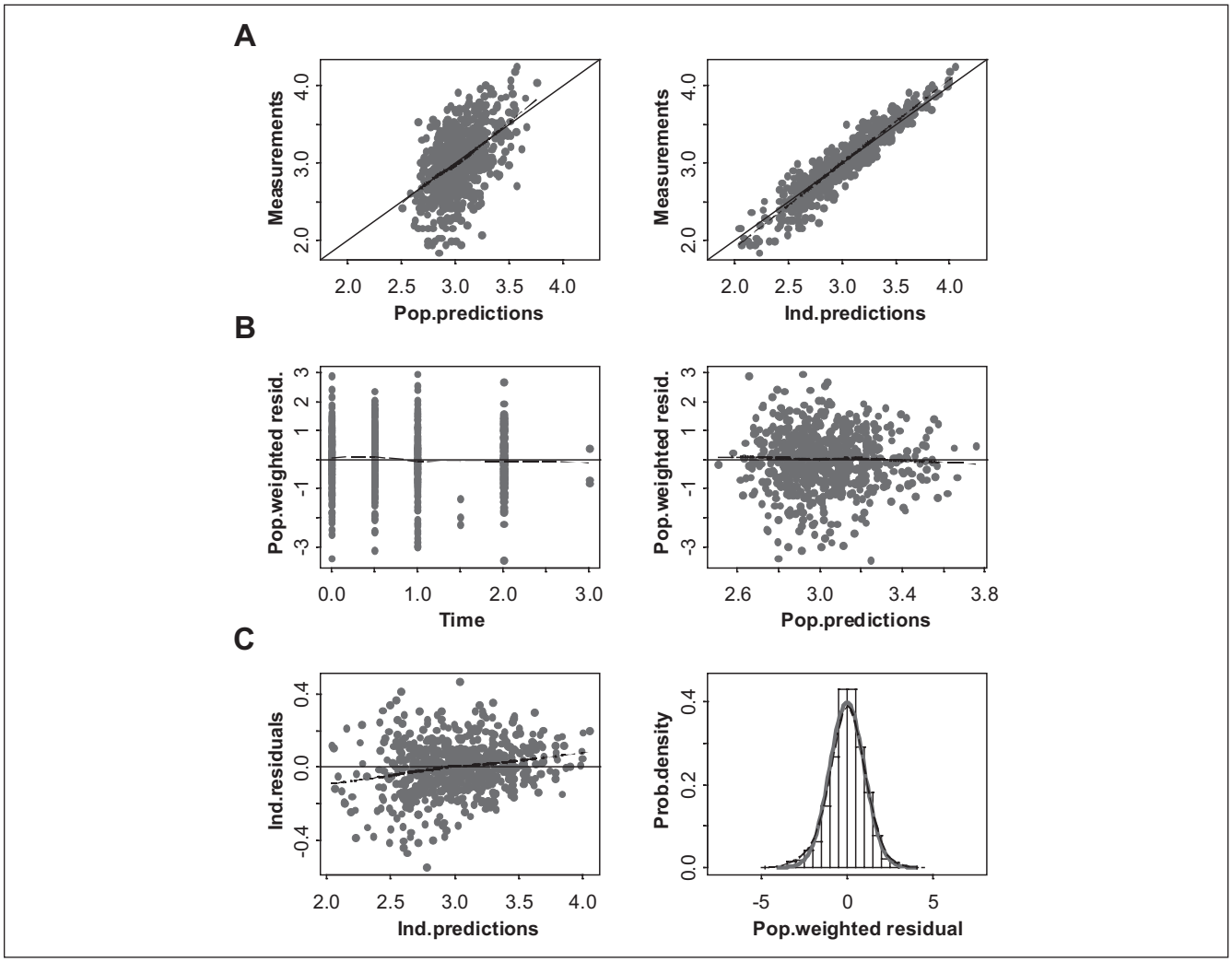

Figure 1. Goodness-of-fit plots for the final model. (A) Observed versus population and individual predictions. The solid line represents the line of identity. (B) Population-weighted residuals versus time and population predictions. (C) Individual residuals versus individual predictions and distribution of population-weighted residuals. Ordinate value of zero is presented in all the residual plots (solid line). Dashed line represents the LOWESS smoother. In the bottom right panel, the solid line represents the normal density, and the dashed line represents the kernel density of population-weighted residuals.

final model, and Table III provides the final estimates from the population-based disease progression model.

