

Modeling Change in Longitudinal Studies: Use Age Only or Initial Age and Time?

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Abstract

Since many epidemiological studies involve the study of individuals of different ages over time, it often becomes necessary to distinguish between and estimate both longitudinal and cross-sectional differences to overcome the possibility of selection bias. This paper examines how the choice of age and time in modeling observational longitudinal data can affect the results. In particular, age can be decomposed into two components: the age at entry into the study (first age) and the longitudinal follow-up time. The implication of using age or first age and time is described for a number of possible linear mixed-effects models that may be used to describe the longitudinal data. The two approaches are illustrated using a number of different examples of data taken from the Baltimore Longitudinal Study of Aging (BLSA). The examples illustrate that the added flexibility provided by the first age and time approach is usually necessary to adequately describe the data.

Key Words: Mixed-Effects Models, Multilevel modeling, Observational Study, Recruitment Bias, Regression

1. Introduction

Mixed-effects models (Verbeke and Molenberghs, 2001) have become the standard approach to modeling repeated measures, longitudinal data. When modeling data from a longitudinal observational study, the investigator must decide how to handle the confounding relationship of age and time of observation with a response variable. This has been presented in many different ways by various researchers. For example, Zeger, Liang, and Albert (1988) examined respiratory disease in a population of children ages 7 to 10 who were evaluated annually by only using the variable age in their model, thus considering the cross-sectional and longitudinal effect of age to be the same. Similarly, Park and Lee (1999) considered only age in modeling the occurrence of urinary incontinence during a 2-year period in non-institutionalized community dwelling elderly 60 years and over. In data from studies of the effects of a calcium supplement on bone density in a population of post-menopausal women (Smith et al. 1988), Lindstrom and Bates (1988) considered a linear mixed-effects model using only time of measurement of bone density in the treatment groups ignoring any possible age effects. Also, Edwards et al. (2006) in an analysis of data from HIV patients evaluated only longitudinal changes in viral load by using only time from infection in fitting regression splines with a linear mixed-effects model.

Brant and colleagues have presented analyses using a more flexible approach which models the cross-sectional differences among subjects along with the longitudinal changes within subjects by considering for each individual i and examination time j , $Age_{ij} = FAge_i + Time_{ij}$, where $FAge_i$ is used to model a cross-sectional age differences and $Time_{ij}$ the longitudinal trend. This approach was utilized on observational studies of hearing loss (Morrell and Brant (1991), Pearson et al. (1995), Morrell et al. (1997)), prostate disease (Carter et al. (1992), Pearson et al. (1994), Brant et al. (2003)), and cardiovascular function (Morrell et al. (1997), Pearson et al. (1997), Fleg et al. (2005)). Other authors employing a similar approach include Kenward, Lessafre, and Molenberghs (1994) in a study of the treatment of psychiatric patients, Chang (2000) in studies of diabetic retinopathy patients and radio surgery for meningiomas, and Zhang and Davidian (2001) in an analysis of cholesterol data.

Another related issue of concern when modeling observational longitudinal data is the possibility of selection or recruitment bias (for example, see Heckman et al. (1996), Jensen et al. (2000), Korn et al. (2001), Hogan, Lin, and Herman (2004)). In this paper, we consider selection or recruitment bias to correspond to the fact that subjects recruited into an ongoing study at an older age may be different from other subjects who were recruited at a younger age and remained in the study to reach the age of the older person. For example, subjects who begin at age 50 may be different from subjects who started at age 40 and remain in the study for 10 years, i.e., it may be important to

distinguish between people studied at the same age with different starting ages in the study. In this situation the model must be able to account for these differences.

In this paper we examine how choices of age and time in modeling observational longitudinal data can affect the results. In the process, we also compare different approaches for modeling cross-sectional and longitudinal differences. We explore a number of different examples of data taken from the Baltimore Longitudinal Study of Aging (BLSA) to illustrate the different modeling approaches for data sets with different characteristics with regard to age and time in the study. See also Morrell et al. (2008).

