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Final Project on Longitudinal Data with Cholesterol Levels

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Amsterdam Growth and Health Longitudinal Study: Regression Analysis of Cholesterol Levels over Time

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1 Introduction and Data Exploration

In 1974, a study began on the growth and health of boys and girls entering secondary school, known as the Amsterdam Growth and Health Longitudinal Study (AGAHLS). The AGAHLS's goal was to monitor how different factors in lifestyle and health affected the cholesterol levels in adolescence and young adulthood. The study lasted for 32 years, with 350 subjects continuing from the initial study; of these, only 147 subjects had no missing observations. During the study, different factors that were believed to possibly have an effect on cholesterol levels were measured at 6 different time points. A sample of a subject and the data measured is shown in Table 1.

Table 1. Sample data for one subject.

ID	Cholesterol	Fitness	Body Fat	Smoking	Gender	Time
100	5.60	2.07	2.12	N	M	1
100	4.90	2.07	2.03	N	M	2
100	4.60	2.07	2.22	N	M	3
100	4.40	2.07	2.23	N	M	4
100	5.18	2.07	2.70	N	M	5
100	6.51	2.07	3.69	N	M	6

Each subject had a unique ID and the total cholesterol level, measured in millimoles per liter (mmol/l), was the main variable of interest. Other covariates, also known as predictors, considered and measured in this study include body fat (measured with an estimated sum of thickness of skin folds), baseline fitness level (measured as maximal oxygen uptake on a treadmill, measured only at the beginning of the study), gender (male or female), smoking behavior (yes or no), and measurement times (coded as 1 to 6).

1.1 Data Exploration

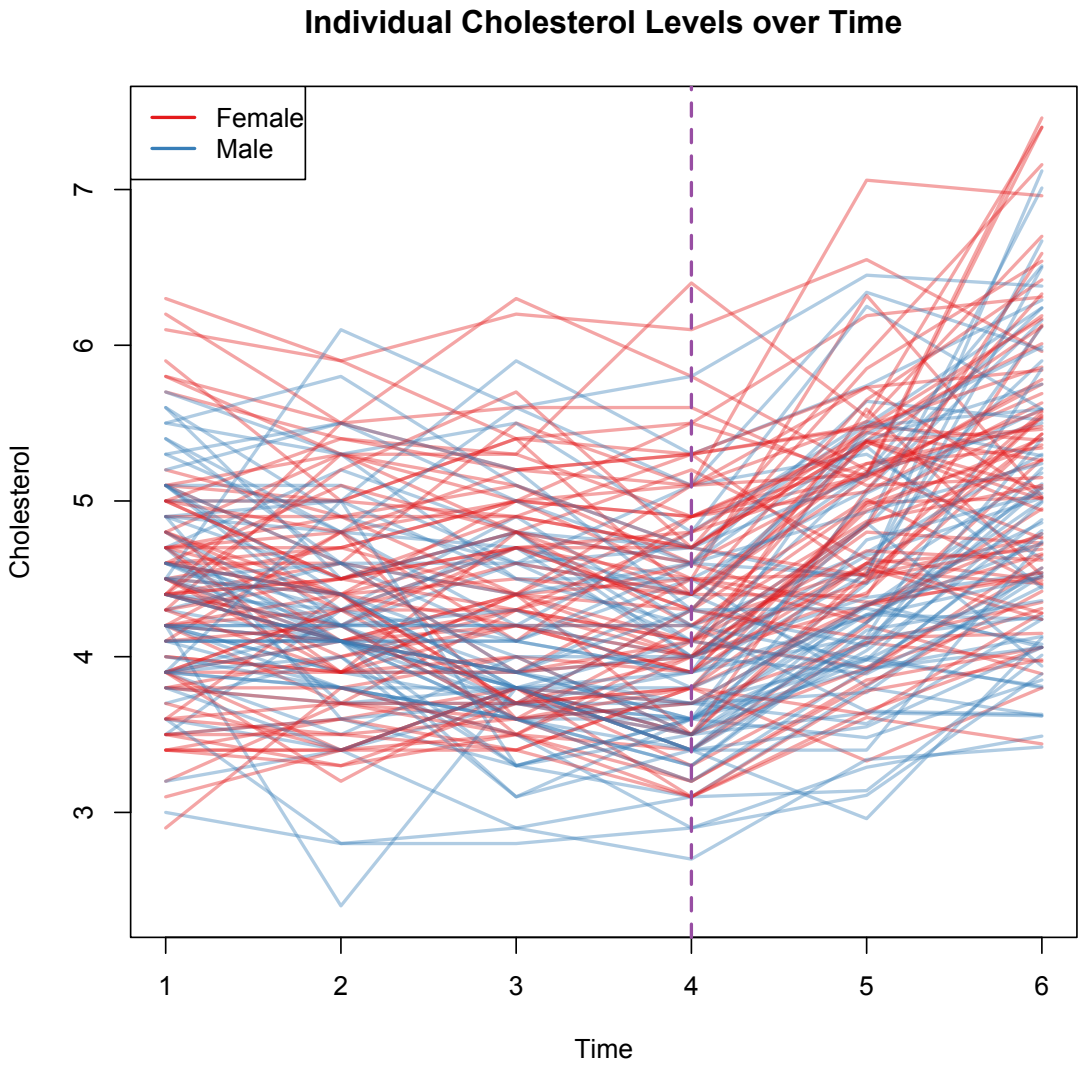

Figure 1. Cholesterol levels over time (per subject).