Model Verification

The results of the nonparametric bootstrap analysis (Table III) supported the parameter estimates of the model. The final parameter estimates are similar to the median value obtained from the bootstrap analysis and are within the 90% confidence interval. The observed scores, the visual predictive check, and median model prediction as a function of time are displayed in Figure 2A. These results confirm that the model is able to describe the individual temporal profiles because the majority of the observations fall within the 90% prediction intervals (Figure 2A). Figure 2B exhibits the AD progression rate as a function of ADAS-cog scores and patient covariates. Progression rate is given by the function $r \cdot ADAScog^{1.52} \cdot (1 - ADAS\text{-}cog/70)$. Individual estimates of r and observed ADAS-cog scores from the ADNI AD patients were used to compute observed progression rates, and the predictions were from 1000 simulated data sets. The progression rate plot (Figure 2B) exemplifies the signature pattern of a logistic model. The

Table III Population Parameters and the Stability of the Parameters Using Nonparametric Bootstrap

	Original Data Set			Bootstrap Replicates (n = 934)		
Parameter[a]	**Estimate**	**90% CI**		**Median**	**90% CI**	
$\theta_{ADAScog0}$	16.3	15.4	17.2	16.4	15.4	17.3
$\theta_{YSO} \times 10^2$	2.19	0.835	3.55	2.20	0.712	3.75
θ_{VVOL}	0.119	0.050	0.188	0.120	0.048	0.194
θ_{HVOL}	−0.479	−0.699	−0.259	−0.468	−0.691	−0.245
$\theta_r \times 10^2$	4.94	0.170	9.71	5.18	1.37	21.0
θ_{AGE}	−2.14	−3.26	−1.02	−2.14	−3.25	−0.912
θ_{TRAB}	0.430	0.188	0.672	0.438	0.191	0.711
θ_{APOE}	1.06	0.817	1.30	1.07	0.847	1.39
θ_{CHOL}	1.19	0.912	1.47	1.20	0.927	1.53
α[b]	1.52	1.23	1.81	1.49	1.06	1.93
SD of $\eta_{ADAS\text{-}cog0}$[c]	0.279	0.252	0.304	0.275	0.249	0.302
SD of η_r[c]	0.522	0.207	0.709	0.517	0.258	0.734
SD of ε	0.170	0.155	0.183	0.169	0.154	0.182

a. These equations describe the relationships between covariates and the typical value of the parameters in the final model:

$$ADAScog_0^* = \theta_{ADAScog0} \cdot e^{\theta_{YSO} \cdot YSO} \cdot \left(\frac{VVOL}{47.9}\right)^{\theta_{VVOL}} \cdot \left(\frac{HVOL}{2834}\right)^{\theta_{HVOL}}$$

$$r^* = \theta_r \cdot \left(\frac{AGE}{76}\right)^{\theta_{AGE}} \cdot \left(\frac{TRAB}{187}\right)^{\theta_{TRAB}} \cdot \theta_{APOE}^{Apoe} \cdot \theta_{CHOL}^{Chol}$$

where Apoe and Chol are 0/1 exponents depending on APOE ε4 noncarrier/carrier status and normal/high cholesterol status, respectively. HVOL, VVOL, TRAB, and CHOL refer to hippocampal volume, ventricular volume, Trails B test, and serum cholesterol, respectively.

b. Final estimated inflection point is 42 based on the formula $\alpha.70/(1 + \alpha)$.

c. Between the base model and final covariate model, the between-subject variability SD estimates improved from 0.308 and 0.640 to 0.279 and 0.522, respectively.

