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ORIGINAL PAPER

Modeling of Functional Assessment Questionnaire (FAQ) as continuous bounded data from the ADNI database

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Abstract An assessment of abilities to function independently in daily life is an important clinical endpoint for all Alzheimer's disease (AD) patients and caregivers. A mathematical model was developed to describe the natural history of change of the Functional Assessment Questionnaire (FAQ) from data obtained in normal elderly, mild cognitive impairment, and mild AD in the AD neuroimaging initiative (ADNI) study. FAQ is a bounded outcome (ranging from 0 to 30), with 0 scored as "no impairment" and 30 as "severely impaired". Since many normal elderly patients had 0 scores and some AD patients had scores of 30 in the ADNI database, a censored approach for handling the boundary data was compared with a standard approach, which ignores the bounded nature of the data. Baseline severity, ApoE4 genotype, age, sex, and imaging biomarkers were tested as covariates. The censored approach greatly improved the predictability of the disease progression in FAQ scores. The basic method for handling boundary data used in this analysis is also applicable to handle boundary observations for numerous other endpoints.

Keywords Bounded outcome data · Disease progression · Alzheimer's disease · ADNI

Introduction

Recent advances in the understanding of the underlying pathophysiology of Alzheimer's disease (AD) have led to clinical testing of numerous new treatment modalities aimed at altering the disease early in its clinical progression, or in some cases, even before the disease manifests clinical symptoms. For trials involving these agents, understanding the natural progression of AD from normal elderly into mild cognitive impairment and into mild AD is critical for almost all avenues of research. Bias in the estimate of the disease progression rate, failure to identify the factors that impact this rate, or the variability in the endpoint itself may all lead to trial failure due to insufficient power, insufficient duration to detect effect, or selection of an insensitive or heterogeneous patient population.

The concept of developing models to describe the progression of disease is not new [1]. In the 1990s Holford et al. [2–4] first reported a disease progression model to describe longitudinal changes in AD Assessment Scale-cognitive (ADAS-cog) data over time in mild to moderate AD patients. Ito et al. [5] applied a similar disease progression model to ADAS-cog data obtained from the literature between 1990 and 2008. Several other disease progression models for ADAS-cog have also been published [6–9] using individual patient level data, enabled

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). 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. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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evaluation of the between subject variability and to test covariates (such as age, gender, ApoE4 genotype) which may be related to disease progression.

Although modeling disease progression for ADAS-cog scores have been intensively studied given its role as a primary endpoint for almost all mild to moderate AD clinical trials, no disease progression modeling to describe functional endpoints has been published (note: Brogren [10] reported the power to detect a hypothetical treatment effect when combining ADAS-cog and FAQ based on simulated values from a linear disease progression model, although the primary objective of the analysis was not to describe FAQ scores). However, functional endpoints are often a co-primary endpoint in many clinical studies. Patient function, behavioral changes and inability to perform daily functional tasks are directly related to caregiver burden, and as such provide a much more meaningful construct to caregivers, practitioners, and payers. Function measurement is also known as activities of daily living (ADL). It usually contains two components; "basic-ADLs" such as bathing, dressing and toileting for basic self-maintenance skills, and "instrumental-ADLs" involving more complex activities, such as preparing a meal, handling finances and shopping. The inability to perform these tasks due to progression of the disease is often the factor that forces caregivers to seek long-term care for patients. Therefore, it is important to develop a quantitative understanding of disease progression from a functional perspective with a functional endpoint suitable for use in populations most likely to be studied, including those who are in earlier stages of the disease, prior to a formal diagnosis of AD. The ADNI study includes those patient populations, i.e., mild cognitive impairment (MCI) and mild AD patients, and a suitable functional instrument for these populations, the Functional Assessment Questionnaire (FAQ), which consists of "instrumental-ADL" questionnaires, that has also been validated in the normal elderly community [11].

The FAQ consists of 10 questionnaires to ascertain the level of performance of daily function activities including: (a) writing checks, paying bills, or balancing a checkbook; (b) assembling tax records, business affairs, or other papers; (c) shopping alone for clothes, household necessities, or groceries; (d) playing a game of skill such as bridge or chess or working on a hobby; (e) heating water, making a cup of coffee, turning off the stove; (f) preparing a balanced meal; (g) keeping track of current events; (h) paying attention to and understanding a TV program, book, or magazine; (i) remembering appointments, family occasions, holidays, medications; (j) traveling out of the neighborhood, driving, or arranging to take public transportation. The four levels ranging from dependence to independence have scores as follows: dependent = 3, requires assistance = 2, has difficulty but does by self = 1, normal = 0. "Never did, but could do now" is assigned a value of 0 and "never did and would have difficulty now", a value of 1. The FAQ score is the sum of the individual activity scores and thus ranges from 0 to 30 inclusive; the data are bounded by 0 and 30 and are considered continuous.

In this analysis, a mathematical model was applied to the FAQ scores in normal elderly (NL), mild cognitive impairment (MCI), and mild AD patients from the AD Neuroimaging Initiative (ADNI) database. The goal of developing this model is to create a tool suitable for trial simulation activities for the FAQ endpoint. As such, it is important that the data simulated reflect the natural distribution of the endpoint, i.e. be bounded between scores of 0–30. The lower and upper boundaries also yield non-normal and atypical data distributions. Lack of normality induced by these boundary constraints could adversely affect fitting, estimation, and model testing, and may result in poor predictions for clinical trial simulations for scores near the boundaries from individuals (0 for normal elderly individuals, for example). Therefore, a method for dealing with these complex types of distributions is applied and compared with a standard approach. In addition, important covariates which may affect the disease progression were also evaluated as a secondary objective in this analysis.

Methods

Population and design

Data used in the preparation of this article were obtained from the ADNI (www.loni.ucla.edu\ADNI). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit 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 mild cognitive impairment (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. Funding for the original ADNI (now called ADNI1) ended October 2010. The ADNI-GO grant will extend the follow-up of subjects who were enrolled in ADNI1 to allow analysis of all of the ADNI data that was not able to be done in the initial grant.

ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the US and Canada. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California—San Francisco. The initial goal of ADNI was to recruit 800 adults, aged 55–90, to participate in the research with approximately 200 cognitively 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.

The dataset contained 817 subjects consisting of 229 normal, 402 MCI and 186 AD 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 the AD and NL groups, with the majority of subjects being White. The distribution of ApoE4 carrier status was more frequent in AD patients.

FAQ scores

The FAQ was administered at baseline and at every subsequent in-clinic visit (every 6 months up to 24 months for AD patients and up to 36 months for NL and MCI patients) during the ADNI study. All data points available for FAQ from all patients in the ADNI database were included in the analysis.

Model building and selection criteria

Base model structure

The underlying concepts for the disease progression model used to describe FAQ scores were similar to those already reported by Holford et al. [2–4] and Ito et al. [5, 6]. for ADAS-cog. A nonlinear mixed-effect likelihood-based approach was used in this analysis. For a non-randomized natural history, non- intervention study of a limited duration, the natural disease progression for FAQ scores can be described as below:

$$FAQ(t) = FAQ_{t=0} + \alpha \cdot t + \varepsilon \quad (1)$$

where $FAQ(t)$ is the FAQ score at time t. $FAQ_{t=0}$ is a parameter predicting the baseline status (=intercept), and α is the rate of progression of the untreated disease.