Due to the nature of the study, we assume that the measurement times are evenly spaced. When considering what models to fit, plotting the data can provide a better understanding of patterns in the data. Figures 1 and 2 visualize the changes in subjects' cholesterol over time.

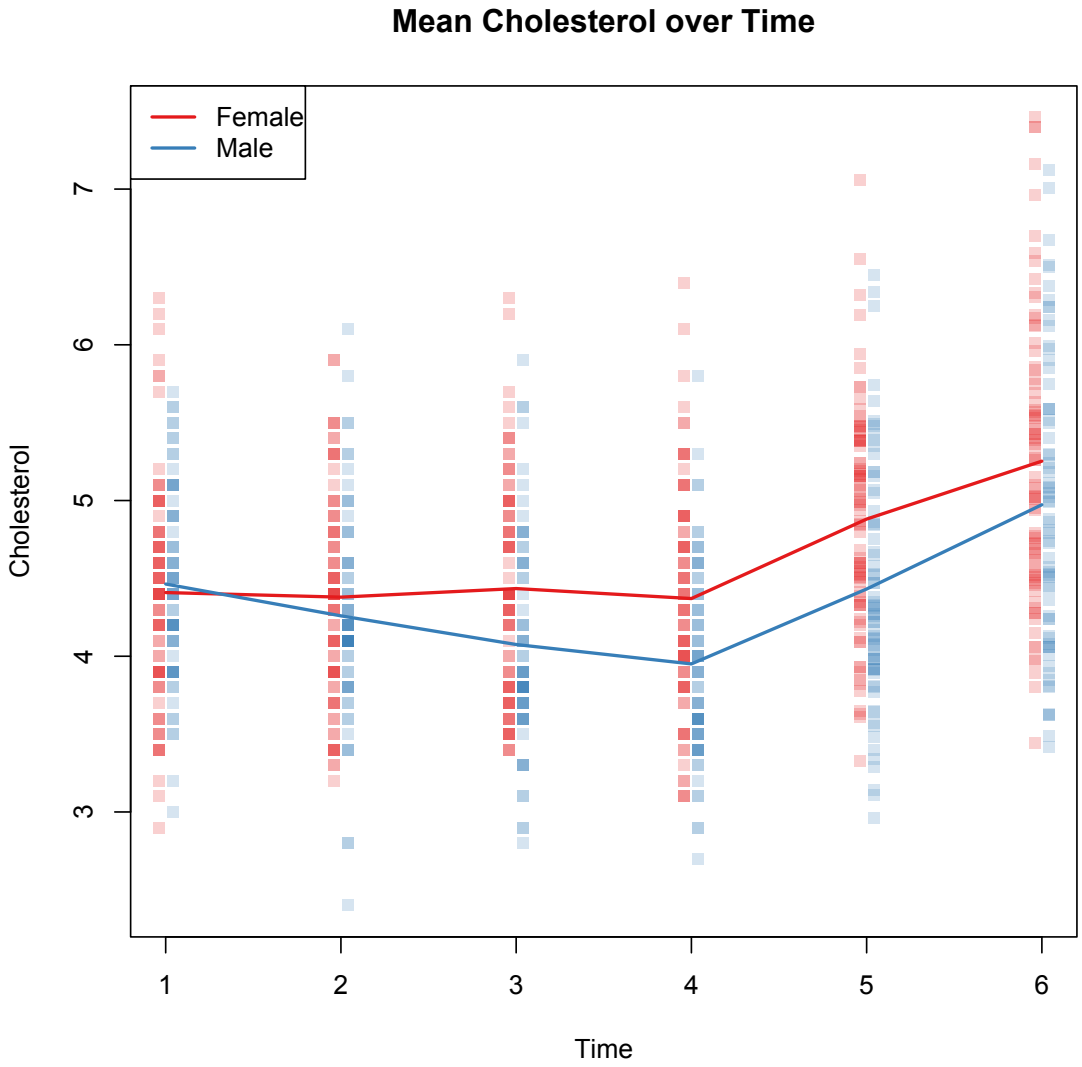

Figure 2. Cholesterol levels over time (averaged across subjects).

In Figure 1, we see that overall, cholesterol levels tend to decrease prior to time 4. After time 4, there is a general pattern of increasing trends. In Figure 2, we can more clearly observe the trends in cholesterol levels by gender, noting again that a change point seems to exist at time 4.