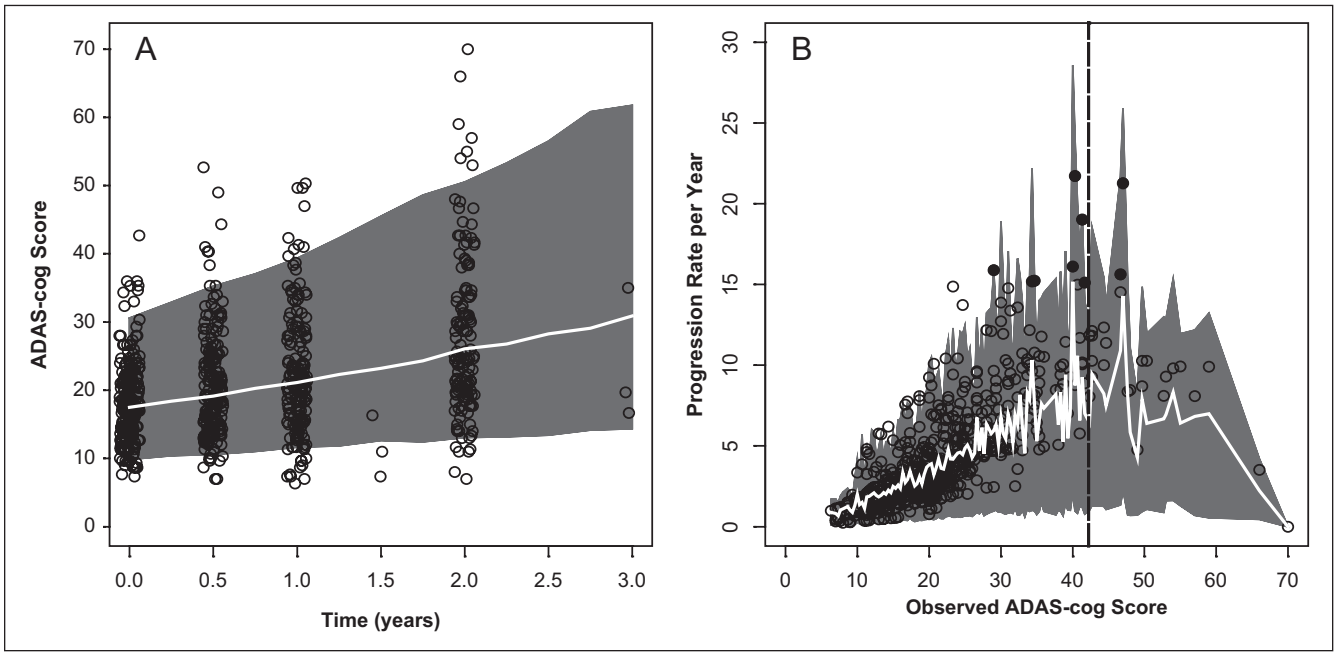

Figure 2. (A) Results of the visual predictive check; the x-axis is jittered for clarity. (B) Progression rate as a function of Alzheimer's Disease Assessment Scale (ADAS-cog) score and covariates. The filled symbols represent 6 patients who exhibited progression rate >15 points/year (see Table IV). Lines and shaded areas represent median and 90% prediction interval. The vertical dashed line is the final estimated inflection point value of 42.

progression rate increases up to the estimated inflection point of 42 (estimate from the final model), after which it declines and decreases to zero at the maximal possible score of 70.

DISCUSSION

Differences Between Previously Published Models and the Current Analysis

Two excellent models have recently been published that characterize AD progression in naturalistic studies.[4,6] Ito et al[4] have modeled AD progression via a linear process where the slope at time zero was influenced by the baseline ADAS–cog score through a curvilinear relationship. The slope stayed constant for the 2-year study duration for AD patients in the ADNI. An improvement provided by Ito et al consisted of the inclusion of covariate effects on the disease progression parameters. However, in this analysis, covariates were not tested on baseline disease status, and relatively few covariates were tested on disease progression rate. The baseline ADAS-cog score was correlated with the Mini-Mental State Examination (MMSE) score, whereas age, APOE ε4 genotype, gender, family history of disease, years of education, and baseline severity were tested as covariates for progression rate. Finally, random effects on the baseline disease score and residual variability were both assumed to be normally distributed. We aimed to update a variety of the modeling aspects reported by Ito et al. Several different structural models (linear and nonlinear) for disease progression were tested in the current analysis. In addition, an expanded list of carefully chosen covariates was assessed in our analysis given the richness of the ADNI database. Last, certain random effect components were updated because a log-normal distribution might be more appropriate for baseline disease score and residual variability.

Ashford and Schmitt[6] have recently used a logistic model to characterize disease progression in AD. The only limitation of the Ashford and Schmitt analysis, which involved the logistic model of AD, is that the work did not incorporate covariate effects on disease progression, whereas our model incorporated covariates. Logistic models have traditionally been used in pharmacodynamic models of tumor growth.[25] However, the application of logistic models to AD disease progression is appropriate for several reasons. The logistic model assumes that the rise in disease scores increases exponentially during the early phase of the disease. Progression rate is initially proportional to the score through a rate constant r. As the score approaches the maximal limit (ie, 70 for ADAS–cog), the progression rate slows down. As AD worsens, the patients experience a loss of language skills.[26] Therefore, performance on the ADAS–cog is subject to floor effects[26] that make it hard to measure the change in disease status in severe AD patients, leading to the plateauing of scores, which is also captured by the logistic model. These models are also characterized by an inflection point, which in the case of ADAS–cog is the point at which the progression rate is the fastest. At scores above and below the inflection point, the progression rate is slower. Stern et al[11] have reported an inflection point at a score of 40 in their ADAS-cog analysis. Similarly, Ashford and Schmitt[6] modeled MMSE scores and reported an inflection point of 10 on the MMSE scale. An MMSE score of 10 corresponds to an ADAS-cog score of 42.[5] Our current analysis also found that the logistic model best described the progression of AD in ADNI patients, and the final model that implemented covariate effects estimated an inflection point of 42. Thus, the use of a logistic model allows characterization of the inherent nature of disease progression that has been observed in AD. The logistic model could also find applications to other chronic illnesses where disease scores are constrained to lie within a certain theoretical range. The logistic model has the ability to capture clinician-rated instruments for assessing disease status that may act as a saturable system, where the intrinsic properties of the functional assessment follow a nonlinear path. Indeed, several aspects of pharmacodynamic systems follow nonlinear and capacity-limited relationships[25] rather than linear processes, and the logistic model offers a flexible approach for capturing these complexities.