2. Comparing and Testing Models for Cross-Sectional and Longitudinal Change

Scenario 2.1.

We first consider a simple model where the response y is modeled as a linear function of age with a random effect for intercept. The model is

$$y = \beta_0 + b_{i0} + \beta_1 \text{Age} + \varepsilon, \quad (1)$$

which can be rewritten as

$$y = \beta_0 + b_{i0} + \beta_1 (\text{FAge} + \text{Time}) + \varepsilon = \beta_0 + b_{i0} + \beta_1 \text{FAge} + \beta_1 \text{Time} + \varepsilon.$$

An alternative model or first age/time approach with separate terms for first age and time is

$$y = \beta_0 + b_{i0} + \beta_1 \text{FAge} + \beta_2 \text{Time} + \varepsilon \quad (2)$$

Note that models (1) and (2) will be the same only if $\beta_1 = \beta_2$ and this hypothesis may be tested within the mixed-model framework. Also, the first age/time approach allows for more flexibility in the model as the cross sectional and longitudinal effects are not constrained to be the same.

Scenario 2.2.

Now suppose that the model also contains a random age or time term to allow subjects to have varying longitudinal rates of change. In this case,

$$y = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) \text{Age} + \varepsilon, \quad (3)$$

which can be rewritten as

$$y = \beta_0 + b_{i0} + (\beta_1 + b_{i1})(\text{FAge} + \text{Time}) + \varepsilon = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) \text{FAge} + (\beta_1 + b_{i1}) \text{Time} + \varepsilon.$$

The corresponding model using first age and time is

$$y = \beta_0 + b_{i0} + \beta_1 \text{FAge} + (\beta_2 + b_{i1}) \text{Time} + \varepsilon. \quad (4)$$

Model (4) is not nested within model (3) since in the Age model the random slope term appears with both the FAge and Time terms when the model is expanded. Consequently one cannot use a Wald or likelihood ratio test to choose between these two models. In this case, we can compare models using the AIC or the BIC. These criteria start with the log-likelihood and penalize the value for the complexity of the model. One can choose between the models based on minimizing the AIC or BIC. It is important to estimate the mixed-models using maximum likelihood (ML), not restricted maximum likelihood (RML), since the models being compared do not contain the same fixed-effects. Restricted maximum likelihood adjusts the likelihood for the fixed-effects in the model. Consequently, if the models do not contain the same fixed effects RML will not produce comparable likelihood values.

Scenario 2.3.

Now we allow a quadratic age effect with a single random effect for intercept.

$$y = \beta_0 + b_{i0} + \beta_1 \text{Age} + \beta_2 \text{Age}^2 + \varepsilon, \quad (5)$$

which can be rewritten as

$$\begin{aligned} y &= \beta_0 + b_{i0} + \beta_1 (\text{FAge} + \text{Time}) + \beta_2 (\text{FAge} + \text{Time})^2 + \varepsilon \\ &= \beta_0 + b_{i0} + \beta_1 \text{FAge} + \beta_1 \text{Time} + \beta_2 \text{FAge}^2 + \beta_2 \text{FAge} \times \text{Time} + \beta_2 \text{Time}^2 + \varepsilon. \end{aligned}$$

The model involving first age and time is

$$y = \beta_0 + b_{i0} + \beta_1 \text{FAge} + \beta_2 \text{Time} + \beta_3 \text{FAge}^2 + \beta_4 \text{Time}^2 + \beta_5 \text{FAge} \times \text{Time} + \varepsilon. \quad (6)$$

To compare these models we need to test: $\beta_1 = \beta_2$ & $\beta_3 = \frac{1}{2}\beta_4 = \beta_5$.

Scenario 2.4.