The question of whether to implement the model with linear or non-linear changes in FAQ over time is complex. One could assume that the disease progression is nonlinear and try to develop a model in which the slope changes over time [12]. However, the current data available from the ADNI database represent only 2–3 years of duration for each patient, whereas the symptoms of AD progress slowly and over a much longer period of time, especially at the early stages of AD. For example, about 10–20 % of people aged 65 and older have MCI, and it is estimated as many as 15 percent of these individuals progress from MCI to dementia each year [13]. From this, about half of all people who have visited a physician with MCI symptoms will develop dementia in three or four years [13]. Duration of illness from diagnosis of AD to death varies, but studies indicate that people aged 65 and older survive an average of 4–8 years after a diagnosis of AD, with some as long as 20 years [13]. These observations are consistent with the simulation work done in cognition, where even when a nonlinear approach is implemented, the disease progression over 2-year period in mild AD patients appear linear [8]. Therefore, a linear approximation with the current available ADNI database is considered reasonable given the 2–3 year duration of data available. A non-linear model approach could be the objective of future research when sufficient longitudinal information in moderate and severe

Table 1 Demographic characteristic from ADNI database

	AD	MCI	NL
No of patients	186	402	229
Age (yr)	75.3 ± 7.6	74.8 ± 7.4	75.9 ± 5.0
Sex female (%)	88 (47.3)	143 (35.6)	110 (48.0)
Baseline FAQ	13.2 ± 6.9	3.9 ± 4.5	0.1 ± 0.6
Baseline MMSE	23.3 ± 2.0	27.0 ± 1.8	29.1 ± 1.0
Baseline CDR-sb	4.3 ± 1.6	1.6 ± 0.9	0.0 ± 0.1
ApoE4 carrier (%)	123 (66.1)	215 (53.5)	61 (26.6)
Race (%)			
American Indian or Alaskan Native	0	1 (0.25)	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 (0.25)	0

Summarized as mean ± standard deviation (SD) for continuous data and count and percentage (%) for categorical data

AD become available to capture the entire time course of disease progression in later stages of AD.

Subject-specific random effects (between subject variability: BSV) were included on the intercept $FAQ_{t=0}$ (η_1) and slope α (η_2) where different estimates of the variance were expected for each patient population (NL, MCI, AD) since NL patients tend to have 0 or lower scores and AD patients have higher scores and more variability (see Fig. 1). Random effects on the intercept $FAQ_{t=0}$ (η_1) were modeled as exponential for a standard approach, since FAQ scores are always positive ($\geq$0); on the other hand, it was modeled as additive for a censored approach since the scores become -∞ to ∞ after the transformation (see Sect. "Censored approach"). Random effects on the slope α (η_2) was model as additive for both approaches, because the disease progression could be either positive (worse) or negative (improve). Random Effects were assumed to have a normal probability distribution with mean 0 and covariance matrix Ω. Residual error (ε) was assumed to have a normal probability distribution with mean 0 and variance σ^2. The observed data indicates that variability of FAQ scores increased at each visit (for example, standard errors estimates were 4.5, 5.3, 6.0, 7.5, 8.6 at 0, 6, 12, 24, 36 months in MCI group) and the residual variability was assumed to increase over time along with the disease progression, a component allowing the magnitude of the variability to increase over time was also tested in the model.

Covariate model

Based on previous knowledge and findings [5–9], covariates of interest included in this analysis were baseline disease severity, disease state, age, ApoE4 genotype, sex, and selected imaging biomarkers, such as hippocampal volume, ventricular volume, and brain volume. Some covariates, such as cerebrospinal fluid (CSF) biomarkers, were not tested in the model as data was missing for nearly half of the patients in the dataset for these covariates. Details for each covariate tested in the model are described below.

Baseline severity From the previously published analysis [5–9], disease severity at baseline is expected to have a significant influence on both intercept and the rate of disease progression (α). Therefore, several clinical end points capturing disease severity were evaluated, including mini mental state examination (MMSE), clinical dementia rating—sum of the boxes (CDR-sb), and a composite of baseline MMSE and FAQ, to find a measure which best predicts the disease progression manifested in the FAQ scores. MMSE is a questionnaire based measurement to screen for cognitive impairment, and typically used in AD

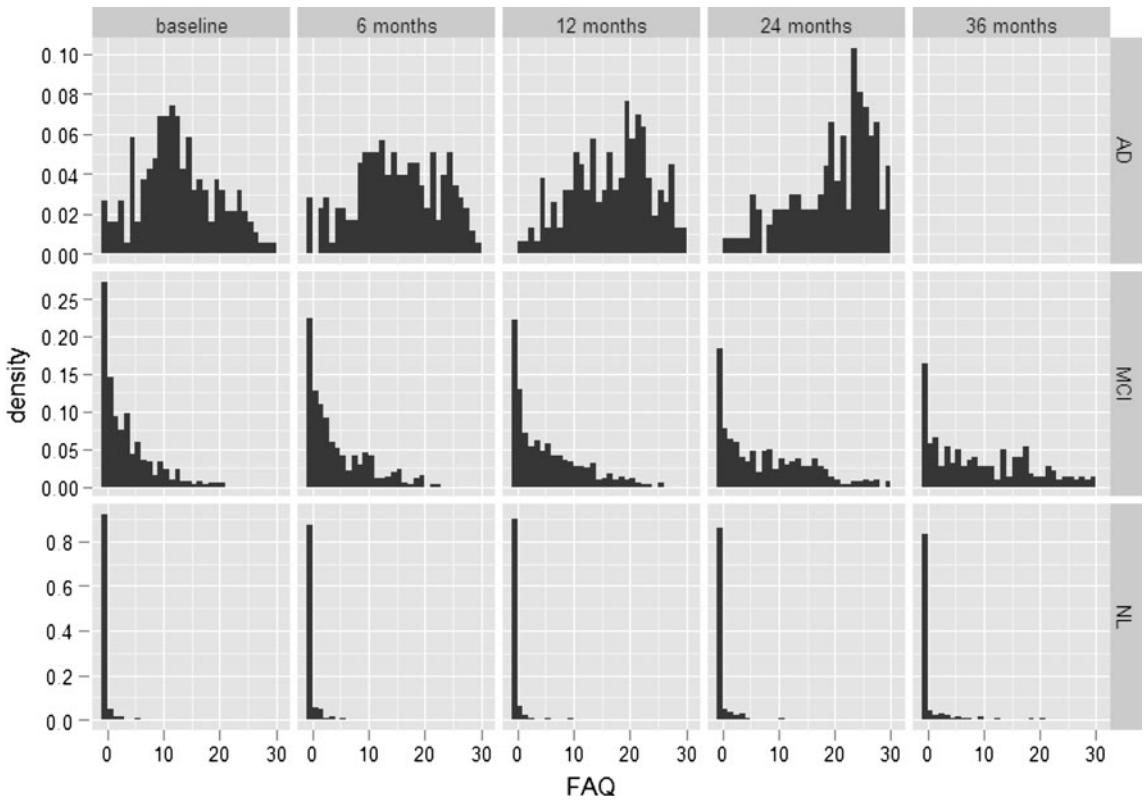

Fig. 1 Histogram of observed FAQ scores by patient populations and by visit

clinical trials as an inclusion/exclusion criterion. The score range for MMSE is 0–30, with greater cognitive impairment having lower scores. The CDR assesses dementia severity by staging, through semi-structured interview of patients and caregivers, and the subject's cognitive status is rated in 6 domains of functioning including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-sb score is obtained by summing each of the domain box scores, with scores ranging from 0 to 18, with more severe patients having higher scores [14].

The ADAS-cog is a cognitive measure similar to MMSE. However, ADAS-cog was not tested in the model as a covariate, because it is not usually measured at screening due to its complicated procedure, and its high correlation with MMSE [5, 6]. A pair plot with correlation coefficient estimates between these clinical endpoints is provided in the online supplemental material (Fig. S1), as well as correlation plots between baseline MMSE and FAQ by patient population (Fig. S2).