Choice of the Covariates Tested in the Model

Covariate data that were available for all patients were considered for testing in this analysis. It is for this reason that PET and cerebrospinal fluid markers were not assessed as covariates because they were captured in only a subset of patients in the ADNI. The other property that characterizes the covariates in this analysis is that they represent baseline/screening descriptors. Thus, the influential covariates identified in this analysis could potentially be used in the design of future trials, identify inclusion/exclusion/stratification criteria, and help with modeling outcomes based on patient characteristics. Thus, the baseline MRI measures, serum markers, vital statistics, and demographics can be justified as reasonable choices for covariate model building.

The testing of other cognitive performance measures as covariates can be justified because these baseline/

screening tests represent domains that are probably not captured by ADAS-cog. It is widely acknowledged that ADAS-cog has limitations for monitoring patients with mild illness, as it focuses only on a few domains (language, memory, and praxis) and does not adequately cover other domains such as delayed recall and executive function.[27,28] We therefore tested cognitive scores that were poorly correlated with ADAS-cog as covariates to understand how impairment in other domains could influence disease progression. These cognitive tests were chosen by correlating their baseline values with baseline ADAS-cog and picking only those tests that had showed $|r| < 0.3$. Because these cognitive tests are poorly correlated with baseline ADAS-cog, they were not tested further as covariates on $ADAS_{cog0}$ but were tested on the progression rate parameter.

Prior Knowledge About AD Progression Covariates

APOE ε4 is the single most significant risk factor identified to date for late-onset AD.[29-31] Ito et al[4] and others have shown that carriers of the APOE ε4 gene show faster disease progression, although this has not been replicated in all studies. APOE ε4 and cholesterol are biologically related because APOE acts as a cholesterol transporter in the brain. Elevated cholesterol is widely recognized as a risk factor in the pathogenesis of AD, and this has led several investigators to assess the role of cholesterol-lowering statins in the treatment of dementia (it should be noted, though, that statins have no benefit on outcome measures such as ADAS-cog).[32] In addition, Notkola et al[16] found that elevated total serum cholesterol level is a risk factor for AD independent of APOE ε4. Finally, Ito et al[4] have recently shown that patients diagnosed with AD at a younger age exhibit faster disease progression. With respect to the baseline disease score, Doraiswamy et al[17] found that baseline cognitive performance is correlated with both AGE and AAGE. This means that if the patient has had AD for a long time, then his or her baseline score would be high, which is expected because AD is a progressive disorder. However, AGE and AAGE are highly correlated ($|r| = 0.95$, $P < .001$), and therefore the new summary variable YSO was created to represent these correlated predictors. Given the progressive nature of AD, YSO was found to be a predictor of baseline ADAS-cog score.

Incorporation of prior known factors in the model led to a significant improvement in the model fit. To allow visualization of the effect that these covariates have on ADAS-cog profiles, a simple diagnostic plot was created (Figure 3). For the purposes of this plot, the continuous covariates were dichotomized (> median and ≤ median) to create roughly 2 equal groups (median YSO and AGE were 3 and 76 years). Categorical covariates APOE4 and CHOL were also dichotomous (see Methods section), and so all prior covariate effects could be plotted as a binary variable on the disease progression plots. The diagnostic plot indicates that YSO affects the baseline disease status because AD is a progressive disease, whereas AGE, APOE4, and CHOL influence the rate of disease progression. The effect of age on disease progression appears to be greatest, followed by cholesterol, which in turn is followed by APOE ε4 status (Figure 3).

It should be noted that the APOE ε4 effect on the progression rate parameter in our final model is somewhat lower (6%; Table III) than the 22% effect reported by Ito et al.[4] This can be attributed to 3 factors: (a) there is a difference in the methodology by which the progression rate is modeled in the current report versus the analysis presented by Ito et al.[4] Ito et al assume linear disease progression, whereas our analysis assumes that progression is nonlinear. (2) Notkola et al[16] have shown that APOE ε4 and cholesterol both influence AD but also found that the association between AD and APOE ε4 became weaker after adjustment for serum total cholesterol. Because our model includes both APOE ε4 and cholesterol, the magnitude of the APOE ε4 effect could be attenuated as previously seen by Notkola et al. (3) The statistically significant covariates in our analysis were age, APOE ε4 status, serum cholesterol, and Trails B test, whereas Ito et al[4] identified age and APOE as the predictors of progression rate. Because we identified a few more covariates, the absolute value of the parameter estimates may be somewhat different between the 2 analyses.