Finally, adding an age or time random effect yields:

$$y = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) \text{Age} + \beta_2 \text{Age}^2 + \varepsilon, \quad (7)$$

which can be rewritten as

$$y = \beta_0 + b_{i0} + (\beta_1 + b_{i1}) (\text{FAge} + \text{Time}) + \beta_2 (\text{FAge} + \text{Time})^2 + \varepsilon$$

$$= \beta_0 + b_{i0} + (\beta_1 + b_{i1})FAge + (\beta_1 + b_{i1})Time + \beta_2 FAge^2 + 2\beta_2 FAge \times Time + \beta_2 Time^2 + \varepsilon.$$

The model involving first age and time is:

$$y = \beta_0 + b_{i0} + \beta_1 FAge + (\beta_2 + b_{i1}) Time + \beta_3 FAge^2 + \beta_4 Time^2 + \beta_5 FAge \times Time + \varepsilon. \tag{8}$$

These models are again not nested but may be compared using AIC or BIC.

Note: As illustrated in the motivating example, all the models described above may contain additional explanatory variables without compromising our discussion (unless the other factors have interaction terms with the Age, FAge, or Time terms). It is likely that that in some cases the Age/FAge/Time terms may lose their significance after the addition of additional explanatory variables. However, it is likely that the change in significance will be similar in the FAge&Time model and the Age model.

3. Examples

All the examples presented in this paper use data from the Baltimore Longitudinal Study on Aging (BLSA) to illustrate various points using variables that, in some cases, are restricted to certain age ranges of the participants.

Example 1.

Consider the body weights of the 43 women in the BLSA over 70 years old who had at most 3 visits. The resulting data contains 103 observations with a mean of 2.4 repeated observations per subject shown in Figure 2. Note that a data set containing only participants with at most 3 visits was selected so that most of the subjects exhibit similar longitudinal patterns of change that appear to be linear and hence models (1) and (2) from Scenario 2.1 will be fit to this data. Also participants with at most 3 visits require a model with only a single random effect in order to provide a satisfactory description of the data. Models with additional random effects for age or time were also fit but the additional random effect was not necessary to describe this data. Table 1 compares the results of the fit of the models from Scenario 2.1 to this data. The t-statistic testing the equality of the first age and time coefficients is statistically significant at the 5% level, and both the AIC and BIC suggest that the FAge&Time model (2) is more appropriate. Figure 1 also gives the plot of the fitted models (1) and (2) which clearly shows the differences between the models as well as the selection bias present in the data. Note that women beginning the study at older ages have lower predicted body weights than the body weights for women who attained the same age while beginning the study at a younger age. Note also that the Time coefficient is not statistically significant in the FAge&Time model. If this term were removed from the model, the reduced model would suggest that there are cross-sectional differences in body weight with age but no longitudinal changes over the short follow-up time in this data set.

Also, note that the estimated random effects for the Age model (1) given in the right panel of Figure 2 show a clear downward trend with age. This suggests that the Age model has a deterministic component that has not been accounted for in the model. In contrast, the estimated random effects for the FAge&Time model (2) (left panel, Figure 2) appear to be randomly scattered with no correlation.

Table 1: Parameter estimates (p-value) and comparisons between models from Scenario 2.1 for Example 1. $\hat{\sigma}^2$ is the estimate of the error variance while $\hat{\sigma}_I^2$ is the between subjects estimate of the variance of b_{i0} .

