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Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database

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Abstract

Background: A mathematical model was developed to describe the longitudinal response in Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) obtained from the Alzheimer's Disease Neuroimaging Initiative.

Methods: The model was fit to the longitudinal ADAS-cog scores from 817 patients. Risk factors (age, apolipoprotein ε4 [*APOE* ε4] genotype, gender, family history of AD, years of education) and baseline severity were tested as covariates.

Results: Rate of disease progression increased with baseline severity. Age, *APOE* ε4 genotype, and gender were identified as potential covariates influencing disease progression. The rate of disease progression in patients with mild to moderate AD was estimated as approximately 5.5 points/yr.

Conclusions: A disease progression model adequately described the natural decline of ADAS-cog observed in Alzheimer's Disease Neuroimaging Initiative. Baseline severity is an important covariate to predict a curvilinear rate of disease progression in normal elderly, mild cognitive impairment, and AD patients. Age, *APOE* ε4 genotype, and gender also influence the rate of disease progression.

Keywords: Disease progression model; Natural history; ADAS-cog; MCI; Alzheimer's disease; Age; *APOE* ε4 genotype

1. Introduction

Understanding the natural progression of Alzheimer's disease (AD) is critical for almost all avenues of research in the AD community. An understanding of how clinical outcomes change in relation to underlying biological changes that are reflected by changes in plasma and cerebrospinal fluid biomarkers and brain imaging is a fundamental requirement in moving toward qualified biomarkers of disease, much like how high-density lipoprotein and low-density lipoprotein have been accepted as surrogates for cardiovascular disease. It is also crucial to understand how rapidly the disease progresses so as to test and design new trials for drugs that may go beyond a simple symptomatic effect, such as disease modifiers that may be used to prevent development or slow progression of AD. Given the number of risk factors associated with AD and its progression, it is likely that these relationships will be complex, multivariate, nonlinear, and differ in their temporal relationship in many cases.

In a previous analysis, we developed a disease progression model to describe the longitudinal changes in Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) in patients with mild to moderate AD, using data from all available literature from 1990 to 2008 for acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, rivastigmine) [1]. In that analysis, the average rate of disease progression (α) was estimated as 5.5 points per year ($\pm$.229, standard error) for a patient population with mean baseline ADAS-cog score of 25. Baseline ADAS-cog score was found to be a significant covariate on the rate of disease progression. The results indicated that the milder the baseline cognitive impairment in

Alzheimer's Disease Neuroimaging Initiative: Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at www.loni.ucla.edu\ADNI\Collaboration\ADNI_Authorship_list.pdf).

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a population observed within a trial, the slower the disease progression, and that the more severe the cognitive impairment, the faster the deterioration. For example, if the baseline ADAS-cog was 10, 20, 30, 40 points, then the slope estimate from the model is 2.97, 4.73, 6.20, and 7.52 points per year, respectively. These findings are consistent with the current understanding of cognitive deterioration, as assessed by ADAS-cog, in that it is slow during the early stages of AD or in mild cognitive impairment (MCI), and more rapid during the middle stages. The analysis provided quantitative estimates of the mean yearly effect and the variability surrounding it. It also provided an overall summary of the treatment effect of AChE inhibitors across all studies in the published data.

However, there were limitations of this meta-analysis conducted on published study-level data. In the published data, typically only summary results are reported, (i.e., mean values and standard errors), and, therefore, the model was not able to detect the effect of potential factors influencing scores at an individual level such as age, apolipoprotein (*APOE*) ε4 genotype, gender, and duration of education. In contrast, clinical information from individual patients would be significantly more useful in analyzing the effect of these covariates on model parameters, such as rate of disease progression (slope).

In this analysis, we fitted a model to individual ADAS-cog scores obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (available at https://www.loni.ucla.edu/ADNI) to describe the typical disease progression. Furthermore, we evaluated potential covariates which may influence disease progression.

The goal of this analysis was to develop a mathematical model to describe the longitudinal changes in ADAS-cog (11-item) using individual data, to enable a quantitative understanding of the disease progression in AD with an estimate of between-patient variability, as well as the potential influence of important covariates which can be used for predicting the disease progression. These estimates (and the associated uncertainties in the estimates) can then be used as informative priors in aiding in the evaluation of various study designs, and in understanding the complex relationship between patient risk factors, biomarkers, imaging data, genotypes, and clinical endpoints, such as ADAS-cog. The characterization of such relationships is required to qualify biomarkers and imaging data as surrogates of clinical outcome, allowing for potentially more efficient clinical designs in the future.

2. Methods

2.1. Data

Data used in the preparation of this article were obtained from the ADNI database (available at www.loni.ucla.edu\ADNI). 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 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to characterize 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.

ADNI is the result of the efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, aged 55–90, to participate in the research; approximately 200 cognitively normal elderly (NL) individuals to be followed up for 3 years, 400 people with MCI to be followed up for 3 years, and 200 people with early AD to be followed up for 2 years. All subjects had clinical or cognitive assessments and 1.5 T structural magnetic resonance imaging at specified intervals for 2–3 years. AD subjects (n = 200) were studied at 0, 6, 12, and 24 months. MCI subjects at high risk for conversion to AD (n = 400) were studied at 0, 6, 12, 18, 24, and 36 months. Age-matched NL controls (n = 200) were studied at 0, 6, 12, 24, and 36 months. Detailed protocol information can be found at www.adni-info.org.

2.2. Model development

2.2.1. Base model structure

For a nonrandomized natural history nontreatment study, the natural disease progression in AD can be described as following [2]:

$$ADAS_{cog}(t) = ADAS_{cog,t=0} + \alpha\, t + \epsilon$$

where $ADAS_{cog}(t)$ is the ADAS-cog score at time t. $ADAS_{cog,t\,=\,0}$ is the baseline status, and α is the rate of progression of the untreated disease.

