Two-level models for continuous outcomes

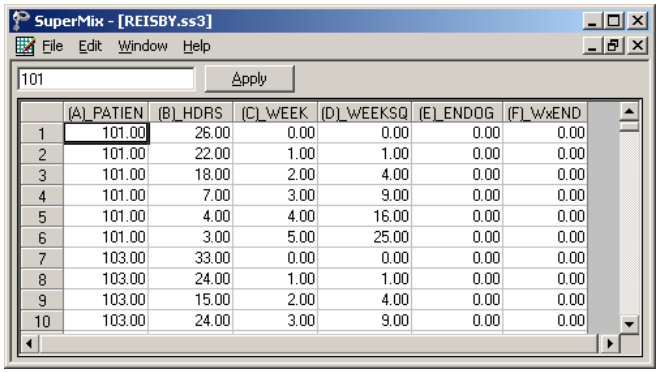
Contents

3.1 Models based on the Reisby data

3.1.1 The data

The data set is from a study described in Reisby *et. al.* (1977) that focused on the longitudinal relationship between imipramine (IMI) and desipramine (DMI) plasma levels and clinical response in 66 depressed inpatients (37 endogenous and 29 non-endogenous). Following a placebo period of 1 week, patients received 225 mg/day doses of imipramine for four weeks. In this study, subjects were rated with the Hamilton depression rating scale (HDRS) twice during the baseline placebo week (at the start and end of this week) as well as at the end of each of the four treatment weeks of the study. Plasma level measurements of both IMI and its metabolite DMI were made at the end of each week. The sex and age of each patient were recorded and a diagnosis of endogenous or non-endogenous depression was made for each patient.

Although the total number of subjects in this study was 66, the number of subjects with all measures at each of the weeks fluctuated: 61 at week 0 (start of placebo week), 63 at week 1 (end of placebo week), 65 at week 2 (end of first drug treatment week), 65 at week 3 (end of second drug treatment week), 63 at week 4 (end of third drug treatment week), and 58 at week 5 (end of fourth drug treatment week). The sample size is 375. Data for the first 10 observations of all the variables used in this section are shown below in the form of a SuperMix spreadsheet file, named **reisby.ss3**.



	(A)_PATIEN	(B)_HDRS	(C)_WEEK	(D)_WEEKSQ	(E)_ENDOG	(F)_WxEND
1	101.00	26.00	0.00	0.00	0.00	0.00
2	101.00	22.00	1.00	1.00	0.00	0.00
3	101.00	18.00	2.00	4.00	0.00	0.00
4	101.00	7.00	3.00	9.00	0.00	0.00
5	101.00	4.00	4.00	16.00	0.00	0.00
6	101.00	3.00	5.00	25.00	0.00	0.00
7	103.00	33.00	0.00	0.00	0.00	0.00
8	103.00	24.00	1.00	1.00	0.00	0.00
9	103.00	15.00	2.00	4.00	0.00	0.00
10	103.00	24.00	3.00	9.00	0.00	0.00

The variables of interest are:

- Patient is the patient ID (66 patients in total).
- HDRS is the Hamilton depression rating scale.
- WEEK represents the week (0, 1, 2, 3, 4 or 5) at which a measurement was made.
- WEEKSQ represents the squared values of WEEK.
- ENDOG is a dummy variable for the type of depression a patient was diagnosed with (1 for endogenous depression and 0 for non-endogenous depression).
- WxENDOG represents the interaction between WEEK and ENDOG, and is the product of WEEK and ENDOG.