Age Model (1)	FAge&Time Model (2)
$\hat{\beta}_A = -0.2418$ (0.0213)	$\hat{\beta}_F = -0.9285$ (0.0033)
	$\hat{\beta}_T = -0.1698$ (0.1160)
$\hat{\sigma}^2 = 9.2822$	$\hat{\sigma}^2 = 9.1879$
$\hat{\sigma}_I^2 = 81.7874$	$\hat{\sigma}_I^2 = 72.4302$
	$H_0: \beta_F = \beta_T$ $t = -2.43$, p-value = 0.0182
-2 lnL = 654.1	-2 lnL = 648.5
AIC = 662.1	AIC = 658.5
BIC = 669.2	BIC = 667.3

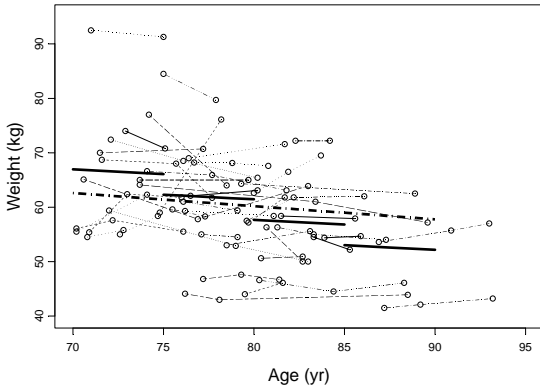


Figure 1: Observed (thin lines) and modeled body weights of women with first age at least 70 years old and at most 3 repeated measurements. The thick dash-dot line is from the Age model (1) and the thick solid lines are from the FAge&Time model (2).

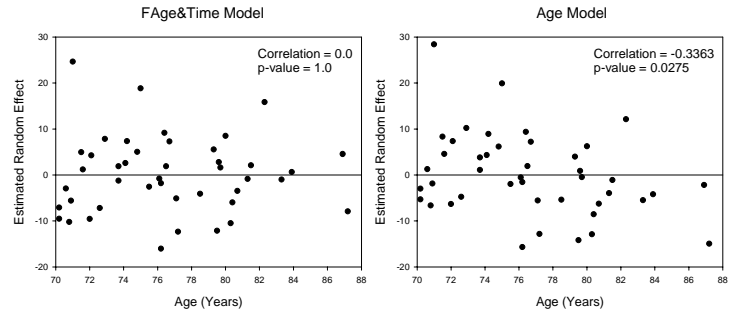


Figure 2: Plots of estimated random effects vs. age for models (1) and (2) in Example 1.

Example 2:

This example considers the cholesterol levels of 202 male participants over the age of 60 who had between 2 and 4 visits resulting in 616 observations and 3.0 observations per participant. The models (3) and (4) presented in Scenario 2.2 with an additional random effect for age or time are fit to this data. Table 2 gives a summary of the two models and Figure 3 plots the observed cholesterol levels as well as the fitted models. For this data, the plots of the fitted models in Figure 3 indicate that there again appears to be a selection bias and that the longitudinal and cross-sectional changes are not the same. In addition, both the AIC and BIC prefer the FAge&Time model to the Age model. In the FAge&Time model, the FAge term is not statistically significant and could be eliminated from the model. In this case, the data would suggest that there are no cross-sectional differences in cholesterol but that there are longitudinal declines.

Again the estimated random effects from the FAge&Time model (two left panels of Figure 4) exhibit no association with age and a constant variability with age while the estimated random effects from the Age model (two right panels of Figure 4) exhibit significant associations with age and they also exhibit decreasing variability.

Table 2: Parameter estimates (p-value) and comparisons between models from Scenario 2.2 for Example 2. $\hat{\sigma}^2$ is the estimate of the error variance, $\hat{\sigma}_I^2$ is the between subjects estimate of the variance of b_{I0} , and $\hat{\sigma}_A^2$ and $\hat{\sigma}_T^2$ estimate the between subjects variance of b_{I1} for models (3) and (4), respectively.