An examination of the data points in Figure 2 suggest another pattern in the data: the variability of the data appears to change over time. In order to more thoroughly examine

this pattern, we observed how much the cholesterol levels vary at each time by obtaining the sample variance at each time point. In Table 2, the variances are shown for each time point, and we can observe an overall increasing trend in variances, especially after time 4.

Table 2. Variances of cholesterol levels over time.

Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
0.454	0.443	0.499	0.493	0.612	0.853

2 Fixed Effects Model Selection

In a regression model setting involving multiple predictor variables, model selection addresses the question of which variable effects should be included in the final model. If too many predictors are included relative to the sample size of the data, the model may fit the data too closely; such a model would be unlikely to predict new observations well. Conversely, if too few predictors are included, the model may no longer fit the data well, failing to capture important features in the underlying process. The model's goodness of fit must be balanced with its parsimony.

When modeling longitudinal data, an additional dimension is added to the model selection problem. As in a usual regression modeling context, predictor variables must be selected for inclusion in the model; that is, a model must be selected for the mean structure. In addition to the mean structure, longitudinal models must also consider the covariance structure. The mean structure of a model describes how, on average, the response variable changes with the predictor variables. In a longitudinal context, the covariance structure describes the relationship between repeated measures within a subject over time, as well as the variability between subjects over time. As with the mean structure, more complex covariance structures tend to achieve a better fit to the data, while simpler covariance structures require estimation of fewer parameters and are more parsimonious.

2.1 A Strategy for Model Selection

The model selection heuristic applied here is as follows: given a set of candidate models, each model within the set is fit to the data and is evaluated on the basis of a criterion function called AIC. AIC decreases with goodness of fit, but increases with number of parameters in the model, quantifying the model's balance between goodness of fit and parsimony. The model in the candidate set with the lowest AIC (i.e., the model that performs best as evaluated by AIC) is selected as the final model. For longitudinal data, the model selection process proceeds in two stages. In the initial stage, covariance structures are compared while assuming an initial guess for the mean structure (referred to as the maximal model). In the second stage, mean structures are compared using the covariance structure selected during the first stage.

While this model selection approach provides us with a method for selecting a final model, it introduces a new problem: how do we define the set of candidate models? Ideally, inclusion of models in the candidate model set should be informed by theoretical or prior empirical knowledge. We can apply such knowledge when constructing the candidate model set for selecting the covariance structure: since the data are collected over time, the structure should account for association between observations made at different times on the same subject, and it should allow for variability between subjects to change over time. There exists a set of covariance structures that satisfy these requirements and are commonly used when modeling longitudinal data. In the absence of theoretical or prior empirical justification for the mean structure, we consider a broad model set, including a model for each possible combination of predictors found in the maximal model. Models containing interaction effects without their associated main effects are excluded from the model set.

2.2 The Maximal Model

In order to proceed with model selection, we must first define the maximal model for the mean structure. The maximal model chosen for our analysis is the model including all main effects (time, baseline fitness, body fat, smoking status, and gender), all one-way interaction effects between time and other covariates, and the gender-body fat interaction. Since the data are longitudinal and the analysis is intended to examine how cholesterol levels change over time, we include time-covariate interaction effects in the maximal model. We additionally include the gender-body fat interaction effect because there is a well-established gender difference between healthy levels of body fat (Robergs and Roberts 1997).

2.3 Covariance Structure Selection

Now that the maximal model has been defined, we can proceed with covariance structure selection. We consider four potential covariance structures for our model (arranged in order of descending complexity): unstructured, Toeplitz, first-order autoregressive, and compound symmetric. Due to the increasing variability of cholesterol over time suggested by the data, we specifically consider variants of these structures allowing for this pattern of changing variances. For a simpler covariance structure which is a special case of a more complex covariance structure (i.e., Toeplitz as a special case of unstructured, autoregressive and compound symmetric as special cases of Toeplitz), we can, in addition to using AIC, perform a likelihood ratio test for goodness of fit. This test compares the simpler structure's goodness of fit to the data relative to that of the more complex structure. Comparing these results, shown in Table 3, we find that the unstructured covariance has the best AIC despite its complexity. Likewise, the goodness-of-fit tests show that autoregressive and compound symmetric structures show significant lack of fit relative to the Toeplitz structure, and the Toeplitz structure in turn shows significant lack of fit relative to the unstructured model. This suggests that the other covariance structures considered impose too much structure

and are too rigidly defined to fit the data well. Based on these results, we select the unstructured covariance structure for our model.

Table 3. Comparison of fixed-effects covariance structures.