Since MMSE and FAQ measure different aspects of disease, namely cognitive and functional domains respectively, a composite of baseline MMSE and FAQ scores was proposed as an indicator for the baseline severity. To account for the opposite direction of MMSE and FAQ scores (i.e., MMSE = 0 or FAQ = 30 is the maximum cognitive or functional impairment, MMSE = 30 or FAQ = 0 is no impairment), the composite score (SEV_b) was derived as shown below:

$$SEV_b = ((30 - MMSE_b) + FAQ_b) \tag{2}$$

The baseline severity was tested in the model either as a power function or as a linear function. In addition, an inverse-U type function [15] was tested to describe the non-linear relationship between the rate of change (slope) and severity. Although we assumed a linear approximation for individual patient disease progression (see above), the population mean slope prediction over a longer period of time would be theoretically non-linear, i.e., NL or very early stage of AD would likely have a slope of near 0, a steeper slope in the middle of the disease stage, and a slope of near 0 again in later stages of AD as subjects reach the FAQ boundary. The parameterization below allowed the model to predict a zero slope at both ends of SEV_b (0 and 60), and for the shape of the U-curve to change as a function of two power coefficient parameters. Figure S3 in the online supplemental material illustrates the different shapes obtained with the inverse-U function with different coefficients. 20 is the approximate mean of the severity index (SEV_b) from the ADNI populations and baseline severity is described with a function of:

$$f(SEV_b) = \left(\frac{SEV_b}{20}\right)^{coef_1} \cdot \left(\frac{60 - SEV_b}{40}\right)^{coef_2} \tag{3}$$

Disease state ("AD pathology") The neurodegenerative process associated with AD is thought to be caused by various processes that cause neuronal damage. Neuropathological observations of the postmortem AD brain include the presence of senile plaques—containing primarily β-amyloid (Aβ) peptide aggregates—and tangles comprised of highly phosphorylated τ proteins, and it is considered that Aβ lesions proliferate within and among brain regions once initiated [16]. While some plaques and tangles may be present in normal elderly, it is considered that normal elderly (NL) differ in disease state from MCI and AD patients who manifest "AD pathology" as clinical symptoms. Therefore, disease state (NL vs AD pathology) was tested in the model in addition to the disease severity.

Covariate evaluation The effects of continuous covariates (other than baseline severity described above) were modeled using a normalized power model.

$$TVP = \theta_{TVP} \cdot \left(\frac{cov_i}{cov_{ref}}\right)^{\theta_x} \tag{4}$$

where TVP is the typical value of a model parameter, θ_{TVP} is an estimated parameter describing the typical population parameter value, cov_i is the individual continuous covariate, cov_{ref} is the reference continuous covariate value (i.e., approximate median for the population), and θ_x is an estimated parameter (power coefficient) describing the magnitude of the covariate-parameter relationships.

Dichotomous covariates (ApoE4 genotype, sex) were mapped to a value of 0 or 1 and their effects were estimated in the model as below. ApoE4 genotype was categorized into "non-carrier" ($APOE4 = 0$) and "carrier" ($APOE4 = 1$), where subjects having at least 1 ApoE4 allele ($\varepsilon 4$) were considered carriers. Gender was Male ($SEX = 0$) or Female ($SEX = 1$).

$$TVP = \theta_{TVP} \cdot \theta_x^{\text{cov}} \tag{5}$$

where cov is the value assigned to designate the presence or absence of the discrete covariate, θ_x is an estimated parameter describing the magnitude of the covariate-parameter relationship.

For the censored approach, covariates were tested in a linear fashion to allow flexibility during parameters estimation since FAQ scores become $-\infty$ to ∞ after the transformation (see Sect. "Censored approach").

$$TVP = \theta_{TVP} + \sum_{i=1}^{n} cov_i \cdot \theta_i \tag{6}$$

Censored approach

The range of the FAQ is 0–30, and these lower and upper boundaries can result in non-normal and atypical data distributions. These issues have been discussed, and a method to handle bounded outcome data was recently published by Hutmacher et al. [17]. For this method, the non-boundary data are scaled between 0 and 1 and a transformation family is applied which provides flexibility for handling the difficult data distribution shapes. The approach considers the boundary data as censored when formulating the likelihood. This is based on the assumption that the boundary data are reported as such because the measurement instrument lacks sufficient precision to differentiate the underlying true measurements from the boundaries. This is a similar concept to the censoring approach applied to PK concentration data that are below limit of quantification [18].

For FAQ, the "non-boundary data" (ranging from 1 to 29; 1 and 29 being the smallest and largest FAQ values that are not on the boundary) are divided by 30 to yield a result between 0 and 1—i.e. z = FAQ/30. Then the transformation is applied:

$$y = h(FAQ(t)) = \begin{cases} \log\left[\frac{(1-z)^{-\lambda}-1}{\lambda}\right] & \text{if } \lambda \neq 0 \\ \log(-\log(1-z)) & \text{if } \lambda = 0 \end{cases} \quad (7)$$
$$z \in (0,1), y \in (-\infty, \infty)$$

The parameter λ governs the transformation. When $\lambda = 1$ the transformation reflects a logit function, and for $\lambda = 0$, the complimentary log–log.

A general nonlinear mixed effects model can be constructed using the transformed response:

$$y = h(FAQ(t)) = FAQ_{t=0} + \alpha \cdot t + \varepsilon = \mu(t) + \varepsilon \quad (8)$$

Because the range of y is $(\infty, -\infty)$ and a flexible transformation has been applied, the normality assumption of ε is more tenable, but is not guaranteed.

As stated, the data on the boundaries, $FAQ = 0$ or 30, are considered censored observations when constructing the likelihood. The conditional likelihood contribution with respect to the original *FAQ scale* for a single observation is:

$$\ell(FAQ|\boldsymbol{\eta}) = \left[\phi\left(\frac{h(FAQ)-\mu(t)}{\sigma}\right)J(FAQ;\lambda)\right]^{I(FAQ\in\{0,30\})} \Phi\left(\frac{y_L-\mu}{\sigma}\right)^{I(FAQ=0)}\left[1-\Phi\left(\frac{y_H-\mu}{\sigma}\right)\right]^{I(FAQ=30)} \quad (9)$$

where μ (conditional mean) is defined in (8); ϕ is the normal density; σ is variance for FAQ in the transformed scale; $J(FAQ;\lambda) = \partial[h(FAQ)]/\partial FAQ$ is the Jacobian; Φ is the cumulative normal distribution function; $y_L = h(FAQ = 1)$ and $y_H = h(FAQ = 29)$ are the transformed values of $FAQ = 1$ and $FAQ = 29$, respectively; and $I(\bullet)$ is the indicator function which equals 1 when the logical expression is true and 0 otherwise. Using the minimum ($FAQ = 1$) and maximum ($FAQ = 29$) values from the open interval maximizes the conditional likelihood [19]. The subject's aggregate conditional likelihood is the product of his individual likelihoods assuming independence.

Model selection criteria

The model building strategy is based on modification of different approaches previously discussed and widely used in pharmacometrics communities [20–23]. Covariates were added one by one in a forward stepwise manner, examining the change in minimum objective function values (OFV) in hierarchical models, and also the precision of the parameter estimates. During model building, the hypotheses and goodness of fit of different models to the data were evaluated using the following criteria: change in the minimum objective function, 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 hierarchical models is assumed to have an approximate χ^2 probability distribution with the number of degrees of freedom 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 ($p < 0.01$). The covariate(s) of interest were kept in the model if the model was stable and its parameter estimate demonstrated acceptable precision (e.g., the relative standard error (RSE) <50 %), also monitor the ratio of eigenvalues (condition number) <1000 at each model run to evaluate any sign of over parameterizations, regardless of its statistical significance (using OFV as reference).

Model fitting was performed using a population analysis approach (NONMEM Version VII, Level 1.2, ICON Development Solutions, Ellicott City, MA) with FOCE for the standard approach and Laplace Conditional Estimation method for the censored approach. Diagnostic graphics and post-processing of NONMEM output, and simulation were performed using R (version 2.13.2 or higher).

Performance evaluation (predictive check)

Once the final model was identified, 500 datasets identical in structure and covariate values to the original dataset

were simulated, using the parameter estimates from the final model to evaluate the model performance. The longitudinal FAQ scores over time by population group (AD, MCI, NL) were generated and visually compared with the observed data at each selected percentile (5th, 50th, 95th). The reason for visualizing the data by population group (AD, MCI, NL), rather than "binned" by the baseline severity is because most clinicians and researchers in the AD community are accustomed to categorizing patients into NL, MCI, and AD groups. A complete description of the diagnosis criteria for categorization of NL, MCI, and AD is found in the ADNI protocol (www.adni-info.org). The number of observations at both ends (FAQ scores of 0 and 30) were also counted from observed data and the simulated data and then compared (reported as a percentage) to check whether the model was able to adequately recreate the frequency nature of the bounded data.