Age Model (3)	FAge&Time Model (4)
$\hat{\beta}_A = -1.4814 (<0.0001)$	$\hat{\beta}_F = -0.6150 (0.0714)$
	$\hat{\beta}_T = -2.6613 (<0.0001)$
$\hat{\sigma}^2 = 470.84$	$\hat{\sigma}^2 = 455.83$
$\hat{\sigma}_I^2 = 13260$	$\hat{\sigma}_I^2 = 1204.75$
$\hat{\sigma}_A^2 = 1.7972$	$\hat{\sigma}_T^2 = 2.7582$
$-2 \ln L = 5971.2$	$-2 \ln L = 5957.5$
AIC = 5983.2	AIC = 5971.5
BIC = 6003.0	BIC = 5994.6

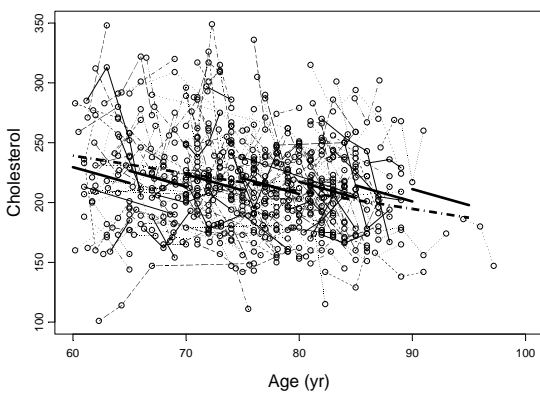


Figure 3: Observed (thin lines) and modeled cholesterol levels of men with first age at least 60 years old with 2 to 4 repeated measurements. The thick dash-dot line is from the Age model (3) and the thick solid lines are from the FAge&Time model (4).

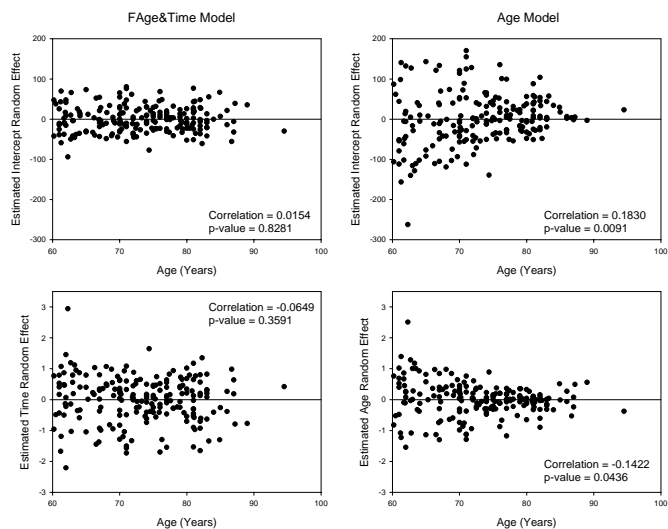


Figure 4: Plots of estimated random effects vs. age for models (3) and (4) in Example 2.

Example 3:

This example again considers the weight of BLSA women volunteers. In this case we use data from participants who had exactly 2 visits, thus making the inclusion of a random age or time term unnecessary. This data set consists of 198 women. Here, we include a random intercept as well as the fixed components given in the models in Scenario 2.3 with an additional Age^2 term in model (5) or additional $FAge^2$, $Time^2$, and $FAge \times Time$ terms in model (6).

While there is not much follow-up time and it is not anticipated that the fixed-effects $Time^2$ term will be significant, it is retained in the model to make the FAge&Time model comparable with the Age model. The results of the analysis are provided in Table 3, below, as well as in Figure 5. As expected, the $Time^2$ coefficient in model (6) is not statistically significant but the $FAge^2$ and $FAge \times Time$ coefficients are significant while the Age^2 coefficient in model (5) is statistically significant. The test of the contrast of the parameters and both the AIC and BIC clearly indicate a preference for the FAge&Time model over the Age model.

As before, the plot of the estimated random intercepts in Figure 6 from the Age model (right panel) shows a significant association with age. This again suggests that the model has a deterministic component that has not been accounted for in the Age model.