The linear relationship between baseline ADAS-cog and baseline MMSE over the entire range of ADAS-cog scores has been characterized previously [1,3,4]. In this analysis, therefore, baseline ADAS-cog ($ADAS_{cog,t\,=\,0}$) was described by a linear relationship with baseline Mini-Mental State Examination (MMSE):

$$ADAS_{cog,t=0} = Intercept + Slope * bMMSE$$

Random effects were included on the intercept (η_1) and slope (η_2) as additive error assumed to have a normal probability distribution with mean 0 and variance ω_1 and ω_2. Residual error (ϵ) was assumed to have a normal probability distribution with mean 0 and variance σ [2].

2.2.2. Covariate evaluation

Covariates of interest included in this analysis were age, *APOE* ε4 genotype, family history of AD, gender, years of

education, and baseline ADAS-cog. Baseline ADAS-cog was used as a marker of disease severity, which is hypothesized to influence the rate of disease progression (α).

Similar to the approach previously reported by Ito et al [1], continuous variables (age, education, baseline ADAS-cog) were normalized to a value representative of the population for that variable, that is, the approximate mean value of the dataset. They were incorporated into the model using a power function (power function model) described as following:

$$\alpha = \alpha_{pop} \cdot \left(\frac{AGE}{75}\right)^{\theta_{AGE}} \cdot \left(\frac{bADAS_{cog}}{20}\right)^{\theta_{ADAS}} \cdot \left(\frac{YEAR_{education}}{15}\right)^{\theta_{EDCT}}$$

where α_{pop} is the population estimate of rate of progression and θ_x are the power coefficients that are fitted. The power function allows for the relationship between the covariates and slope to take different nonlinear forms (for example, 0 being no relationship, and 1 approximating a linear relationship). Normalization to the mean of the dataset allows for a more numerically stable model.

For baseline severity, we tested an inverse-U type function (modified inverse-U function) in addition to the power function, to describe the nonlinear relationship between the rate of change (slope) and severity (baseline ADAS-cog score). This parameterization allows the model to go through zero at both ends, and it is divided by 1000 ($=20 \times 50$) so that α_{pop} can be interpreted as the population mean slope at a baseline ADAS-cog of 20:

$$\alpha = \alpha_{pop} \cdot \left(\frac{AGE}{75}\right)^{\theta_{AGE}} \cdot \left(\frac{bADAS_{cog}}{20} \cdot \frac{70 - bADAScog}{50}\right)^{\theta_{ADAS}} \cdot \left(\frac{YEAR_{education}}{15}\right)^{\theta_{EDCT}}$$

We also tried a model similar to that of Ashford and Schmitt [5], which allows a change in the shape of the U-curve by two power coefficient parameters. As mentioned earlier, the model is formulated so that α_{pop} can be interpreted as the population mean slope at a baseline ADAS-cog of 20:

$$\alpha = \alpha_{pop} \cdot \left(\frac{AGE}{75}\right)^{\theta_{AGE}} \cdot \left(\frac{bADAS_{cog}}{20}\right)^{\theta_{ADAS1}} \cdot \left(\frac{70 - bADAScog}{50}\right)^{\theta_{ADAS2}} \cdot \left(\frac{YEAR_{education}}{15}\right)^{\theta_{EDCT}}$$

Categorical variables (*APOE* ε4 genotype, family history of AD, gender) were modeled as dichotomous data as following.

$$\alpha = \alpha_{pop} \cdot \theta_i^{APOE4} \cdot \theta_{i+1}^{SEX} \cdot \theta_{i+2}^{FH}$$

where *APOE4*, *SEX*, and *FH* dichotomous variables take the value 0 or 1. *APOE* ε4 genotype was categorized into "non-carrier" (*APOE4* = 0) and "carrier" (*APOE4* = 1), where subjects having at least 1 *APOE* ε4 allele (ε4) were considered carriers (*APOE4* = 1). Gender was male (*SEX* = 1) or female (*SEX* = 0). Family history of AD was categorized as "Yes" (*FH* = 1) or "No" (*FH* = 0). The "No" (*FH* = 0) group is defined by neither mother nor father having a clinical diagnosis of AD. "NA" (not available) values for family history of AD were present in the dataset, and therefore the test for family history was completed with the subset with available data.

Model fitting was performed using a population analysis approach (NONMEM version VI, Level 1.2, ICON Development Solutions, Ellicott City, MA). Diagnostic graphics and postprocessing of NONMEM output and simulation were performed using S-Plus Professional Edition (version 7.0) for Windows XP (Insightful Corporation, Seattle, WA) and R (version 2.7.1).

2.2.3. Model selection criteria and performance evaluation

The model building strategy is based on modification of different approaches discussed by Beal et al [6], Mandema et al [7], Maitre et al [8], and Ette and Ludden [9]. Covariates were added one by one in a stepwise manner, examining the change in minimum objective function (MOF) values in hierarchical models, and also the precision of the parameter estimate.

During model building, the goodness of fit of different models to the data and hypotheses testing were evaluated using the following criteria: change in the MOF, visual inspection of different scatter plots including population and individual predicted versus observed value and conditional weighted residuals, precision of the parameter estimates, as well as decreases in both inter-individual variability and residual variability. These criteria were used only when the minimization step was successful and standard errors of parameter estimates were obtained using the covariance step. The difference in MOF values between 2 hierarchically nested models has an approximate χ^2 probability distribution with the number of degrees of freedom for the χ^2 distribution equal to difference in the number of parameters between the 2 models. Any decrease of >6.6 in the objective function during model building indicated that a proposed model with 1 additional parameter provided a better fit than the reduced reference model ($P < .01$). The covariate(s) of interest were kept in the model if the model was stable and its parameter estimate demonstrated acceptable precision, regardless of its statistical significance (using MOF as reference).