Model	df	AIC	Nested Model	χ^2_{LR}	p-value
Unstructured	32	1404.68	-	-	-
Toeplitz	22	1445.06	Unstructured	60.38	< 0.001
AR(1)	18	1487.49	Toeplitz	50.43	< 0.001
CS	18	1480.81	Toeplitz	43.75	< 0.001

2.4 Mean Structure Selection

With the selection of the covariance structure completed, we can now proceed to the second stage and choose a mean structure for our model. As previously discussed, we define the set of candidate mean structures by including a model for each possible combination of predictors in the maximal model. This yields a set of models where the most complex model in the set is the maximal model and the least complex model in the set is the intercept-only model excluding all predictors. Fitting each of these models, we find that the following mean structure has the best AIC:

$$\begin{aligned} y_{ij} = \beta_1 &+ \beta_2(\text{time}) + \beta_3(\text{body fat}) + \beta_4(\text{smoking}) + \beta_5(\text{gender}) \\ &+ \beta_6(\text{time} \cdot \text{body fat}) + \beta_7(\text{time} \cdot \text{smoking}) \\ &+ \beta_8(\text{time} \cdot \text{gender}) + \beta_9(\text{body fat} \cdot \text{gender}) + \varepsilon_{ij} \end{aligned} \tag{2.1}$$

This model includes all terms found in the maximal model except for the fitness main effect and fitness-time interaction effect. Since fitness is a baseline variable measured only once at the start of the study, its ability to provide information relevant to a participant's cholesterol level at later measurement times is limited. Given that the stated study goals do not specifically involve examining the effect of baseline fitness on cholesterol level, we drop these terms from the model and choose (2.1) as our mean structure.

2.5 Improving the Mean Structure

Having selected the unstructured covariance structure and the set of predictors for the mean structure, we now turn our attention to refining and improving the mean structure. During the preliminary data exploration, we noted a distinctive pattern in cholesterol level trends over time: prior to the fourth measurement event, mean cholesterol levels appear to be constant or slightly decreasing with time, while after the fourth measurement event, mean cholesterol levels appear to be increasing with time. To capture this pattern in our model, we introduce a set of terms called spline terms for the time variable into the model. The spline time main effect, denoted as time*, is constructed by creating a new variable from the time variable. This new variable will have a value of zero at time points before the fourth measurement event; for subsequent time points, it will equal the distance in time from the fourth measurement. For example, consider Observation A, occurring at time = 3 and Observation B, occurring at time = 5. For Observation A, time < 4, so time$^* = 0$. For Observation B, time > 4, so time* = time$-4 = 5-4 = 1$. In addition to this main effect, we also introduce interaction effects between the spline time term and the body fat, smoking, and gender covariates. Under the mean structure as described by (2.1), the cholesterol rate of change (given that other covariates are fixed) is assumed to be constant with respect to time. By introducing spline terms to the model, we allow for distinct cholesterol rates of change before and after the fourth measurement event.

Table 4. Comparison of fixed-effects linear and spline models.

Model	df	AIC	χ^2_{LR}	p-value
Spline	34	1225.78	-	-
Linear	30	1348.27	130.50	< 0.001

Comparing the two models (shown in Table 4), we find that the spline model has the best AIC. Additionally, since the original model is a special case of the spline model, we can use a likelihood ratio test of the original model's goodness of fit relative to the spline model, finding a significant lack of fit in the original model. Therefore, we select the following mean structure for the final fixed-effects model:

$$\begin{aligned} y_{ij} = {} & \beta_1 + \beta_2(\text{time}) + \beta_3(\text{time}^*) + \beta_4(\text{body fat}) + \beta_5(\text{smoking}) + \beta_6(\text{gender}) \\ & + \beta_7(\text{time} \cdot \text{body fat}) + \beta_8(\text{time}^* \cdot \text{body fat}) + \beta_9(\text{time} \cdot \text{smoking}) \\ & + \beta_{10}(\text{time}^* \cdot \text{smoking}) + \beta_{11}(\text{time} \cdot \text{gender}) + \beta_{12}(\text{time}^* \cdot \text{gender}) \\ & + \beta_{13}(\text{body fat} \cdot \text{gender}) + \varepsilon_{ij} \end{aligned} \tag{2.2}$$

2.6 Model Checking and Residual Analysis

As in a typical regression context, our model makes certain assumptions; if these assumptions are violated, our analysis will not be valid. We use residual analysis in order to validate our modeling assumptions. For a non-longitudinal model, the residuals (that is, the difference between the observed value of the response variable and the fitted value under the model) should be normally distributed around zero, and scatterplots of residuals against covariates and residuals against fitted values should show no pattern. Due to the covariance structure required to model longitudinal data, we cannot directly use the residuals from our model. Instead, we transform the residuals in a way that takes this covariance structure into account. With the transformed residuals, we can then proceed with residual analysis as usual. Residual diagnostic plots are shown in Figure 3.