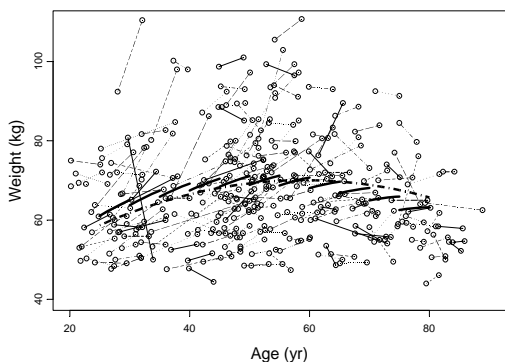


Figure 5: Observed (thin lines) and modeled body weight of women with 2 repeated measurements. The thick dash-dot line is from the Age model (5) and the thick solid lines are from the FAge&Time model (6).

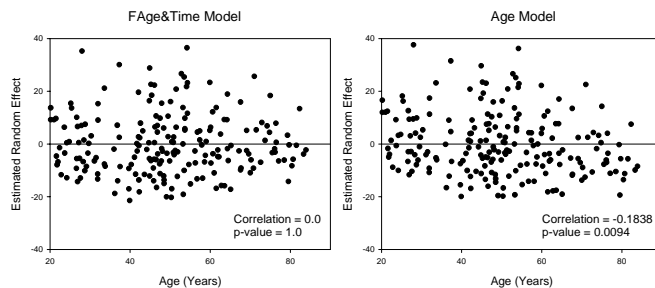


Figure 6: Plots of estimated random effects vs. age for models (5) and (6) in Example 3.

Table 3: Parameter estimates (p-value) and comparisons between models from Scenario 2.3 for Example 3.

Age Model (5)	FAge & Time Model (6)
$\hat{\beta}_A = 1.1570$ (<0.0001)	$\hat{\beta}_F = 1.1565$ (0.0002)
$\hat{\beta}_{A^2} = -0.0098$ (<0.0001)	$\hat{\beta}_T = 1.2394$ (0.0001)
	$\hat{\beta}_{F^2} = -0.01127$ (0.0002)
	$\hat{\beta}_{T^2} = -0.02181$ (0.3041)
	$\hat{\beta}_{F \times T} = -0.01329$ (0.0072)
$\hat{\sigma}^2 = 15.9065$	$\hat{\sigma}^2 = 14.6797$
$\hat{\sigma}_I^2 = 145.01$	$\hat{\sigma}_I^2 = 140.08$
	$H_0: \beta_F = \beta_T$ & $\beta_{F \times F} = \beta_{T \times T} = \frac{1}{2}\beta_{F \times T}$ F = 8.03, p < 0.0001
-2 lnL = 2819.0	-2 lnL = 2795.7
AIC = 2829.0	AIC = 2811.7
BIC = 2845.5	BIC = 2838.0

Example 4:

As a part of the testing performed in the BLSA related to body composition and fitness, a treadmill test is performed on the participants (Fleg et al., 2005). One variable measured during this test is the maximum systolic blood pressure (MaxSBP) attained during the test. In this example, we use data from 274 women over 40 years old who have at most 5 measurements of MaxSBP. The data set contains 744 observations resulting in 2.72 observations per participant. We fit the models (7) and (8) in Scenario 2.4 to this data (see Table 4). For this data the fitted lines for both models (Figure 7) appear to be almost indistinguishable and there appears to be no selection bias. The AIC prefers the FAge&Time model while the BIC prefers the Age model. In the FAge&Time model, the FAge² term is not statistically significant and could be eliminated from the model resulting in a more parsimonious description of the data. The estimated random effects (Figure 8) are not significantly associated with age for either model suggesting that, in this case, either model provides a good description of the data.