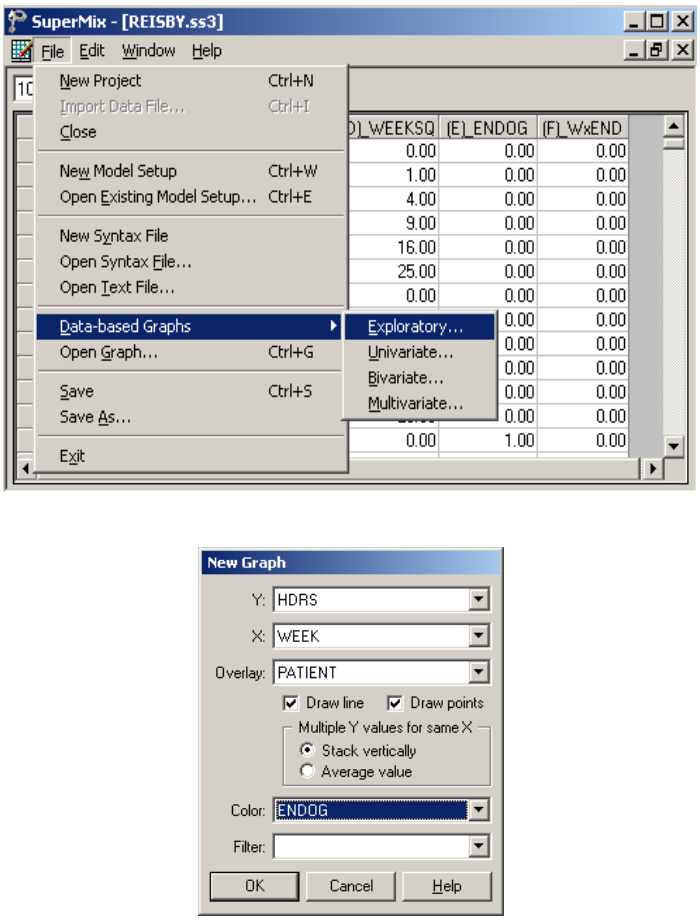
3.1.1.1 Exploring the data

Graphing the observed data

In the previous example, we have shown a number of data-based graphs. Here, we use the **Exploratory** option of the **Data-Based Graphs** menu to explore the data in the **reisby.ss3** spreadsheet, stored in the **Continuous** subfolder.

Start by opening the data file in the SuperMix spreadsheet. Then select the **Data-based Graphs**, **Exploratory** option on the **File** menu as shown below to activate the **New Graph** dialog box.

Specify HDRS as the dependent (vertical axis) variable by selecting it from the **Y** drop-down list box and WEEK as the independent (horizontal axis) variable by selecting it from the **X** drop-down list box. A graph on the same axis system is created for each patient by selecting the variable Patient from the **Overlay** drop-down list box. Furthermore, each graph is assigned a color by selecting ENDOG from the **Color** drop-down list box to produce the following **New Graph** dialog box.



Click on the **OK** button to produce the following graph of the reaction trajectories over time for the 66 inpatients.

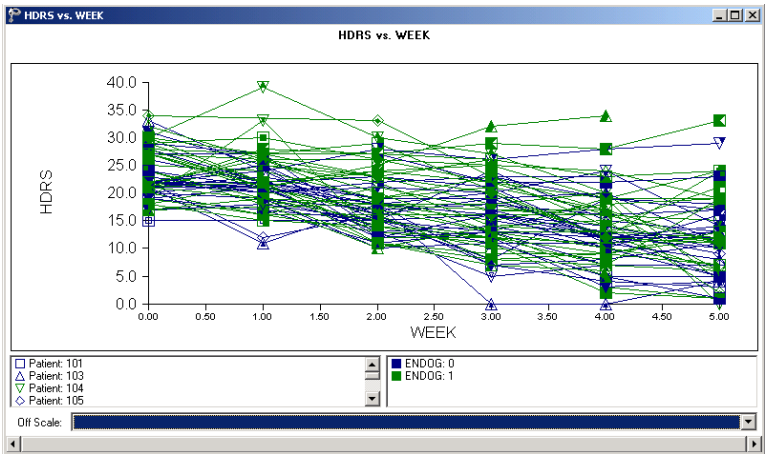
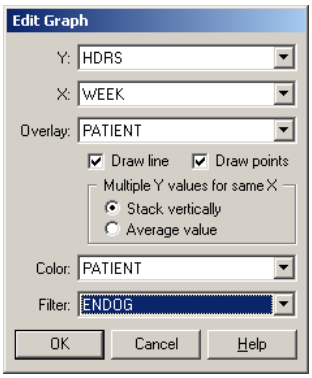