Correlation Between APOE4 and AGE

Among the 3 covariates (APOE4, AGE, and CHOL) that were introduced in the model based on prior knowledge, AGE and APOE4 were correlated (Figure 4A). The median age for APOE ε4 carriers and noncarriers at baseline was 75 and 80 years, respectively. This observation is not surprising because it is well established that the presence of the APOE ε4 genotype is associated with a lower age of onset for AD.[30] To assess whether the AGE and APOE4 effects were independent, APOE ε4 carriers and noncarriers were further dichotomized into a low and high age categories based on the median age for the respective groups. The temporal profile for ADAS-cog for the following 4 subgroups is presented in Figure 4B: lower age APOE4 carriers, lower age APOE4 noncarriers, higher age APOE4 carriers, and higher age APOE4

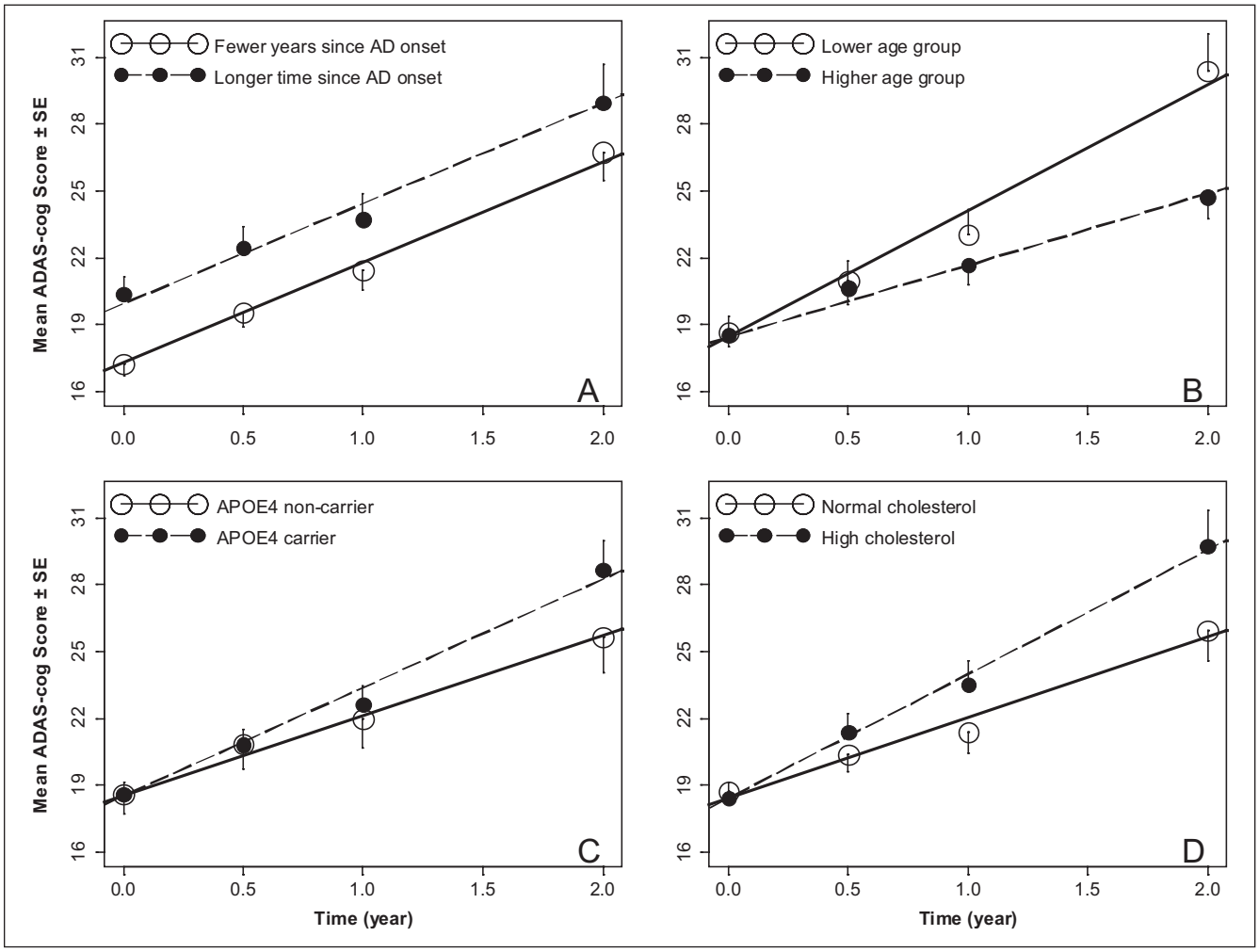

Figure 3. Covariates introduced into the disease progression model based on prior knowledge. Influence of (A) YSO, (B) AGE, (C) APOE4, and (D) CHOL on disease progression. YSO and AGE were dichotomized to create roughly equal groups (> median and ≤ median); median YSO and AGE were 3 and 76 years. Error bars represent standard error (SE), and lines represent simple linear regression through the data to allow visualization of the trends. ADAS-cog, Alzheimer's Disease Assessment Scale; AD, Alzheimer disease.