After the final model was identified, 100 datasets identical in structure and covariate values to the original dataset were simulated, using the parameter estimates and uncertainties from the final model to evaluate the model performance. The longitudinal ADAS-cog scores over time by population group (AD, MCI, NL) were generated with 90% and 95% prediction intervals simulated from the final model.

3. Results

3.1. Data characteristics

The dataset available as of December 10, 2009 contained 817 subjects consisting of 229 normal, 402 MCI, and 186 AD

Table 1
Demographic characteristics

	AD	MCI	NL
No. patients	186*	402	229
Age (yr)	75.3 ± 7.6	74.8 ± 7.4	75.9 ± 5.0
Female (%)	47.3	35.6	48.0
Baseline ADAS-cog	18.7 ± 6.3	11.5 ± 4.4	6.2 ± 2.9
Baseline MMSE	23.3 ± 2.0	27.0 ± 1.8	29.1 ± 1.0
Education (yr)	14.7 ± 3.2	15.7 ± 3.0	16.0 ± 2.9
APOE ε4 status			
ε4 non-carrier (%)	63 (33.9)	187 (46.5)	186 (73.4)
ε2, ε2 (%)	0	0	2 (.9)
ε2, ε3 (%)	5 (2.7)	17 (4.2)	31 (13.5)
ε3, ε3 (%)	58 (31.2)	170 (42.3)	135 (59.0)
ε4 carrier (%)	123 (66.1)	215 (53.5)	61 (26.6)
ε2, ε4 (%)	4 (2.1)	11 (2.7)	3 (1.3)
ε3, ε4 (%)	83 (44.6)	157 (39.1)	53 (23.1)
ε4, ε4 (%)	36 (19.4)	47 (11.7)	5 (2.2)
Race (%)			
American Indian or Alaskan Native	0	1 (.2)	0
Asian	2 (1.1)	9 (2.2)	3 (1.3)
Black or African American	8 (4.3)	15 (3.7)	16 (7.0)
White	174 (93.5)	376 (93.5)	210 (91.7)
More than one race	2 (1.1)	1 (.2)	0

*Mild = 171, moderate = 13, severe = 1, NA = 1.

patients (Table 1). Overall, the age distributions are similar among these populations. The proportion of females in the MCI group is slightly lower but similar between AD and normal, with the majority of subjects classified as white. The distribution of *APOE* ε4 (ε3ε4 and ε4ε4) carrier status was more frequent in patients with AD. As expected, baseline MMSE scores and baseline ADAS-cog are highly correlated.

Observed longitudinal ADAS-cog data are visualized in Fig. 1A (line: loess) and the linear relationship between baseline ADAS-cog and baseline MMSE is presented in Fig. 1B (line: linear regression). Because of the number of superimposed data points at the same time point, visit values (month) in Fig. 1A and actual score (MMSE) in Fig. 1B were slightly jittered in the figures to aid visual interpretation.

3.2. Final model compared with base model

As described in the Methods section, covariates of interest were tested in a forward stepwise manner. Baseline ADAS-cog, *APOE* ε4 genotype, and age were significant covariates affecting rate of disease progression. *APOE* ε4 effect was further evaluated by patient population to account for the unbalanced *APOE* ε4 carrier prevalence among NL, MCI, and AD patients. Gender was not statistically significant but showed some trend with reasonable precision (relative standard error [RSE] = 13.2%); therefore, it was also included in the final model. Year of education was neither statistically significant nor was its precision acceptable (RSE = 9.7%); it was not included in the final model. Family history of AD was excluded because it was not significant and did not show any trend toward significance with the limited data available.

The parameter estimates from the base model and the final model are summarized in Table 2. Overall, the final model parameters were well estimated with reasonable confidence intervals.

To ascertain the appropriateness of covariates included in the final model, plots of random effect (interindividual variability: IIV) estimates on slope (η_2) were generated by study population as well as by covariates of interest (*APOE* ε4 genotype, gender, baseline ADAS-cog) from the base and final model (Fig. 2). Trends in the distribution of random effects for the base model (no covariates in the base model) were observed. On inclusion of the covariates into the model, the trends observed by visual inspections in the distribution of random effects were removed, with the distribution dispersed around zero, confirming appropriateness of the final model. It