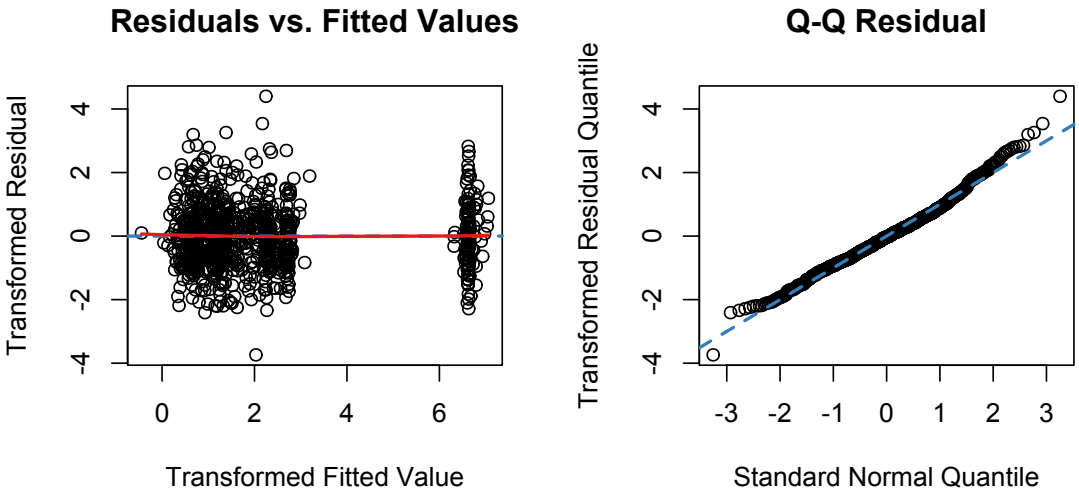

Figure 3. Transformed residuals plotted against transformed fitted values (left) and Q-Q plot of transformed residuals (right).

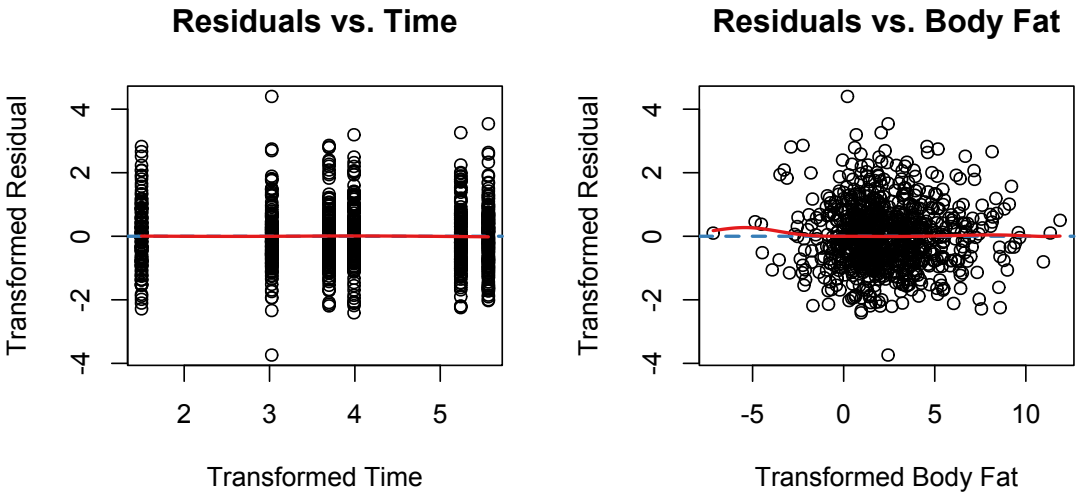

Figure 4. Transformed residuals plotted against transformed time (left) and body fat (right).

The Q-Q plot in Figure 3 visually compares the observed distribution of the residuals

to a standard normal distribution. If the residuals are normally distributed, the points should follow the diagonal line. In this case, we see that the points approximately follow the line, suggesting that our assumption of normality holds. The results of the residual vs. fitted value scatterplot shown in Figure 3 and the residual vs. covariate scatterplots shown in Figure 4 show that the residuals are distributed around zero with no apparent pattern, indicating that the assumptions made by our mean and covariance structures are not violated. Note that the horizontal clustering pattern of residuals does not indicate an issue with the modeling assumptions, while a vertical pattern of clustering would. Overall, the residual diagnostic plots suggest that the modeling assumptions made by Model (2) hold.

3 Mixed Effects Model Selection

An alternative approach to modeling correlated data is to consider a mixed-effects model framework. In a mixed-effects model, we allow there to be both fixed population coefficients as well as random, zero-mean coefficients that are specific to each subject. This amounts to saying that the correlation among observations on the same subject arises from these observations sharing some unobserved variables. The regression coefficient of random effects represent the effect of the explanatory variables on an individual subject, while the fixed effects coefficients still describe the effect of the explanatory variables on the population average. The ability to model subject-specific trajectories via the random effects is one of the key benefits of using mixed-effects models as opposed to fixed effects models. Another key benefit to using mixed-effects models is that it gives us a straightforward, parsimonious way to estimate the within-subject covariance when we include a random effect on time.