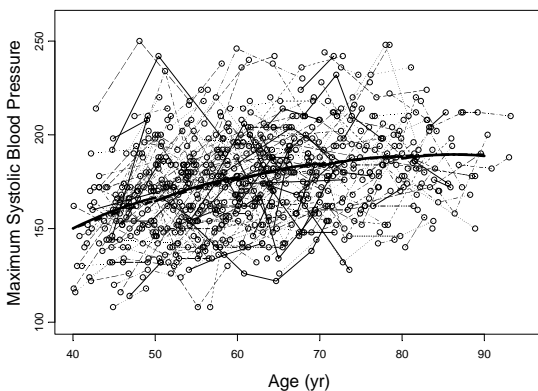


Figure 7: Observed (thin lines) and modeled maximum systolic blood pressure of women over 40 years of age with at most 5 repeated measurements. The thick dash-dot line is from the Age model (7) and the thick solid lines are from the FAge&Time model (8).

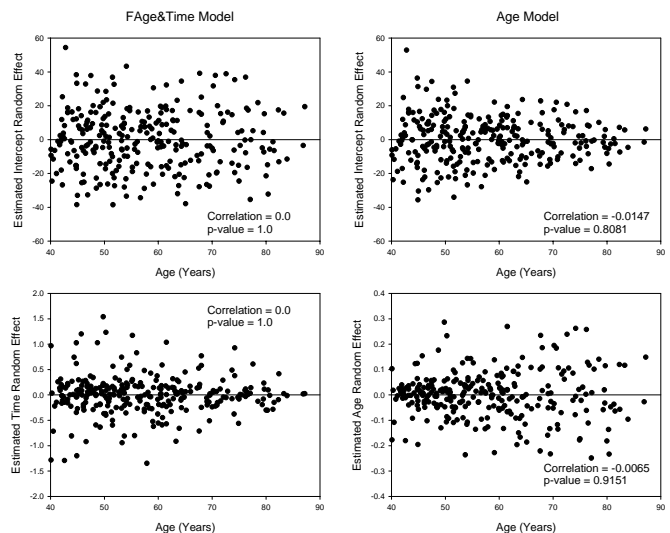


Figure 8: Plots of estimated random effects vs. age for models (7) and (8) in Example 4.

Table 4: Parameter estimates (p-value) and comparisons between models from Scenario 2.4 for Example 4.

Age Model (7)	FAge & Time Model (8)
$\hat{\beta}_A = 3.1002 (<0.0001)$	$\hat{\beta}_F = 3.0133 (0.0100)$
$\hat{\beta}_{A^2} = -0.01780 (0.0019)$	$\hat{\beta}_T = 3.6822 (<0.0001)$
	$\hat{\beta}_{F^2} = -0.01734 (0.0688)$
	$\hat{\beta}_{T^2} = -0.05472 (0.0287)$
	$\hat{\beta}_{F \times T} = -0.03738 (0.0118)$
$\hat{\sigma}^2 = 207.69$	$\hat{\sigma}^2 = 187.77$
$\hat{\sigma}_I^2 = 525.26$	$\hat{\sigma}_I^2 = 377.96$
$\hat{\sigma}_A^2 = 0.09078$	$\hat{\sigma}_T^2 = 0.9543$
$-2 \ln L = 6570.6$	$-2 \ln L = 6559.7$
AIC = 6584.6	AIC = 6579.7
BIC = 6609.9	BIC = 6615.8

4. Conclusions

In this paper we have examined the implications of modeling the longitudinal and cross-sectional components in a linear mixed-effects model using either Age or FAge&Time terms. We have presented models for the two cases and shown how to compare models fit in both ways. The examples presented show that the FAge&Time approach is more flexible and in many cases will provide a better description of the data than using only Age terms. As we have seen, in a longitudinal study of normal healthy individuals, individuals who enter the study at older ages often have more favorable covariate values (e.g. less obese, lower cholesterol, etc.) than persons of the same age who began the study at an earlier age. While using only terms involving Age yields predicted curves that are continuous, they are not adequate in accurately describing the real longitudinal and cross-sectional differences that are usually present in observational studies with longitudinal measurements.

Acknowledgements

This research was supported (in part) by the Intramural Research Program of the NIH, National Institute on Aging.

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