Results

Observed longitudinal FAQ data are visualized as histograms by patient group (NL, MCI, AD) and by visit (month) in Fig. 1. The histograms highlight the complex distribution of the data. A large number (87.9 %) of zero scores (lower boundary) were observed in NL patients during the whole study duration, and at baseline (27.3 %) in the MCI patients. Also, scores of 30 (upper boundary) were observed in AD patients (1.5 %) toward the end of the study.

Base model versus final model (standard approach)

As described in the methods section, model development was initiated with the base model, and covariates of interest were tested in a forward step-wise fashion. Baseline severity, disease state, and ApoE4 genotype were significant

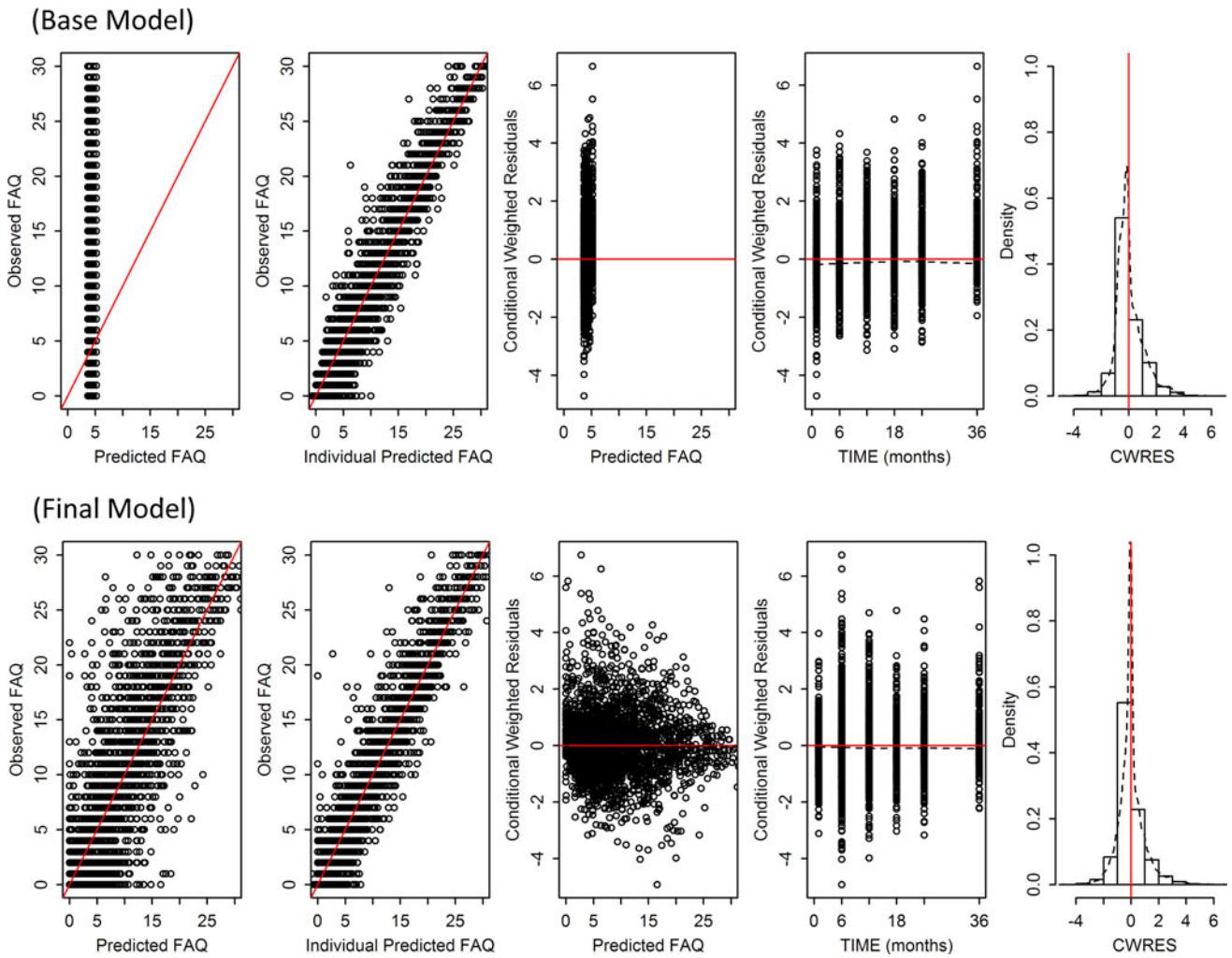

Fig. 2 Diagnostic plots for base model versus final model (standard approach)

covariates impacting the rate of disease progression (α). Baseline severity and disease state were covariates on the intercept (*Int*). Age, sex, hippocampal volume and ventricular volume were not statistically significant covariates either on the intercept or slope.

A composite of baseline MMSE and FAQ scores (composite baseline severity) was the best indicator for baseline severity (based on the objective function values and diagnostic plots), compared with other severity indicators (baseline MMSE or baseline CDR-sb). For disease progression, an inverse-U as a function of composite baseline severity, in which slope theoretically becomes zero at both ends, best described the relationship for the change in slope (i.e., patients with 0s (normal elderly) were likely to stay 0 or show little progression from 0, and patients with 30s were unlikely to show a large decline (improvement) or worsening). In clinical terms, the rate of disease progression is, in part, a function of the baseline severity of the cognitive or function deficits, with more moderately affected populations demonstrating more rapid deterioration in cognition or function compared to more mildly impacted populations. The mathematical expression of the final model is as below:

$$FAQ(t) = Int \cdot \left(\frac{SEV_b}{20}\right)^{\theta i} \cdot \exp(\eta_1) + \left(\alpha \cdot f(SEV_b) \cdot \theta_{i+1}^{ApoE4} + \eta_2\right) \cdot t + \varepsilon$$

where intercept (*Int*) and slope (α) were estimated for each disease state (NL vs AD-pathology). The parameter estimates from the base model and the final model using the standard approach are summarized in Table 2. The goodness of fit plots were also evaluated (Fig. 2). Overall, the final model parameters were well estimated with reasonable confidence intervals, and the model prediction was improved from the base model to the final model, with good correlation between population level predictions and individual predictions versus observations. The weighted residuals were in general randomly scattered across the range of predicted values.

To ascertain the appropriateness of covariates included in the final model, plots of random effect estimates on

Table 2 Parameter estimates for standard approach

Parameter		Parameter estimates (%RSE)		Bootstrap[a] Median [95 % CI]
		Base model	Final model	
FAQ_b	Int_{NL}	3.62 (9.50)	1.53 (30.8)	1.74 [0.257–8.79]
	$Int_{AD\text{-}pathology}$	–	13.0 (1.35)	13.0 [12.6–13.3]
	bSEV effect	–	1.34 (2.30)	1.34 [1.28–1.40]
Slope (rate of disease progression)	α_{NL} (pt/month)	0.0438 (7.72)	0.0422 (33.6)	0.0385 [0.00671–0.0856]
	$\alpha_{AD\text{-}pathology}$	–	0.220 (12.2)	0.220 [0.163–0.276]
	Inv-U $coef_1$	–	0.819 (21.9)	0.849 [0.413–1.29]
	Inv-U $coef_2$	–	2.63 (25.9)	2.73 [1.05–4.54]
	ApoE4 on α	–	1.48 (11.6)	1.47 [1.18–1.89]
BSV (η_1) for FAQ_b	NL	531 (35.8)	5.21 (9.25)	4.82 [0.00052–21.4]
	MCI	1.1(11.8)	0.175 (18.3)	0.175 [0.114–0.243]
	AD	1.72 (13.6)	0.0201 (24.7)	0.0200 [0.0116–0.0321]
BSV(η_2) for Slope	NL	NA	NA	NA
	MCI	0.0722 (12.6)	0.0469 (15.6)	0.0464 [0.0346–0.0649]
	AD	0.142 (16.5)	0.077 (27.9)	0.0737 [0.0400–0.123]
Correlation η_1 and η_2	NL	NA	NA	NA
	MCI	−0.0224	0.0178	0.0170 [0.0005–0.0331]
	AD	0.281	0.0197	0.0194 [0.00517–0.0353]
Residual variability		2.22 (3.36)	1.71 (9.67)	1.71 [1.53–1.90]
Time-varying residual variability		–	0.019 (18.3)	0.0188 [0.0106–0.0259]
OFV (objective function value)		12,839	11,281	