3.1 Introducing Random Effects

Now that we have established the benefits of using mixed-effects models, we must still determine which random effects to use in analyzing our data. The approach we have used in our random-effects model selection is similar to that of our fixed-effects model selection process. Given the model we have selected using fixed effects, we consider a set of three models that only differ in which random effects are included. These three models are the intercept-only random-effects model, the intercept and time random-effects model, and the intercept, time, and spline-time random-effects model. Each of these models is fit with the assumption that all correlation in the data is within-subject correlation, and we allow for an unstructured covariance structure on the random effects at first. The results of this comparison are displayed in Table 3. We can see that of the three, the model that adds an intercept, time, and spline-time random effect yields the smallest AIC, and so we conclude that this model fits the best of the three.

Table 5. Comparison of random effects.

Model	df	AIC
Intercept	20	1219.35
Int. + Time	22	1217.78
Int. + Time + Spline	25	1213.20

Now that we have chosen the appropriate random effects, we should compare the performance of different within-subject covariance structures. The three covariance structures we choose to evaluate are unstructured, compound symmetric, and diagonal. Unlike the unstructured and compound symmetric covariance structures previously discussed, the diagonal covariance structure assumes that there is no correlation between the random effects. The results in Table 4 show that the model using the unstructured covariance structure yields the smallest AIC.

Table 6. Comparison of random-effects covariance structures.

	Diagonal	Unstructured	Compound Symmetric
AIC	1213.299	1213.199	1387.446

Therefore, the final mixed-effects model has an unstructured random-effects covariance structure and the following mean structure, where each b_{1i}, b_{2i}, and b_{3i} are all random coefficients that are normally distributed with mean zero.

$$\begin{aligned} y_{ij} = {} & \beta_1 + \beta_2(\text{time}) + \beta_3(\text{time}^*) + \beta_4(\text{body fat}) + \beta_5(\text{smoking}) + \beta_6(\text{gender}) \\ & + \beta_7(\text{time} \cdot \text{body fat}) + \beta_8(\text{time}^* \cdot \text{body fat}) + \beta_9(\text{time} \cdot \text{smoking}) \\ & + \beta_{10}(\text{time}^* \cdot \text{smoking}) + \beta_{11}(\text{time} \cdot \text{gender}) + \beta_{12}(\text{time}^* \cdot \text{gender}) \\ & + \beta_{13}(\text{body fat} \cdot \text{gender}) + b_{1i} + b_{2i}(\text{time}) + b_{3i}(\text{time}^*) + \varepsilon_{ij} \end{aligned} \tag{3.1}$$

3.2 Model Checking and Residual Analysis

For the mixed-effects model, we proceed with our residual analysis in the same fashion as we did for the fixed-effects model. The Q-Q plot in Figure 5 shows that the points approximately follow the diagonal line and so the normality assumption holds. The residual plots in Figures 5 and 6 are troublesome, however.

If we look specifically at the transformed residuals vs. transformed fitted values plot, we can see that the trend is no longer a horizontal line at 0 and, more strikingly, the variation in the two clusters are quite different. What this pattern indicates is that both the mean and variance structure are not being captured well by this model. The plot of transformed residuals vs. time in Figure 6 indicates that the variation in residuals changes with respect to time, a clear indication that the covariance structure is being misspecified by this model.

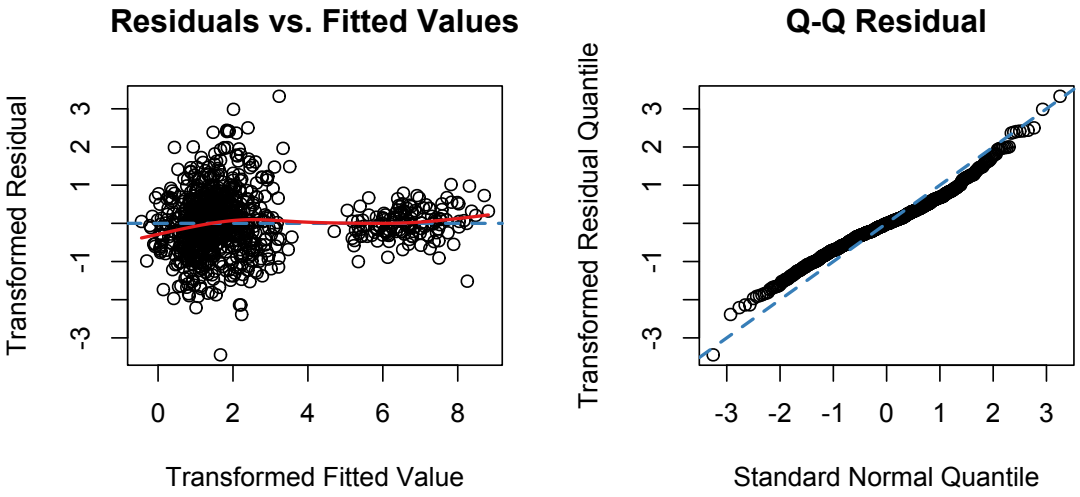

Figure 5. Transformed residuals plotted against transformed fitted values (left) and Q-Q plot of transformed residuals (right).