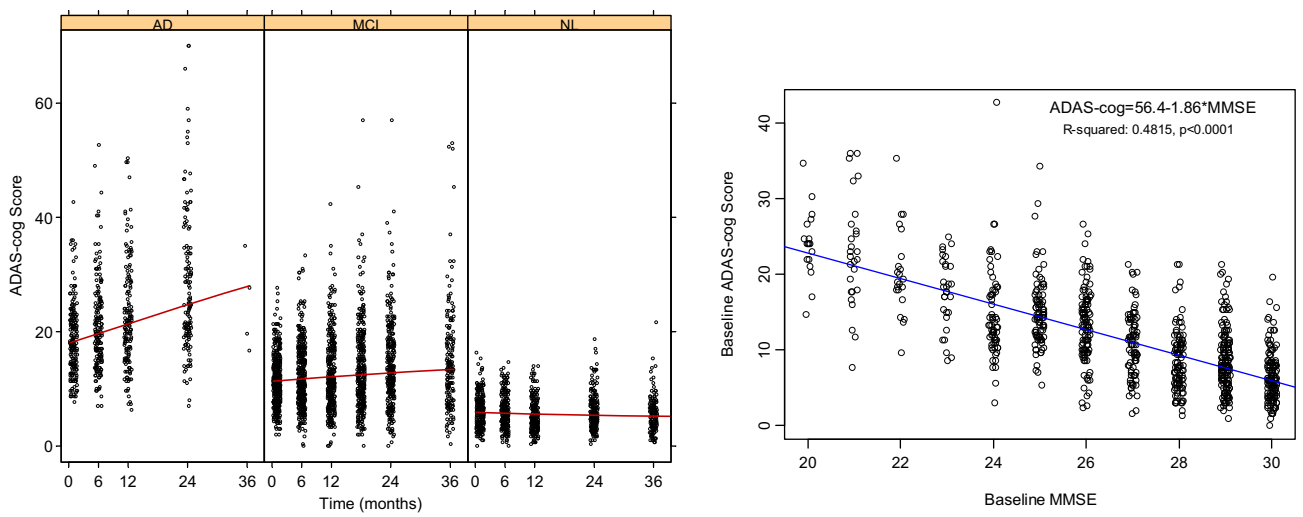

Fig. 1. Clinical data obtained from ADNI. (A) Longitudinal ADAS-cog by patient population, (B) Linear relationship between baseline ADAS-cog and baseline MMSE. Loess lines for (A) and linear regression line for (B).

Table 2
Model parameter estimates

	Base model		Final model		
Objective function	14,014.818		13,752.884		
Parameter	Estimate	RSE (%)	Estimate	RSE (%)	95% CI*
Disease progression (α) (point/yr)	1.87	7.86	4.83	11.9	(3.63, 6.00)
$ADAS_{t=0}$-intercept	52.9	3.82	56.4	2.98	(53.4, 59.9)
$ADAS_{t=0}$-slope	-1.53	4.76	–1.68	3.58	(–1.80, –1.58)
Covariate					
Baseline ADAS-cog	—‡	—‡	3.45	9.57	(2.82, 4.07)
Age	—‡	—‡	–1.80	35.2	(–3.24, –.593)
APOE ε4 effect (MCI)†	—‡	—‡	1.21	21.9	(.823, 2.24)
APOE ε4 effect (AD)†	—‡	—‡	1.22	23.0	(.775, 2.03)
Sex (male)	—‡	—‡	.893	13.2	(.684, 1.11)
Random effect					
sqrt of η_1 on $ADAS_{t=0}$	3.81	9.93	3.78	10.0	(3.42, 4.16)
sqrt of η_2 on α (point/yr)	3.12	15.7	2.47	18.4	(2.04, 2.90)
Covariance of random effect	.465	17.6	–.099	58.7	(–.20, .0056)
Residual error					
Standard deviation (SD)	2.81	2.29	2.83	2.33	(2.72, 2.96)

*95% CI are obtained from non-parametric bootstrap (n = 500).
†Estimated within the patient population.
‡Not estimated (covariates are not included in the base model).

should be emphasized that the random effect by patient population showed a clear trend in the base model (Fig. 2, top-left panel), suggesting unexplained variability for the patient population with the base model; that is, the random effect was shifted higher in the AD population because the base model attempted to capture the higher slope estimate with AD population by adjusting the random effect term for AD patients. However, these trends were corrected (Fig. 2,