Shrinkage for η_1 (intercept) are 66.0, 34.4, 20.6 % for NL, MCI, AD, respectively, and shrinkage for η_2 (slope) are 11.2, 14.1 % for MCI, AD, respectively

BSV between subject variability, *NA* not estimated (model didn't converged); –, not included in the base model

[a] Nonparametric bootstrap stratified by patient population ($n = 1000$)

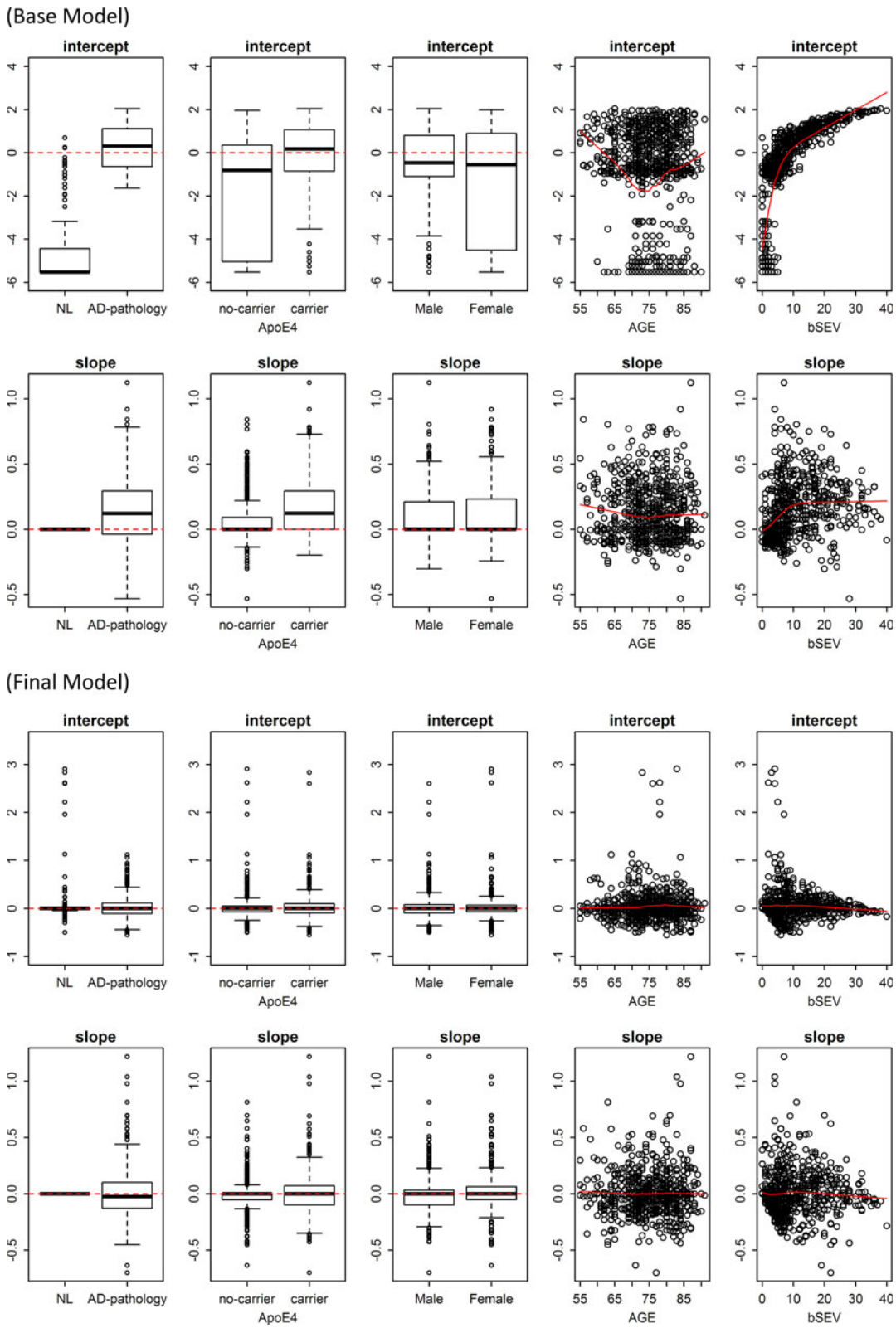

Fig. 3 ETA plot by covariate for base model versus final model (standard approach). *Note* age and gender were not significant covariates and not included in the final model

intercept (η_1) and slope (η_2) were generated by covariates of interest (disease state, ApoE4 genotype, sex, age, baseline severity) from the base and final model (Fig. 3). Trends in the distribution of random effects for the base model (no covariates in the base model) were observed. Upon inclusion of the covariates into the model, the trends were reduced, with the distribution dispersed around zero, confirming appropriateness of the final model. Sex and age were not significant in the covariate evaluation, and it was also visually confirmed that there was no trend in the distribution of random effects for both base and final model.

Base model versus final model (censored approach)

A censored model was tested with the FAQ data using a similar model building/covariate testing approach as described above, and these results were compared with the standard approach.

Very similar to the standard approach, baseline severity, disease state, and ApoE4 genotype were significant covariates impacting the rate of disease progression, and baseline severity and disease state were significant covariates on the intercept. Like the uncensored approach, age and sex were not statistically significant covariates either on the intercept or slope. An attempt was made to test imaging biomarkers, but the results were similar to the standard approach in that these were not significant, probably due to the confounding effects amongst imaging biomarkers, and correlation with the severity and/or ApoE4 genotype, which were already in the model. The NONMEM control file for the final model using the censored approach is provided in the "Appendix" section. The mathematical expression of the final model is as below:

$$FAQ(t)_{transformed} = (Int + SEV_b \cdot \theta_i + \eta_1) + (\alpha + SEV_b \cdot \theta_{i+1} + ApoE_4 \cdot \theta_{i+2} + \eta_2) \cdot t + \varepsilon$$

where intercept (*Int*) and slope (α) were estimated for each disease state (NL vs AD-pathology) in a transformed scale. The parameter estimates from the base model and the final model using the censored approach are summarized in Table 3. Similar to the standard approach, the final model parameters were well estimated with reasonable confidence intervals, and the model prediction was improved from the

Table 3 Parameter estimates for censored approach

Parameter		Parameter estimates (%RSE)		Bootstrap[a] 95 % CI
		Base model	Final model	
FAQ_b	Int_{NL}	−2.57 (0.147)	−5.51 (5.17)	−5.50 [−5.97, −4.58]
	$Int_{AD\text{-}pathology}$	–	−3.82 (1.62)	−3.82 [−3.96, −3.67]
	bSEV effect	–	0.197 (2.67)	0.198 [0.185, 0.213]
Slope (rate of disease progression)	α_{NL} (pt/month)	0.0506 (0.0630)	−0.0579 (24.2)	−0.060 [−0.0878, −0.0354]
	$\alpha_{AD\text{-}pathology}$	–	0.0263 (22.6)	0.0263 [0.0139,0.0384]
	λ (transform)	1.73 (0.0728)	1.87 (5.45)	1.91 [1.57, 2.32]
	bSEV effect	–	0.00142 (29.6)	0.00144 [0.000502, 0.00255]
	ApoE4 effect	–	0.0268 (21.4)	0.0270 [0.0156, 0.0386]
BSV (η_1) for FAQ_b	NL	8.92 (19.2)	1.52 (48.1)	1.52 [0.101, 2.81]
	MCI	1.93 (9.38)	0.394 (14.5)	0.390 [0.295, 0.507]
	AD	8.57 (10.9)	0.0972 (45.4)	0.109 [0.0465, 0.204]
BSV(η_2) for Slope	NL	0.0331 (29.0)	0.00644 (34.8)	0.00640 [0.00326, 0.0106]
	MCI	0.00296 (12.9)	0.0032 (13.6)	0.00324 [0.00230, 0.00458]
	AD	0.00268 (22.4)	0.00347 (24.3)	0.00358 [0.00183, 0.00657]
Correlation η_1 and η_2	NL	0.495	0.0512	0.0455 [0.00296, 0.108]
	MCI	0.0092	0.00404	0.00392 [−0.00274, 0.0107]
	AD	0.0712	0.0183	0.0168 [0.00842, 0.0261]
Residual variability		0.774 (0.0984)	0.656 (8.19)	0.657 [0.595, 0.721]
Time-varying residual variability		–	0.0123 (17.0)	0.0124 [0.00632,0.0187]
OFV (objective function value)		14,667	13,180	