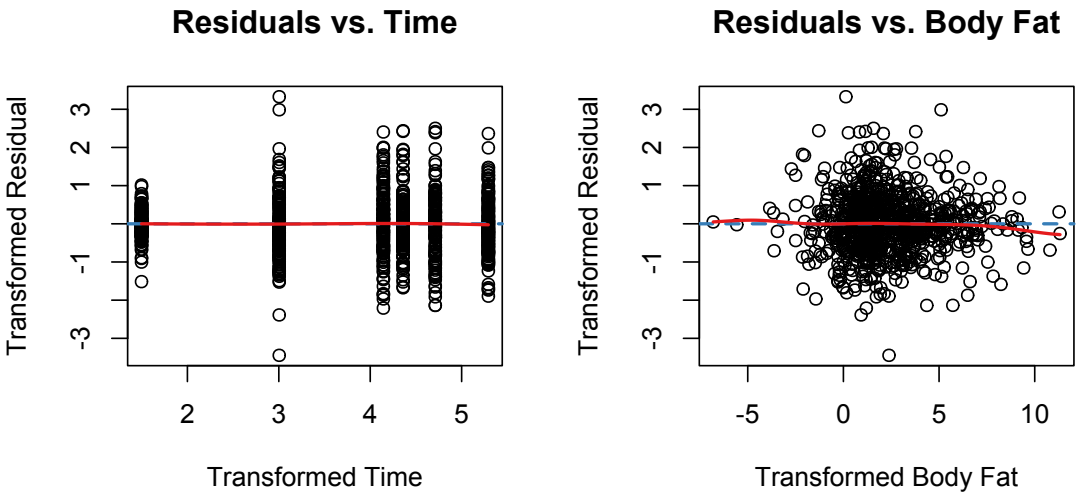

Figure 6. Transformed residuals plotted against transformed time (left) and body fat (right).

4 Final Model

While the fixed-effects and mixed-effects models are comparable in terms of AIC, the residual diagnostics for the mixed-effects model suggest that the mean and covariance structures may be misspecified. Notably, the residual plots suggest that there is too much structure imposed on the covariance. In other words, the covariance structure is too specific and inconsistent with the true pattern of covariance in the data. While we considered various other mixed-effects models, residual diagnostic results for these models showed the same pattern of unequal variances. By using the fixed-effects model described in (2.2), we allow the data to speak for itself with regard to the specification of the covariance structure. Based on this, we select the fixed-effects model as the final model for performing inference.

5 Inference

When making inference about our final model, we will be using the Wald test (analogous to the F-test in ordinary linear regression) to determine the significance of several hypotheses. In order to calculate the Wald test statistic, we must first calculate the "sandwich estimator" for the covariances of the coefficients. The purpose of using the sandwich estimator for the covariances is that it is less susceptible to bias, which leads to invalid inference. In the context of our model, bias may arise from a misspecification of the covariance structure. While we have performed a number of tests and model diagnostic procedures in the hopes of specifying the correct covariance structure, the sandwich estimate provides us with some assurance that our inferences will be valid even if the covariance structure has been misspecified.

Before we proceed to formal hypothesis testing, we should recall the fact that baseline fitness was removed from the model entirely in the model selection process. Since this covariate is not present in the model, we cannot make formal inferential statements about

its relationship to total serum cholesterol level. Therefore, in this section, we will only consider hypotheses about time, gender, smoking, and body fat.

The meaning of all hypothesis tests done in this section will be expressed in words, but the meaning of these tests can be verified in terms of the coefficients of the model by comparing the test number in Tables 7-10 to that of Tables 12-14 in Appendix A.

5.1 Time Hypotheses

Since we are dealing with repeated measurements on the same subjects over time, it seems that we should first consider the relationship between time and cholesterol level. In Table 7, we can see that time has a significant effect on cholesterol levels ($p < 0.001$). As was established earlier, there is a change point at time 4 in the model, and so it may also be interesting to investigate whether the effect of time on cholesterol level differs before and after the change point. After a formal test, it is clear that there is a significant difference between cholesterol levels before time 4 and after time 4 ($p < 0.001$).

Table 7. Time hypothesis tests.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
1	No time trend in cholesterol levels	310.61	< 0.001
2	No change in time trend of cholesterol levels at time 4	198.01	< 0.001

5.2 Gender Hypotheses

Now that it is clear that cholesterol levels are changing over time, it may be interesting to investigate the effects of gender on cholesterol levels. In Table 8, we can see that there is a relationship between gender and cholesterol levels ($p < 0.001$) and the rate of change in cholesterol levels ($p < 0.001$). We can see, however, that the difference in the rate of change of cholesterol levels by gender is only significant before time 4 ($p < 0.001$) and not after time 4 ($p = 0.26$). Since we have now established that there is a non-significant difference in cholesterol levels by gender before time 4, but a significant difference in cholesterol levels by gender after time 4, it may also be of interest to consider whether the change at

time 4 effects both genders equally. In other words, we want to test to see whether there is a significant difference in the *change* in rate of change at time 4 by gender. In Table 8, we can see that there is indeed a significant difference in the change of rate of change by gender at time 4 (p = 0.01).