noncarriers. Comparison of the age effect in the APOE4 noncarriers clearly indicates that AD patients in the lower age group, even without this risk factor, show faster disease progression. This is suggestive of the fact that the AGE effect is independent of the APOE4 genotype. Similarly, comparison of the lower age group and higher age group shows that the APOE4 effect is present in both clusters, which may be an indication that the APOE effect is independent of AGE.

Additional Covariates Identified in the Current Analysis

The analysis identified additional covariates such as HVOL and VVOL on ADAScog$_0$ and Trails B test on r. Hippocampal atrophy and ventricular enlargement were associated with poor baseline cognitive performance. This is characterized by negative and positive exponents associated with HVOL and VVOL, respectively (Table III). The influence of HVOL and VVOL is depicted in Figure 5A,B, where these covariates were dichotomized for visualization purposes as described in the previous section. These findings for HVOL and VVOL are consistent with the MRI literature where cognitive decline has been shown to be associated with changes in volumetric measures on the MRI.[33,34]

Inspection of Figure 5A,B may suggest that results are somewhat inconsistent with the normal expectation for AD progression. Low HVOL and high VVOL patients exhibit higher ADAS$_{cog0}$ but progress at

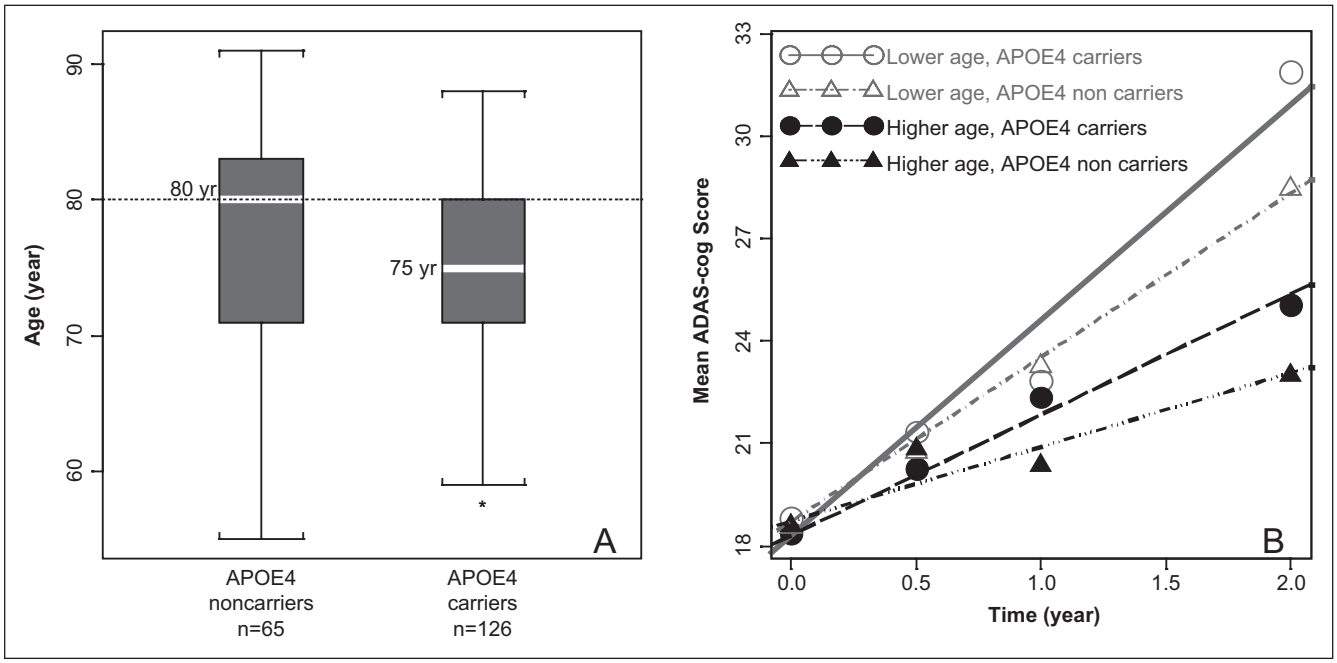

Figure 4. (A) Correlation between age and APOE ε4 status. (B) AGE and APOE4 have independent effects on progression rate. Error bars are not shown to allow clarity. Lines represent simple linear regression through the data to allow visualization of the trends. ADAS-cog, Alzheimer's Disease Assessment Scale.