Parameter estimates are on transformed scale

Shrinkage for η_1 (intercept) are 51.0, 23.7, 11.6 %, and shrinkage for η_2 (slope) are 53.4, 20.1, 31.2 % for NL, MCI, AD, respectively

BSV between subject variability; –, not included in the base model

[a] Nonparametric bootstrap stratified by patient population ($n = 1000$)

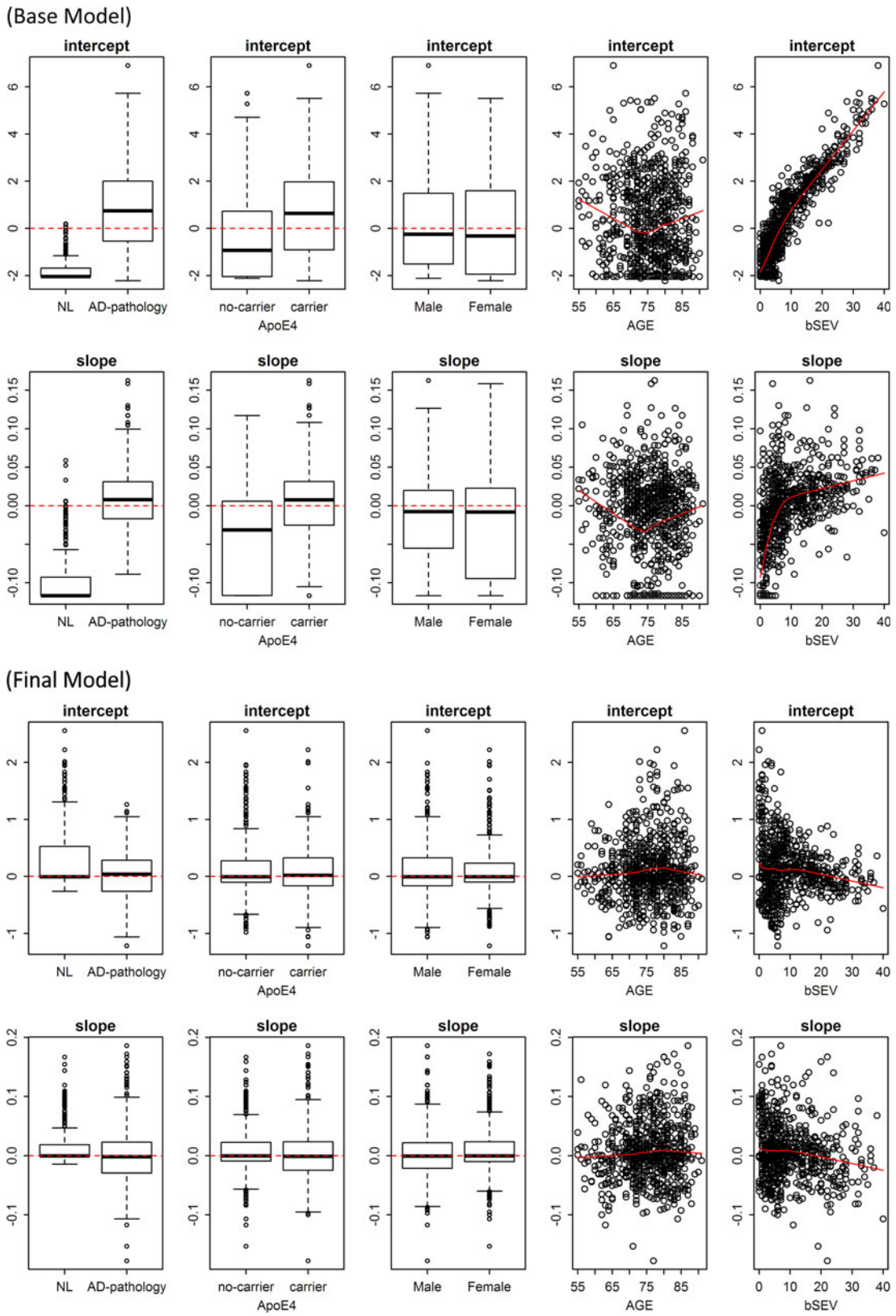

Fig. 4 ETA plot by covariate for base model versus final model (censored approach). *Note* age and gender were not significant covariates and not included in the final model

base model to the final model. The diagnostic plot showed that the final model was improved with good correlation between population level predictions and individual predictions versus observations (Fig. S4 in the online supplemental material), and the boxplots of random effect estimates on intercept (η_1) and slope (η_2) demonstrated that the trend in the distributions were reduced and dispersed around zero with the final model (Fig. 4). Note that predictions from the censored model can be back transformed to the original FAQ score scale whereas its parameter estimates can't, and the parameter estimates in Table 3 are reported on a transformed scale. Therefore, it is difficult to directly compare the population parameter estimates (such as slope estimate, α) with those from the standard approach.

Model evaluation

The predictive performance of the final model was assessed by evaluating whether the selected statistics of the observed data were contained within those predicted by the final model over a number of simulations. Five hundred data sets were simulated from the final model for each of the standard and censored approach. For the censored model, the simulated values less than 1 were treated as 0, and simulated values greater than 29 were treated as 30 during the numerical predictive check.

The median, 5th and 95th percentile for 90 % predicted intervals from the model (shade area) were compared with the observed data in Fig. 5 (median is solid line, 5th and 95th percentile are dashed lines). Overall, the median predictions were comparable with those for observed data for both the standard and censored model approaches, but the censored model captures the median value as well as 5th and 95th percentiles for NL, MCI, and AD patient populations better than the standard approach. In addition, negative values (<0) were simulated for NL and MCI patients and >30 values in AD patients with the standard approach. These problems were corrected with the censored approach. Note that the 5th percentile prediction intervals with the censored approach are "0" for NL and MCI patients and overlapped with the horizontal line at zero; therefore it is not clearly seen in these plots.

To further investigate the predictive performance of the censored approach, the number of simulated values for bounded data values (0 and 30) were counted from each simulation and compared with the percentage of total counts observed in the original data (Table 4). The percentage for FAQ = 0 and FAQ = 30 were 36.6 % and 0.463 % respectively in the observed data, and 34.2 % [32.5–35.8] (95 % prediction intervals) and 0.354 % [0.191–0.572] from the simulations. When these results were further evaluated by patient population, the percentage for observed FAQ = 0 were 24.6, 11.7, 0.272 % for NL, MCI, AD patients respectively, and 25.2 [24.2–26.1], 8.87 [7.41–10.2], 0.136 % [0.00–0.354] from simulations, indicating that FAQ = 0 was slightly under predicted in MCI patients, reflecting the slight under prediction for overall FAQ = 0 (36.6 % observed vs 34.2 % [32.5–35.8] simulated). The percentage for observed FAQ = 30 were 0.0, 0.136, 0.327 % for NL, MCI, AD patients, and the percentage from the simulations were 0.0 [0.0–0.0272], 0.0545 [0.0–0.163], 0.300 % [0.163–0.490], respectively. The trends were consistent with observed data across patient populations for both boundaries (FAQ = 0 and 30) demonstrating that the censored model was able to predict the boundary data.