Table 8. Gender hypothesis tests.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
3	No gender difference in cholesterol levels	22.54	0.002
4	No gender difference in rate of change of cholesterol	18.00	< 0.001
5	No gender difference in rate of change of cholesterol before time 4	17.00	< 0.001
6	No gender difference in shift of rate of change of cholesterol at time 4	6.04	0.014
7	No gender difference in rate of change of cholesterol after time 4	1.27	0.260

5.3 Smoking and Body Fat Hypotheses

Since we have considered the relationship between gender and cholesterol levels, it is straightforward that we would consider the relationship between smoking and cholesterol levels. In Table 9, we can see that there is no significant difference in cholesterol levels for smokers versus non-smokers. Given that we fail to reject the null hypothesis that there is no difference in cholesterol levels from smokers to non-smokers, we do not proceed to make any further smoking-related inferences and continue under the assumption that all smoking effects are non-significant.

Table 9. Smoking hypothesis test.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
8	No difference in cholesterol levels by smoking group	5.81	0.121

Finally, we should consider the relationship between body fat and cholesterol levels. We see from Table 10 that there is a significant effect of body fat on the overall cholesterol levels (p < 0.001) and the cholesterol rate of change (p < 0.007).

Table 10. Body fat hypothesis tests.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
9	No effect of body fat change on cholesterol levels	39.75	< 0.001
10	No effect of body fat on rate of change of cholesterol levels	9.80	0.007

6 Results

From our analyses in the previous section, we can see that gender, body fat, and time have a significant effect on total serum cholesterol level. Cholesterol level for men changes at a rate of -0.21 mmol/l before time 4, which is significantly different from the -0.06 mmol/l cholesterol level rate of change for women during the same time frame. After time 4, however, the cholesterol level rate of change for men increases to 0.32 mmol/l and the rate of change for women increases to 0.24 mmol/l. A point of interest here is that the change in cholesterol rate of change for men at time 4 is 0.54 mmol/l, whereas the change in rate of change for women at time 4 is 0.30 mmol/l. While the rate of change of cholesterol level for both groups increases at time 4, the increase in the cholesterol rate of change for men is significantly larger than the increase in cholesterol rate of change for women.

With respect to body fat, we see that the cholesterol level rate of change is -0.05 mmol/l before time 4. After time 4, however, the rate of change per unit increase in body fat increases to 0.28 mmol/l, which is now significantly different from 0. Thus, before time 4, an increase in body fat did not have a significant effect on the rate of change of cholesterol level. After time 4, however, we have a significant positive effect of body fat on the rate of change of cholesterol.

7 Discussion

A mixed-effects model offers an advantage over its fixed-effects equivalent because it allows for prediction on an individual level. While the mixed-effects models we considered compared favorably to the fixed-effects model in terms of AIC, the residual diagnostics

for these models suggested that the covariance structure was misspecified. Our subsequent selection of the fixed-effects model to conduct the analysis provides us with stronger assurances that the modeling assumptions hold, but to some extent limits the scope of our analysis.

In a longitudinal study, the effect of a covariate on the response variable may change over time. For example, a baseline variable may have a large effect near the baseline time, but its effect may decrease over time. The mean structure of the model we have considered includes time-covariate interaction effects, but these interaction effects assume a linear change and complicate interpretation. An alternative model, called a time-varying coefficient model, could be considered. In a time-varying coefficient model, covariate effects are modeled as functions of time, without assuming a specific functional form. Using a time-varying coefficient model for the data could improve interpretability and more flexibly model the covariates' effects; however, this approach complicates model fitting and inference.

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Appendix A: Tables

Table 11. Comparison of fixed-effects and mixed-effects models.

Model	df	AIC
Mixed Effects	25	1213.20
Fixed Effects	34	1225.78

Table 12. Time hypothesis tests.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
1	$\beta_2 = \beta_3 = \beta_7 = \ldots = \beta_{12} = 0$	310.61	< 0.001
2	$\beta_3 = \beta_8 = \beta_{10} = \beta_{12} = 0$	198.01	< 0.001

Table 13. Gender hypothesis tests.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
3	$\beta_6 = \beta_{11} = \beta_{12} = \beta_{13} = 0$	22.54	0.002
4	$\beta_{11} = \beta_{12} = 0$	18.00	< 0.001
5	$\beta_{11} = 0$	17.00	< 0.001
6	$\beta_{12} = 0$	6.04	0.014
7	$\beta_{11} + \beta_{12} = 0$	1.27	0.260

Table 14. Smoking and body fat hypothesis tests.

Test No.	Null Hypothesis	Wald (χ^2)	p-value
8	$\beta_5 = \beta_9 = \beta_{10} = 0$	5.81	0.121
9	$\beta_4 = \beta_7 = \beta_8 = \beta_{13} = 0$	39.75	< 0.001
10	$\beta_7 = \beta_8 = 0$	9.80	0.007