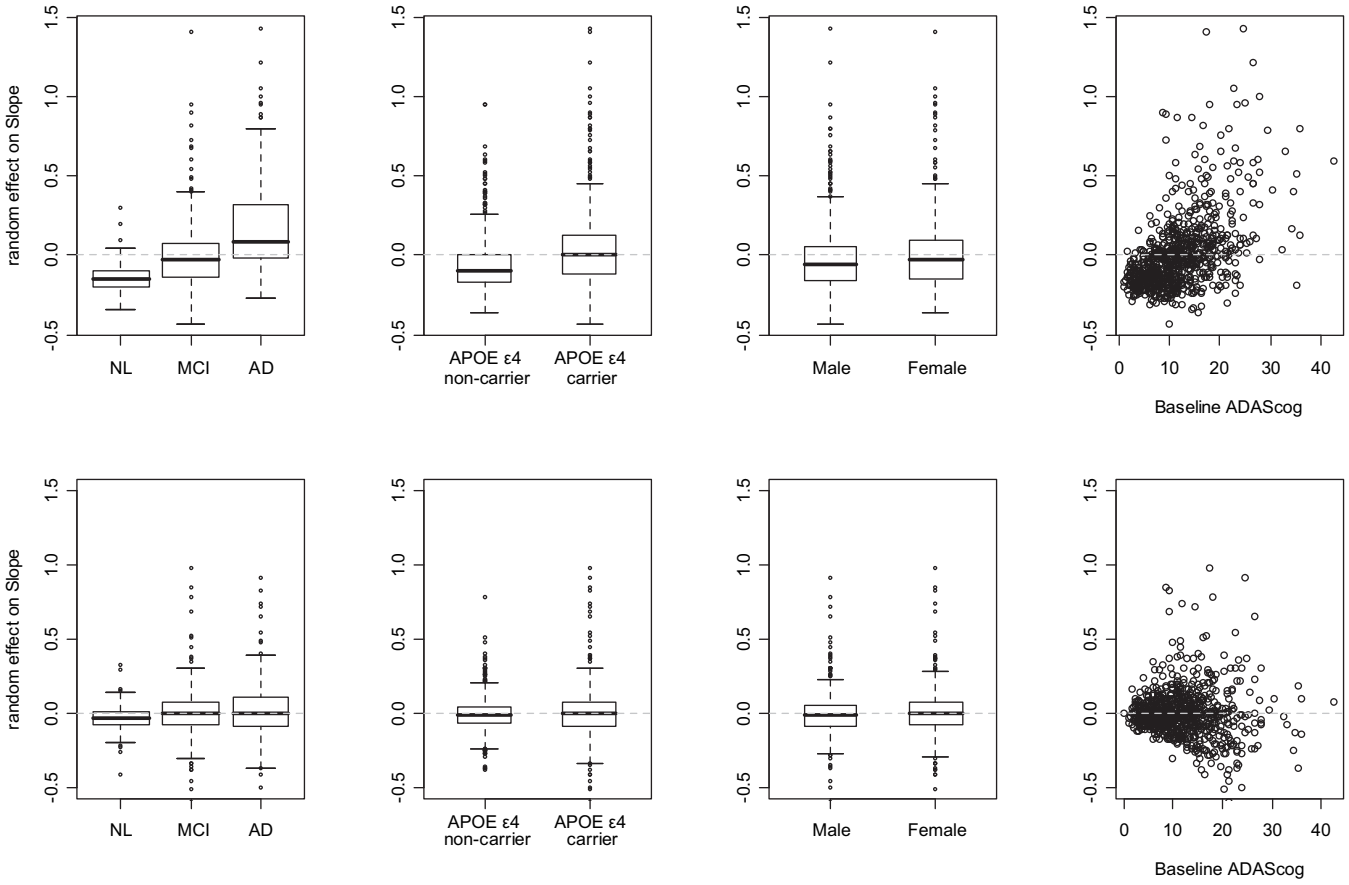

Fig. 2. Random effect (interindividual variability) on slope (base model vs final model).

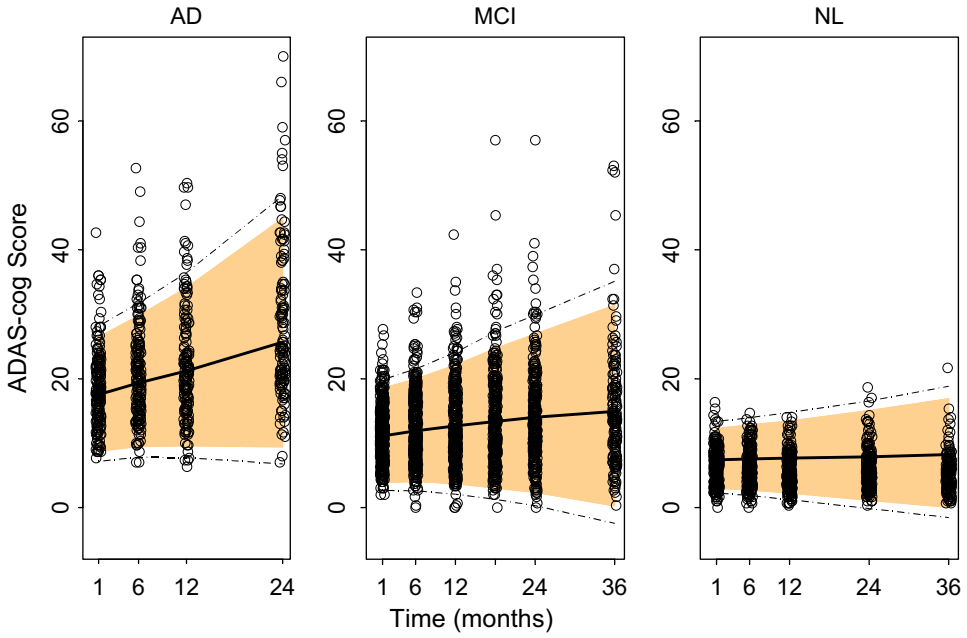

Fig. 3. Final model visual predictive check from 100 simulations with 90% and 95% predicted interval (shaded area and dashed lines).

bottom-left panel) after including these covariates, indicating that *APOE* ε4 genotype, gender, and baseline ADAS-cog account for some of the interindividual variability in the slope.

The predictive performance of the final model was assessed by evaluating whether the distribution of the observed data was contained within the empirical distribution of the estimates predicted by the final model over a number of simulations. For this evaluation, 100 data sets were simulated from the final model (and its uncertainty in parameter estimates) using the original dataset. Figure 3 shows the time-course of ADAS-cog, with both the 90% and 95% prediction intervals (shaded area and dashed-line, respectively) for each population. These results indicate that the final model prediction is reasonable for both the point estimates as well as the distributions.

Table 3
Slope estimate by baseline ADAS-cog and age (*APOE* ε4 negative)

Baseline $ADAS_{cog}$	Baseline MMSE*	Age	Slope estimate (95% CI) (point/yr)
5	30	75	.10 (–1.02, 1.22)
10	>27	75	.83 (–.29, 1.95)
15	25	75	2.49 (1.36, 3.61)
20	22	75	4.83 (3.71, 5.95)
25	19	75	7.25 (6.13, 8.37)
30	16	75	9.06 (7.94, 10.2)
35	13	75	9.73 (8.60, 10.9)
40	<10	75	9.06 (7.94, 10.2)
20	22	65	6.25 (5.13, 7.37)
20	22	70	5.47 (4.35, 6.59)
20	22	75	4.83 (3.71, 5.95)
20	22	80	4.30 (3.18, 5.42)
20	22	85	3.86 (2.73, 4.98)

*Baseline MMSE was approximately calculated based on the linear regression relationship with baseline ADAS-cog.