Figure 3.4: Reaction trajectories over time for 66 patients

To modify the existing graphic display, select the **Edit Graph** option from the **Settings** menu to load the **Edit Graph** dialog box. To obtain different graphs for the two categories of the

covariate ENDOG, select it from the **Filter** drop-down list box to produce the following **Edit Graph** dialog box.



Click on the **OK** button to open the following graphics window.

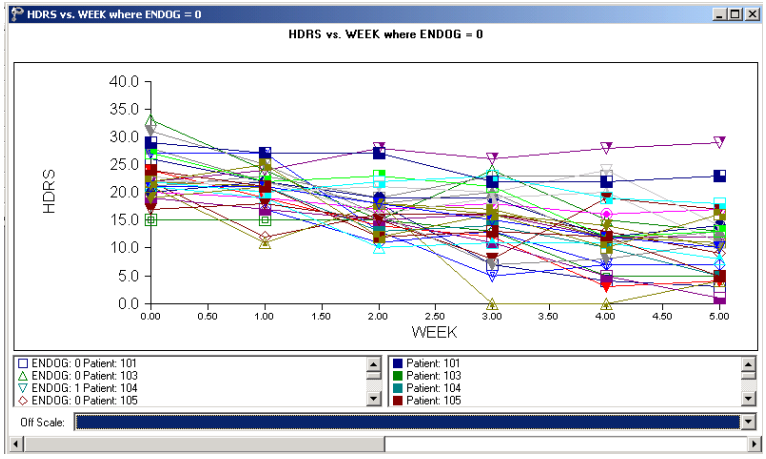


Figure 3.5: Reaction trajectories over time for patients with ENDOG=0

At the bottom of the graphics window is a "slider" with left and right arrows. By clicking on the right arrow, one can obtain the next graphic shown below and by clicking on the left arrow, the graphic above.

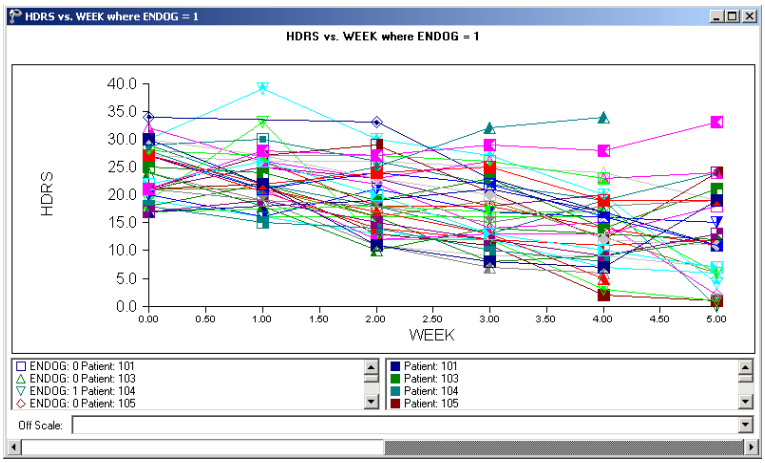


Figure 3.6: Reaction trajectories over time for patients with ENDOG=1

The above graphs show a general, approximately linear decline over time and an increase in the variability of the HDRS scores across time for both types of depression.