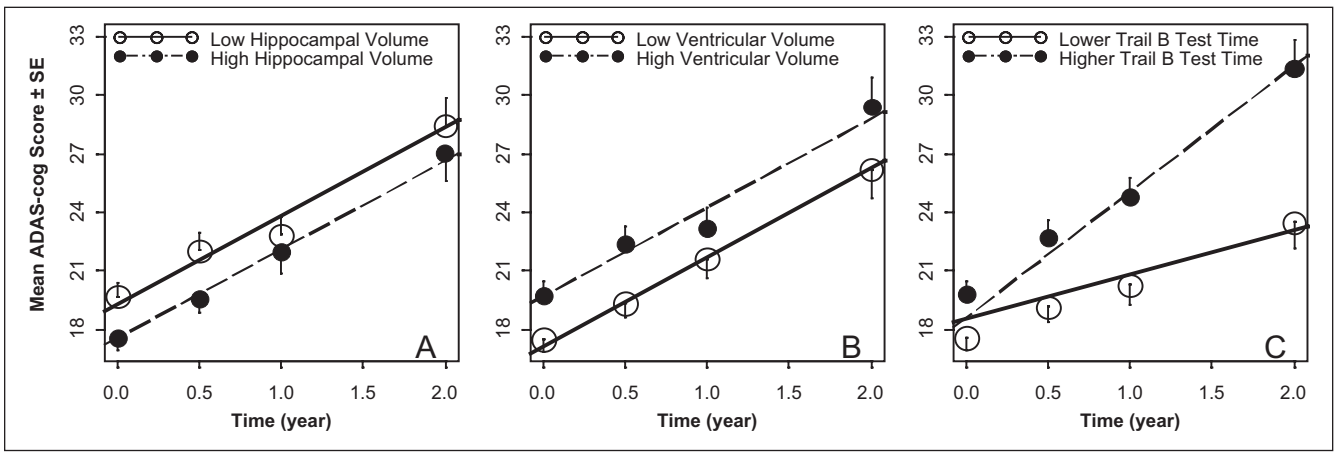

Figure 5. Newly identified covariates for Alzheimer disease (AD) progression: (A) HVOL, (B) VVOL, and (C) Trails B test. Covariates were dichotomized (> median and ≤ median) to create roughly 2 equal groups. Median HVOL, VVOL, and Trails B test values for the Alzheimer's Disease Neuroimaging Initiative (ADNI) AD population at baseline were 2834 mm^3, 47.9 mL, and 187 seconds, respectively. Error bars represent standard error (SE), and lines represent simple linear regression through the data to allow visualization of the trends. ADAS-cog, Alzheimer's Disease Assessment Scale.

roughly the same rate as patients with high HVOL and low VVOL. Interestingly, HVOL was negatively correlated with AGE ($|r| = 0.33$, $P < .001$), whereas the correlation between VVOL and AGE was positive ($|r| = 0.26$, $P < .001$). These age-related changes in HVOL and VVOL observed in the ADNI database are consistent with the MRI literature as well.[33,35] This confounding effect of AGE (higher age is associated with slower disease progression) explains why the cluster of patients with low HVOL and high VVOL exhibit a higher baseline ADAS-cog score but do not progress faster.

Table IV Description of 6 Patients Exhibiting a Progression Rate >15 Points/y

Patient ID	Time, y	ADAS-cog	Trails B Test*, s	Age*, y	APOE ε4 Status	Cholesterol*, mg/dL	Progression Rate, y^{-1}
88	0.5	29.0	300	66	2 Alleles	272	15.9
88	1.0	41.3	300	66	2 Alleles	272	19.0
109	2.0	41.7	165	71	1 Allele	280	15.1
343	2.0	46.7	300	72	1 Allele	219	15.6
366	1.0	34.3	300	57	0 Alleles	249	15.2
366	2.0	40.0	300	57	0 Alleles	249	16.1
627	2.0	34.7	196	59	2 Alleles	189	15.2
1397	0.5	40.3	300	55	0 Alleles	145	21.7
1397	1.0	47.0	300	55	0 Alleles	145	21.3

* Value of the covariate at baseline. ADAS-cog, Alzheimer's Disease Assessment Scale; Trails B Test, Trail Making Test, part B.