Discussion

A disease progression model to describe longitudinal FAQ scores in healthy normal elderly (NL), MCI and mild AD patients was developed. For this analysis, we assumed a linear disease progression within an individual patient based on the available data (up to 3 years). A non-linear curvature of disease progression within a patient can typically be seen if patients are followed long enough, such as in a community-based 10-year follow up study, but typically not within the time frame of a randomized controlled clinical trial. Nevertheless, the rate of progression will be dependent on the baseline severity of disease. The linear progression on the transformed scale for the censored approach will lead to nonlinearity when predicting or simulating FAQ scores.

One of the important elements for disease progression modeling in AD is to use the model as a tool to simulate potential ranges of possible clinical trial outcomes, and to identify designs and inclusion/exclusion criteria that may lead to more sensitive trials. This can be accomplished by either by selecting a population or study design that leads to decreased variance in the endpoint for the population studied, or by selecting a population that progresses more rapidly, such that a greater magnitude of treatment effect would be observed over a shorter period of time. As such, it is important to find covariates and baseline characteristics which are good predictors of disease progression and that are easy to implement or collect. Baseline disease severity was the most influential covariate on the intercept (OF decrease $\sim$1078) as well as for determining the rate of change in patient function (additional OF decrease $\sim$229). ApoE4 carrier status was also indentified as a covariate in the model. These findings are very similar with the previous analyses for rates of change for ADAS-cog [6–9]. Imaging biomarkers (hippocampal volume and brain

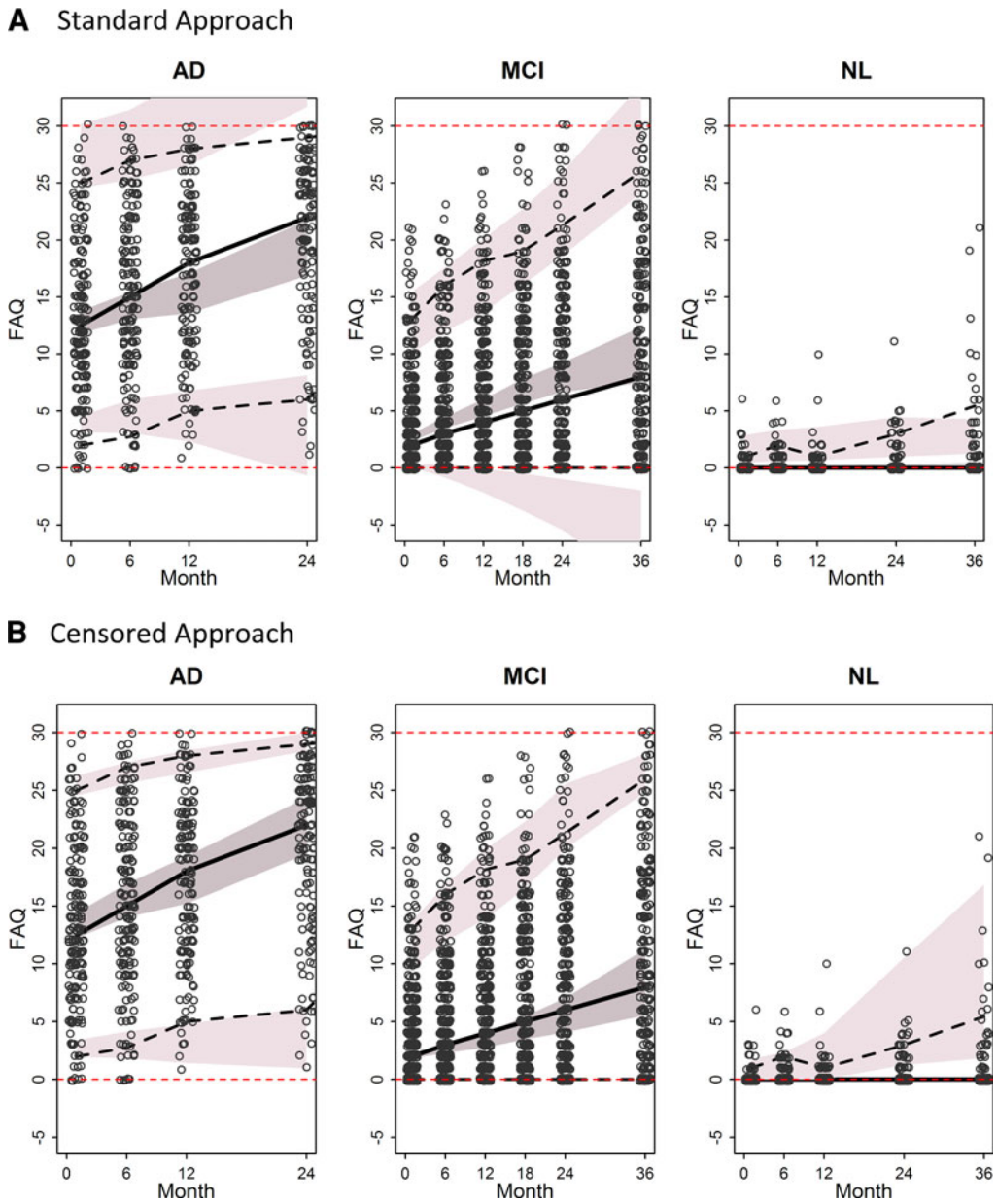

Fig. 5 Visual predictive check from 500 simulations: standard approach (**a**) versus censored approach (**b**). *Note* 5th percentile prediction intervals with censored approach are "0" for NL and MCI patients; therefore it is not clearly seen in these plots

volume) were not found to be significant covariates, likely due to the confounding effects between these imaging biomarkers and baseline severity, ApoE4 status or age, all of which were already in the model. A thorough analysis will be necessary with a much larger database to evaluate all the possible covariates and the confounding nature of them in future work. It is possible that in the future models other genotypes recently identified in large genome-wide association study (GWAS) studies [24] may also be important covariates, along with other known risk factors such as cardiovascular risk.

The diagnosis of NL, MCI, and AD are very complex, including cognitive, functional, and global tests and sometimes including caregiver impression. While all these clinical endpoints (MMSE, FAQ, CDR-sb) are validated tools to evaluate each component of disease, there is no single measurement which can describe the patient's disease severity. A composite score comprised of MMSE and FAQ (severity composite score) was selected as the severity index in this analysis, as was the best predictor of baseline FAQ compared to other baseline severity scores (baseline MMSE alone or baseline CDR-sb). ADAS-cog

Table 4 Percentage of simulations for bounded outcomes (FAQ = 0 and 30) with censored approach

	FAQ = 0		FAQ = 30	
	Observed (%)	Simulated (%)	Observed (%)	Simulated (%)
Total	36.6	34.2 [32.5–35.8]	0.463	0.354 [0.191–0.572]
NL	24.6	25.2 [24.2–26.1]	0.0	0.0 [0.0–0.0272]
MCI	11.7	8.87 [7.41–10.2]	0.136	0.0545 [0.0–0.163]
AD	0.272	0.136 [0.00–0.354]	0.327	0.300 [0.163–0.490]

[]—95 % predicted intervals, $n = 500$ simulations

was another candidate to describe baseline severity but it is often not measured at screening due to its complexity and need for trained staff to conduct the test. Another future possibility based on item-response theory (IRT) is "cognitive disability" scores which was recently introduced as a new diagnostic approach providing a more sensitive measurement [25], that potentially can allow for a combination of different cognitive assessments, such as the mini-mental state examination (MMSE), into one common pharmacometric model [26]. The IRT theory has a great potential to measure the overall patient disability in AD-pathology, by combining different cognitive and function measurements together, and it may be suitable to describe the patient severity from the very early stage to the advanced AD. Better tools or measurements need to be established and validated to predict disease progression in AD. Various biomarkers such as Aβ amyloid concentrations in CSF or imaging data (MRI, PET) are expected to provide such information in the near future, and many researchers, pharmaceutical companies, and regulatory agencies are currently investigating these for inclusion criteria for clinical trials. These biomarkers may be useful as objective surrogate measures of severity index in the model once established and validated in the future.