The underlying disease progression slope (α) from the model for ADAS-cog was estimated to be 4.83 points per year in female, *APOE* ε4 non-carrier patients whose baseline ADAS-cog was 20 (considered as mild AD patients). Baseline ADAS-cog was negatively related to baseline MMSE (Fig. 1B), and the parameter estimate for the slope was –1.68 ($R^2 = .48$, $P < .0001$). Covariates included in the final model were baseline ADAS-cog, age, *APOE* ε4 status, and gender. Years of education and family history of AD were not significant and did not show any trend. It is noted that the information for family history of AD was only available with 682 of the total 817 subjects. The use of AChE inhibitor as background therapy was also investigated; however, it did not show any difference at baseline. The effect of AChE inhibitors could not be evaluated with the longitudinal data because of the nature of the ADNI study (nonrandomized natural history, nontreatment study).

Baseline severity of disease, as assessed by the ADAS-cog score, was found to have a significant effect on slope (α) with both the power model and the modified inverse-U model, with no statistical superiority demonstrated between the two models. The modified Ashford model was unstable and the estimation algorithm did not converge. This is likely due to insufficient data in patients with severe AD to describe the upper end of the curve. Although both the power model and modified inverse-U models are able to describe the data obtained from ADNI, the change in slope should theoretically go through zero at both ends; therefore, the inverse-U model was selected in the final model. In clinical terms, the rate of disease progression is, in part, a function of the baseline severity of the cognitive deficits, with more moderately affected populations demonstrating more rapid deterioration in cognitive function compared with more mildly affected

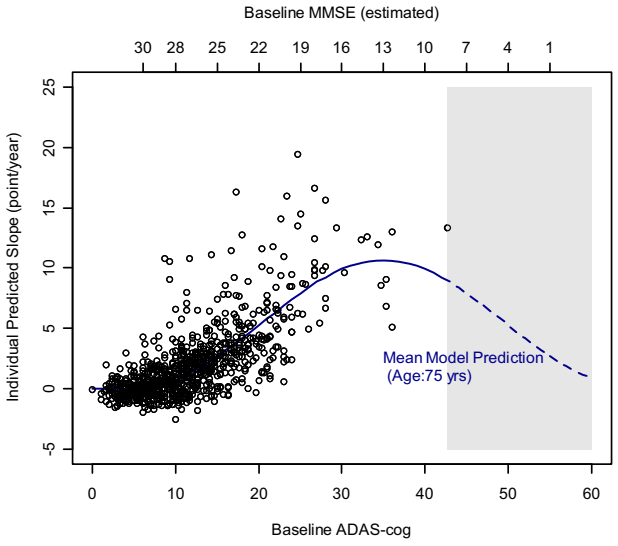

Fig. 4. Individual slope estimate versus baseline ADAS-cog. Gray-shaded area: no data available.

populations on the ADAS-cog (within the range of values available in the dataset). Slope estimates by baseline severity (different baseline ADAS-cog) are summarized in Table 3. The plot shown in Fig. 4 is the model-predicted individual slope (open circle) and mean predicted slope (solid line) from the model versus baseline ADAS-cog, demonstrating that the model is able to predict the curvilinear relationship between disease progression and baseline severity. Note that the gray area in the plot indicates the data are not available in ADNI, and the dotted line is the prediction from the modified inverse-U function.

APOE ε4 effect was a significant covariate when it was included in the model. Because of the different *APOE* ε4 carrier prevalence among patient populations, the parameters were estimated within each individual patient population (estimates of 1.22 and 1.21 for MCI and AD patients, respectively), suggesting that *APOE* ε4 carriers have approximately 22% increase in yearly disease progression compared with non-carrier patients. The parameter could not be estimated for normal elderly (NL) patients, likely due to very small changes in cognition (slope close to zero) for the rate of disease progression in NL patients. Gender effect was estimated as .893 (95% CI: .684–1.11), representing a 10.7% slower decrease in yearly progression in males relative to females.

Year of education was not a significant covariate in this analysis set. The parameter was not well estimated, demonstrated large RSE 90.7% and wide 95% CIs (–.27 to –1.32) from the nonparametric bootstrap, suggesting it may not appropriate to estimate or discuss the effect of education with the data available at this point.

4. Discussion

Two of the stated major goals for the ADNI trial were (1) to acquire a generally accessible data repository that describes longitudinal changes in brain structure and metabolism and in parallel, acquires clinical cognitive and biomarker data for validation of imaging surrogates, and (2) develop methods that will provide maximum power to determine treatment effects in trials involving these patients. The underling progression of disease in AD is a complicated process, and with time, imaging or biomarkers (dependent on stage of disease) will likely become better at quantifying the pathological or physiological disease progression process. Providing a correlation of these markers to clinical outcomes such as cognitive change will be crucial to having the markers become validated for clinical use. It is likely that both the imaging endpoints as well as the clinical outcomes will be nonlinear and differ in the temporal order in which they change. Jack et al [10] propose a framework in which they relate disease stage to AD biomarkers, where Aβ biomarkers become abnormal first before neurodegenerative biomarkers and cognitive symptoms, and neurodegenerative biomarkers become abnormal later and correlate with clinical symptom severity.

To link the components of this framework, it will be important to understand the relationship between cognitive changes over time (the clinical outcome) and the changes in markers of underlying disease, through the use of disease progression models.

The work here represents an initial model-based attempt to relate these different factors to understand the natural decline of cognitive function. Such a model provides a common quantitative basis for further evaluation of study design and analysis methodologies for clinical studies in the mild to moderate AD population and MCI. These findings can be applied to all stages of drug development; proof of concept, dose-ranging, and confirmatory trial designs. Trial simulation based on quantitative models can support the use of new and innovative trial designs and endpoints across the Alzheimer's community.