Various baseline cognitive tests were screened as covariates on AD progression rate. An example of this type of covariate effect, which was found to be significant in the current analysis, was the influence of the Trails B test on ADAS-cog progression (Figure 5C). The correlation analysis indicated that the baseline Trails B test score is not strongly correlated with baseline ADAS-cog score ($|r| = 0.26$), and thus this cognitive test represents a relatively independent metric. The Trails B test examines a patient's executive function, a domain known to be poorly covered by the ADAS-cog.[28] The analysis confirmed that patients who take a longer time to complete part B of the Trail Making Test exhibit faster disease progression.

Interplay Between Multiple Covariates on Disease Progression Rate

Figure 2B was used to identify 6 patients who progressed at a rate >15 points/y (generally, early AD progression proceeds at a rate of 5.5 points/y[4,5]), and the description of these fast-progressing patients is provided in Table IV. Examination of these patients reveals that over time, ADAS-cog scores increase and the progression rate accelerates (patients 88 and 366) until scores exceed the inflection point of 42, after which progression rate decelerates (patient 1397). Of note, the 6 patients with the fastest progression rate have combinations of the risk factors predicted by the model to predispose them to faster progression. Specifically, these patients have (1) a combination of poor Trails B test score and APOE ε4 genotype (patients 88 and 343), (2) a combination of high cholesterol and APOE ε4 genotype (patient 109), (3) a combination of poor Trails B test score and earlier age of AD onset (patient 366), (4) a combination of earlier age AD onset and APOE ε4 genotype (patient 627), and (5) a combination of poor Trails B test score and earlier age of AD onset (patient 1397).

LIMITATIONS OF THE CURRENT ANALYSIS

There are also a few limitations of the current analysis. Some of the usual covariates that might be expected to influence AD disease progression were not significant in the current analysis. These covariates include gender, years of education, family history of dementia, and various metabolic parameters (blood pressure, fasting serum glucose, and body mass index). One of the possible reasons for this finding could be that the sample size for the current analysis is somewhat limited (n = 191). Because the ADNI trial is still ongoing, these effects could be reassessed when the full data set becomes available in the next few years. Another possible reason is that the magnitude of the covariate effect relative to the sample size could limit the ability to detect some covariate effects (eg, gender could influence baseline disease score, but the expected mean difference in baseline score by gender is about 2 points).[17] Detecting such a small difference in a study with a sample size of n = 191 with a rather variable end point such as ADAS-cog would be somewhat difficult. Last, certain covariates may have a limited or narrow distribution among the study participants, which could hamper the detection of covariate effects (eg, the ADNI AD population was rather well educated, and the maximum baseline diastolic blood pressure observed in the current study was 90 mm Hg). An additional limitation is that the model is built on a limited racial representation because of the characteristics of the data set. Finally, this model of cognitive decline is based on measuring cognition by ADAS-cog, a well-known scale with certain limitations for the early stages of the disease and for more severe AD patients.[26,27] Scales with a broader dynamic range than ADAS-cog may be more suitable for model building in the future.

We did not analyze comedication effects in the current analysis. AChEIs are the mainstay of pharmacologic

treatment for dementia. The prevalence of AChEI use was quite high in the ADNI AD patients, and almost the entire patient population (85% to 86%) reported the use of these medications.[36,37] Because there are too few patients not using AChEIs, the effect of these medications on disease progression could not be investigated in this analysis. Moreover, Ito et al[5] have recently investigated the AChEI effect, which was found to be symptomatic in nature and not disease modifying, where the rate of cognitive decline was parallel to that observed in untreated patients. Finally, the naturalistic nonrandomized nature of the ADNI study further prevents the study of comedication effects on AD progression. The average number (mean ± SD) of medications per ADNI participant was 8 ± 4.[36] There is rarely information available about the dosing time or schedule of administration of the comedications (comedications are checked as being present during regularly scheduled visits, but no information is collected to make sure that they were given continuously during the whole study). Furthermore, the number of patients on a specific medication is often low. Finally, the comedication information has been entered as a mixture of brand and generic names, which complicates the creation of the NONMEM database when some patients in ADNI have been on as many as 23 different comedications.[36] This would make the identification of individual medication effects on AD progression rather difficult.

CONCLUSION

In summary, the developed semi-mechanistic logistic model is suitable for describing the progression of disease in AD. Covariates that were found to influence baseline disease score were years since AD onset, baseline hippocampal volume, and baseline ventricular volume. Similarly, factors that influence disease progression rate are age at baseline, APOE ε4 carrier status, baseline serum cholesterol, current ADAS-cog score, and baseline Trail Making Test (part B) score. The model could represent a suitable tool for clinical trial simulations and could aid in the design of efficient clinical trials in the future.

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