Loss of function is also part of the aging process, and the ADNI data has non-AD healthy elderly controls that provide estimates for the very slow loss of function in this population as well. From a modeling perspective however, the fact that the large portion of data in healthy elderly patients remained as scores of zero during the 36 month study may cause biased estimates in the model parameters and skewed random effects distributions if a standard model development approach is utilized even if normal elderly and AD-pathology patients are estimated separately. In fact, scores below 0 are simulated with the standard approach for the NL and MCI patients (Fig. 5), indicating that there is a limitation of the standard approach model to emulate real world data. On the other hand, the censored approach was able to account for the nature of bounded FAQ scores (Fig. 5), and the simulated percentage (%) of scores at 0 and 30 for each patient population (NL, MCI, AD) are very close to the observed data (Table 4), indicating that the censored approach handles the non-normal and atypical data distribution appropriately.

Very slight under estimates for the simulated percentage (%) of FAQ score zero with MCI patients were observed in the censored model (Table 4). A recent publication indicated that there are bimodal distributions in their biomarker profiles and disease progression characteristics (i.e., converted or not converted from MCI to AD) from ADNI data [27], implying there are hidden covariates that may explain more of the variability observed, and those covariates might be a combination of diagnosis criteria or various biomarkers which are still under investigation discussed above.

The censoring approach is motivated by the assumption that the measurement device, in this case the FAQ score, is "insensitive" near the boundaries (i.e., 0 and 30). That is, subjects might have a 0 score at a certain time point, but if the FAQ were sensitive enough to detect a small difference, a number other than 0 would be reported. For some endpoints or patient populations, this might not be a valid assumption. A 0 might actually represent total absence of disease. When this is the case, a more complicated model must be entertained; one that allows both types of 0s—i.e., a 0 for lack of sensitivity for measuring disease and a 0 that represents lack of disease. For the data within the ADNI dataset, the censored model adequately predicts the percentage of 0s. As an additional evaluation of the censored model, a within-subject mixture model (see Hutmacher et al. [17]) which allows for both types of 0s was fitted. The parameter which governs the probability of a 0 being lack of disease was estimated to be extremely small. As a result, the interpretation that the 0s in the data set are from some lack of resolution of FAQ near 0, which is assumed for the censored model, seems valid.

In conclusion, both standard and censored approaches can describe longitudinal FAQ scores and parameter estimates and the selection of influential covariates for both approaches was similar. However, visual predictive checks showed that a large number of negative scores (less than 0) were simulated for NL and MCI patients with the standard

approach. On the other hand, the censored approach captured well the frequency of the boundary data (0 and 30), indicating that the censored model can describe the boundary observations more precisely. The model predictions at the 5th, 50th and 95th percentiles were also better with the censored approach compared with the standard approach. The censored approach greatly improved the predictability of the disease progression in FAQ scores. The basic method for handling boundary data described here is also generally applicable to handle boundary observations for numerous other endpoints.

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Appendix

```
$PROBLEM run7.mod (censored approach)

$INPUT C ID TIME ADAS FAQ=DV PSTF AGE SEX RACE=DROP EDUC APOF FHAD=DROP ABET=DROP
LEFT=DROP BFAQ BADS BMMS BSEV

;TIME: Time (in month)
;ADAS: ADAS-cog score (0-70)
;FAQ : FAQ score (0-30)
;PSTF: 0=Normal, 1=MCI, 2=AD
;AGE : Age (in year)
;SEX : 1=male, 2=female
;RACE: 1=American Indian or Alaskan Native; 2=Asian; 3=Native Hawaiian or Other Pacific Islander
       ;4=Black or African American; 5=White; 6=More than one race; 7=Unknown
;EDUC; Education (in year)
;APOF: ApoE4 flag, 0=non-carrier, 1=hetero, 2=homo
;FHAD: Family history of AD (0=no AD, 1=either/both mom and dad are AD, NA=Unknown)
;ABET: CSF Abeta
;LEFT: left hippocampal volume
;BFAQ: baseline FAQ
;BADS: baseline ADAS
;BMMS: baseline MMSE
;BSEV: baseline severity; derived as BFAQ + (30-BMMS)


$DATA adni_faq.csv IGNORE=C

$PRED

APF = 0
IF(APOF.GT.0)THEN
APF = 1           ;ApoE4 effect
ENDIF

PST0 = 0
PST1 = 0
IF (PSTF.EQ.0) PST0 = 1
IF (PSTF.GT.0) PST1 = 1   ;AD pathology (MCI and AD)

PBSL = THETA(1)*PST0 + THETA(10)*PST1
PSLP = THETA(2)*PST0 + THETA(11)*PST1

TBSL = PBSL + BSEV*THETA(6) + APF*THETA(8)
TSLP = PSLP + BSEV*THETA(5) + APF*THETA(7)


IF (PSTF.EQ.0)  THEN
BSL = TBSL+ETA(1)
SLP = TSLP+ETA(2)
ENDIF

IF (PSTF.EQ.1)  THEN
BSL = TBSL+ETA(3)
SLP = TSLP+ETA(4)
ENDIF

IF (PSTF.EQ.2)  THEN
BSL = TBSL+ETA(5)
SLP = TSLP+ETA(6)
ENDIF

ALP = THETA(3); Transformation parameter ALP=1 for logit & ALP=0 complimentary log-log
W   = EXP(THETA(4) + THETA(9)*TIME) ; Residual standard deviation on transformed scale


TFV = TBSL+TSLP*TIME   ;PRED on transformed scale
FV  = BSL+SLP*TIME     ;IPRED on transformed scale
```

```
QD=0
IF (FAQ.EQ.0) QD=0.1   ; adjust data on boundary to keep from numerical problems
IF (FAQ.EQ.30)QD=-0.1
TDV = FAQ+QD           ; *** new response variable ***;

MNFAQ=1        ; minimum observed FAQ value that is not on boundary (not equal to 0)
MXFAQ=29       ; maximum observed FAQ value that is not on boundary (not equal to 30)

ZZ=TDV/30;     ; scales FAQ (modified) to a value between 0 and 1
WW=1-ZZ
UU=(WW**(-ALP)-1)/ALP;
HH=LOG(UU)     ; WW UU HH compose the transformation
IWRES = (HH - FV)/W    ; individually weighted residual on transformed scale
JB = ABS((1/UU)*(WW**(-ALP-1))*(1/30)) ; Jacobian used to adjust OFV to lie on FAQ scale
HMN = LOG(((1- 1/30)**(-ALP)-1)/ALP)  ; transformed MNFAQ
HMX = LOG(((1-29/30)**(-ALP)-1)/ALP)  ; transformed MXFAQ
PI=3.141592654

CT1=(HMN - FV)/W       ; This block is used to avoid taking the log of 0
IF (CT1.LT.-6) CT1=-6
IF (CT1.GT. 6) CT1= 6
CT2=(HMX - FV)/W
IF (CT2.LT.-6) CT2=-6
IF (CT2.GT. 6) CT2= 6

IF (TDV.LT.MNFAQ) THEN
  CLKH = PHI(CT1)      ; compute likelihood for FAQ = 0
ELSE
  CLKH = 1-PHI(CT2)    ; compute likelihood for FAQ = 30
ENDIF

IF (TDV.LT.MNFAQ.OR.TDV.GT.MXFAQ) THEN
  LGL = LOG(CLKH)      ; compute log-likelihood for boundary data
ELSE
  LGL = -0.5*LOG(W**2)-0.5*(IWRES**2)-0.5*LOG(2*PI)+LOG(JB) ; compute log-likelihood for
ENDIF                                                       ; non-boundary data

Y = -2*LGL             ; specification of general log-likelihood (-2 x LL)


$THETA
  -6
  -0.01
   2
  -0.4
   0.001
   0.2
   0.01
   0 FIX
   0.01
  -4.0
   0.06


$OMEGA BLOCK(2)
   0.4
   0.002 0.004


$OMEGA BLOCK(2)
   0.4
   0.005 0.004

$OMEGA BLOCK(2)
   0.4
   0.005 0.004


$ESTIMATION MAXEVAL=8000 PRINT=10 METHOD=1 LAPLACE -2LL NOABORT SIGDIGITS=3 FILE=run7.ext
$COV MATRIX=R PRINT=E
```

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