Various disease progression models for AD have been published in the past [2,11–13], and the methods for building and testing these models have been well described [14]. Although the general model building principles and model structure provided similar results and interpretations, the studies on which these initial models were based were of short duration or did not contain more recent key data, such as imaging, proteomic, and genetic biomarkers, now shown to be important covariates in understanding the rate of conversion to AD and the rate of decline in AD patients.

We previously reported a meta-analyses using all available literature data from 1990 to 2008 that estimated the natural history of AD and provided estimates of treatment effects for currently available AChE inhibitor therapies [1]. However, because of the nature of the literature data in that it is only study-level summary data, the model has limited ability to evaluate important individual covariates, such as age and *APOE* ε4 genotype. The meta-analysis model from the literature using study-level data also does not provide inter-subject variability information. Therefore, we applied a similar modeling approach to the ADNI database, which contains a wealth of longitudinal natural history data from more than

800 subjects including individual demographics, and a wide range of patient populations including normal elderly and MCI patients, as well as imaging, proteomic, and genetic biomarkers. As such, the true natural history of changes in cognition (as measured by ADAS-cog) up to mild to moderate AD can be estimated.

There are two core elements in the model structure, one predicts baseline ADAS-cog ($ADAScog_{,\,t\,=\,0}$) and the other estimates the natural disease progression (slope: α). Because a linear relationship between baseline ADAS-cog and baseline MMSE was observed, a linear relationship between ADAS-cog and MMSE was incorporated into the baseline ADAS-cog ($ADAScog_{,\,t\,=\,0}$) model. We also attempted nonlinear relationships (power function normalized by population mean of baseline MMSE score), but the linear model provided a statistically better fit than the power function model within the range of data available. The estimate of intercept and slope are 56.4 and –1.68, respectively, similar to the estimates previously reported by Ito et al (60.9 and –1.85 for intercept and slope, respectively, from literature meta-analyses [1]). Doraiswamy et al and Caro et al also reported a linear relationship between baseline ADAS-cog and baseline MMSE using patient data (ADAS-cog = 72.2–2.41 × MMSE [3] and ADAS-cog = 70–2.33 × MMSE [4]).

Baseline ADAS-cog was a significant covariate for disease progression (α) in our previous analysis [1]. Atchison et al also reported that baseline cognitive function predicted the rate of decline in basic-care abilities with AD patients [15]. We evaluated baseline ADAS-cog as a covariate in this analysis, and found it to be a significant factor for disease progression. This is in keeping with the findings of other investigators who have demonstrated the influential effect of cognitive performance on rates of change in the ADAS-cog [3,16]. The importance of baseline ADAS-cog may in part explain some difference observed between various authors in estimates of yearly progression, and in understanding whether disease progression has changed over the years.

Baseline ADAS-cog was considered an indicator of baseline severity for this analysis, and disease progression (slope) was found to be highly dependent on baseline disease severity. The high correlation amongst patient populations (NL, MCI, AD) and baseline ADAS-cog can be observed in Fig. 1A. In the base model which did not include baseline ADAS-cog on slope (α), the distribution of random effect (IIV) was unbalanced (Fig. 2, top-left and top-right panels); however, the trends disappeared with inclusion of baseline ADAS-cog in the final model (Fig. 2, bottom-left and bottom-right panels). It is noted that patient population (NL, MCI, AD) is not included as a covariate in the model, indicating that baseline ADAS-cog alone is a good predictor of the severity. Because MMSE is used as a standard tool to diagnose patients with AD and for inclusion in trials, we also tested baseline MMSE (test model) instead of baseline ADAS-cog (final model) on the slope estimate. However, goodness of fit, as measured by the MOF, increased 51 points in the test model, indicating that the model fit is worse when using baseline MMSE as a covariate on slope compared with the final model which used baseline ADAS-cog. The reason for this is unclear, but MMSE itself may not be sufficiently sensitive to differentiate disease severity as the disease progresses over time because of the limited range of MMSE values relative to ADAS-cog.

Baseline ADAS-cog also plays an important role in the model to capture the curvilinear relationship of the disease progression (Table 3, Fig. 4). For simplicity, the assumption that disease progression is linear within the study duration of 6–12 months for individual patients appears likely sufficient. However, the mean model prediction describes the curvilinear relationship between disease progression and baseline severity over a longer period, because the slope estimates are dependent on the baseline ADAS-cog through a modified inverse-U function which goes through zero at both ends. This is consistent with a general understanding of disease progression in AD and the different stages of progression of dementia; that is, an early stage in which it may be difficult to diagnose the normal aging process from MCI, followed by mild to moderate AD where the rate of deterioration gradually increases. ADAS-cog scores range from 0 to 70; and scores theoretically plateau as deterioration progresses. However, in severe AD, using cognitive measurements such as ADAS-cog becomes difficult, and other clinical endpoints, such as Severe Impairment Battery, are used. It is also noted that the patients in the ADNI database are not severe enough to observe this plateau phase.

Ashford and Schmitt [5] reported another mathematical approach to describe the rate of disease progression using ''time-index'' intervals, which captures these different stages. We also attempted to apply a similar model to that of Ashford and Schmitt [5], which is theoretically preferable, as it allows more flexibility in the shape of the curve. However, the estimation results showed several signs of model instability or overparameterization. This is probably because of the range of data available within ADNI; we do not have enough information for the later stage of AD to characterize the parts of the curve in more severe disease where change starts to diminish using ADAS-cog.