3.1.2 A 2-level random intercept-and-slope model

From the graphical display obtained in the previous section, it seems as if the HDRS scores follow an approximately linear trend over time, decreasing over the course of the study. It is also apparent, however, that patients not only start out at different levels but also have differences in the slopes of the HDRS against WEEK lines. In this section, we explore a model that allows patients not only to have unique intercepts, but also unique slopes across time. In other words, we allow both intercept and WEEK (slope) to vary randomly over patients. The image below demonstrates the meaning of the random slope and random intercept in a hypothetical 2-level model.

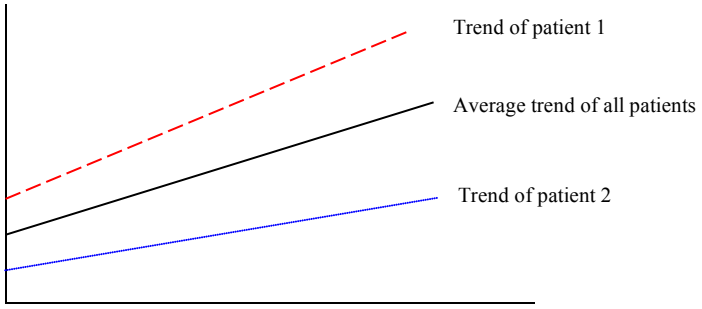


Figure 3.7: Score trends for individual patients

3.1.2.1 The model

The random intercept-and-slope model for the response variable HDRS may be expressed as

$$\text{HDRS}_{ij} = \beta_0 + \beta_1 \times (\text{WEEK})_{ij} + v_{i0} + v_{i1}(\text{WEEK})_{ij} + e_{ij}$$

We can rewrite the model in the following way.

Level-1 model:

$$\text{HDRS}_{ij} = b_{0i} + b_{1i} \times \left(\text{WEEK}\right)_{ij} + e_{ij}$$

Level-2 model:

$$b_{0i} = \beta_0 + v_{0i}$$
$$b_{1i} = \beta_1 + v_{1i}$$

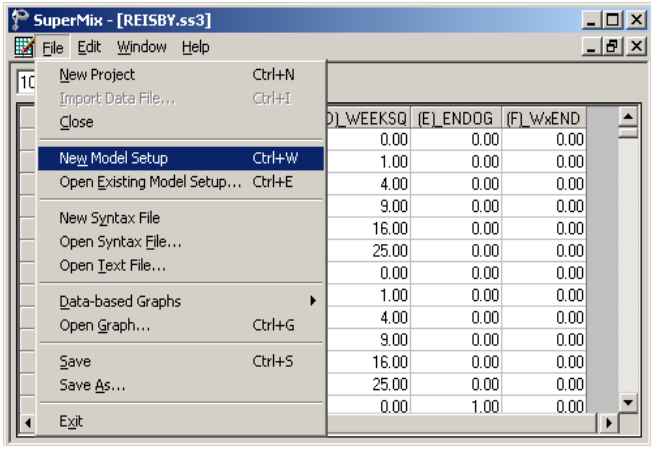
where

$$e_i : N\left(0, \sigma^2 \mathbf{I}_i\right)$$
$$\mathbf{v}_i : N\left(\mathbf{0}, \Phi_{(v)}\right)$$