There are also limitations to using ADAS-cog to adequately predict the severity of disease for early stages of cognitive impairment or patients with severe AD because of the well-known ceiling and floor effects of the ADAS-cog. Grundman et al [17] also reported that the percentage of word list items contributing to the ADAS-cog score is high in the control group (normal) and MCI group (84% and 81%, respectively) compared with AD groups (CDR: .5, group: 68%; CDR: 1.0, group: 58%), although MCI had higher ADAS-cog total scores than control group (MCI: 11.3 ± 4.4, control: 5.6 ± 3.3 expressed mean ± SD). MCI patients had primarily prominent memory impairment, but were also very mildly impaired on other cognitive domains, and these characteristics were not well captured by using only ADAS-cog. Consistent with previous reports [18–20], *APOE* ε4 carriers demonstrated more rapid decline in

cognitive function. On average, approximately 22% increases in yearly deterioration for AD and MCI patients with *APOE* ε4 carriers were predicted from the final model. It is noted that the *APOE* ε4 effect on disease progression is detected with MCI and AD patients, and little or no effect of genotype observed in NL patients. These results are consistent with the more rapid conversion from MCI to AD in *APOE* ε4 carriers observed in clinical trials.

Aging is considered an important risk factor for dementia, and baseline age was tested and shown to be an important determinant of the rate of cognitive decline. The power coefficient of age effect was estimated to be –1.8, indicating that younger subjects have a more rapid decline in cognitive function than older subjects, holding all other factors constant (Table 2). For example, for patients with baseline ADAS-cog score of 20 (mild to moderate AD patients) in 65- and 85-year-olds, the estimated cognitive decline in ADAS-cog scores are 6.25 and 3.86 per/yr, respectively (Table 2). This indicates that the cognitive decline may progress faster with patients who develop dementia in their earlier than those who develop it a later age. It is important to note that this analysis tests the effect of age on cognitive decline using ADAS-cog, and is not intended to predict the probability to develop dementia. Several authors have reported age as a risk factor of incidence of dementia [19–23], and one author reported that age is not a significant factor in predicting progression to AD [24].

A gender effect was also identified in this analysis, with male patients having a 10.7 % slower rate of progression on average compared with female patients. The 95% CI estimates included null values for the gender effect (.684–1.11), indicating that gender may not be a strong predictor for disease progression, or that the data in this analysis were insufficient to obtain a definitive relationship. Like the age risk factor, gender effects are discussed in many articles [20–22,25] and the results are controversial. These different results may be in part due to different distributions of the population, different analysis methods, or insufficient data to detect the signal. The covariate effect will be re-evaluated when all data are available from the ADNI study.

Education effect in this analysis was not significant, with the 95% confidence intervals being large and including the null value. Epidemiologic analysis and several clinical trials have shown that education is a significant risk factor to acquire dementia and there is a significant protective effect of education [20,23,26], whereas others have reported it is not significant [19,22,24,27]. Therefore, the effect of education needs to be re-evaluated when all data are available.

The mean rate of disease progression for mild to moderate AD patients (baseline MMSE 16–26) was estimated as 5.22 points per year for 75-year-old, female, *APOE* ε4 non-carrier patients. If the patient is male, the slope estimate was 4.52 points per year (10.7% decrease), and if *APOE* ε4 carrier, a 22% increase (6.37 and 5.52 points per year for female and male, respectively). To estimate the disease progression for mild to moderate AD patients, the slope was estimated from the model for baseline MMSE score from 16 to 26 and then averaged. The overall mean rate of disease progression was also estimated for 75-year-old mild to moderate AD patients as 5.5 points per year by using the prevalence of *APOE* genotype and gender in ADNI AD patients (female *APOE* ε4 non-carrier: 18.6%, male *APOE* ε4 non-carrier: 15.4%, female *APOE* ε4 carrier: 28.7%, male *APOE* ε4 carrier: 37.2%). The estimates obtained are consistent with the previously reported results using literature data analysis [1]. The benefit with the individual data analysis is that the effect of covariate effects, such as age, *APOE* ε4 genotype, and gender, could be estimated, as discussed earlier, which was not possible in the literature data analysis [1]. Inter-subject variability was also estimated in this analysis, which allows us to calculate power, efficiency, and ruggedness of different study designs, and to simulate individual responses in future clinical trials.

There are limitations in the interpretation of this analysis that should be considered. First, the floor and ceiling effects with ADAS-cog score and use of a linear function over time to describe the natural decline of cognitive function may not be appropriate for longer duration data. The ADNI study does not include patients with severe AD where ceiling effects may appear, and the model may not predict well for those patients. This is likely to be a concern, as ADAS-cog is not used as a primary endpoint in clinical trials of severe AD patients; rather, other endpoints such as the Severe Impairment Battery and Modified Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe AD are used. Second, the correlation between the risk factors identified is still unknown and potential interaction between covariates and/or among patient populations needs to be investigated. Third, we did not include a placebo effect in the model because of the nature of ADNI study. Placebo effects are often seen in AD clinical trials. The ''placebo effect'' component was incorporated in our previous analysis [1] to describe the nonlinear relationship observed over the first 3–6 months. This is important for estimating disease progression from blinded trials, especially if trial simulation is planned for a shorter period study, such as proof-of-concept studies. Finally, dropout is an important factor in real clinical trials and is not currently accounted for in this longitudinal data modeling.

Despite these limitations, the model provides a quantitative understanding of disease progression; that is, the natural decline of cognitive function. It also describes the relationship between covariates and risk factors and clinical outcome. As such, it can be used to simulate disease progression in different populations and to test study designs and scenarios. Ultimately, the understanding of the relationship between biomarkers and imaging data may allow these types of endpoints to be used as surrogates of clinical outcomes, enabling more efficient clinical trial designs for AD.

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