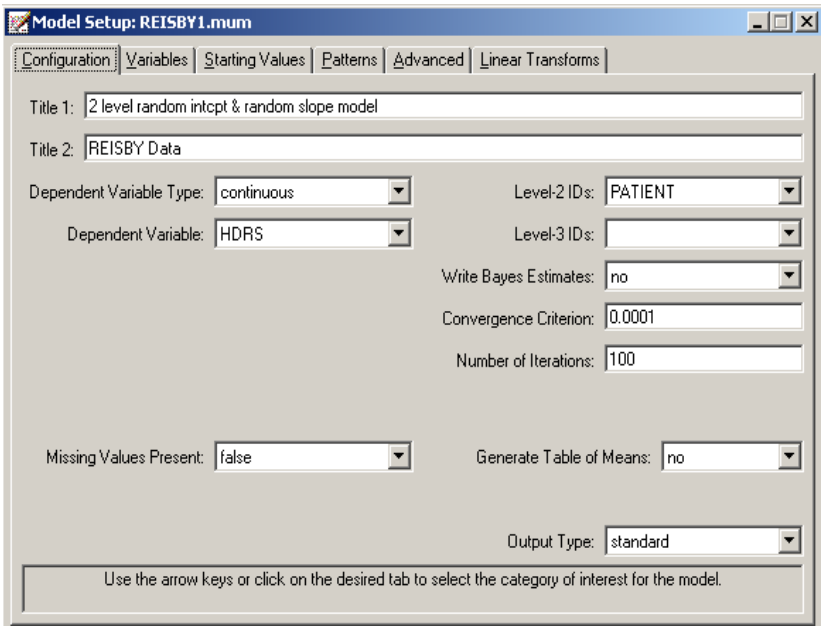
β_0 denotes the average expected depression rating scale value, β_1 denotes the coefficient of the predictor variable WEEK (slope) in the fixed part of the model, v_{1i} denotes the variation in the slopes over patients, and v_{0i} and e_{ij} denote the variation in the average expected HDRS value over patients and between patients respectively. Furthermore, i = 1,2,…,66 refers to the 66 patients; j = 1, 2, …, n_i refers to the j^{th} observation for patient i. The maximum value for n_i is 6.

3.1.2.2 Setting up the analysis

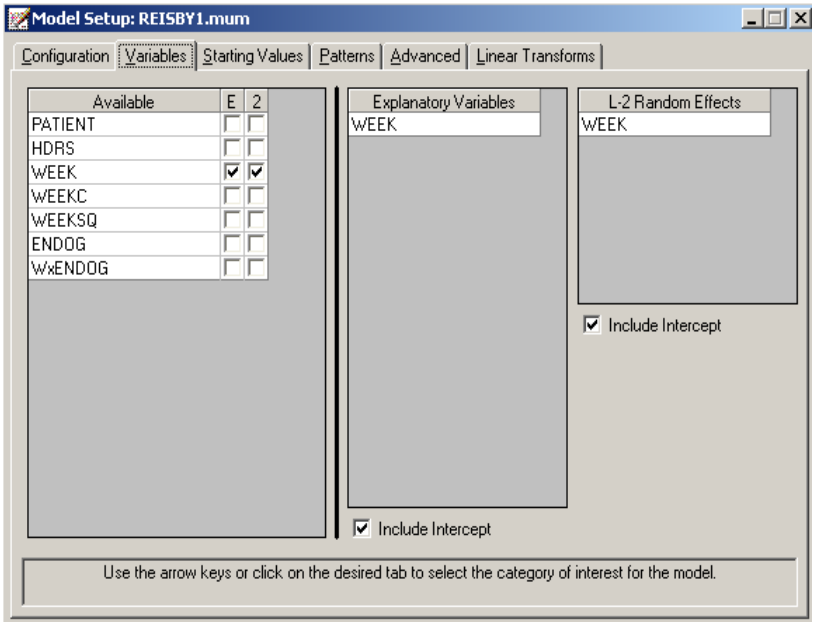
Start by opening the **reisby.ss3** file as a SuperMix spreadsheet. Next, select the **New Model Setup** option on the **File** menu as shown below to load the **Model Setup** window.



Starting with the **Configuration** screen, enter the (optional) title in the **Title 1** and **Title 2** text boxes respectively. The continuous outcome variable HDRS is selected from the **Dependent Variable** drop-down list box. The variable Patient, which defines the levels of the hierarchy, is selected as the Level-2 ID from the **Level-2 IDs** drop-down list box to produce the following **Configuration** screen.



Click the **Variables** tab to proceed to the **Variables** screen of the **Model Setup** window. The variable Week is specified as the covariate of the fixed part of the model by checking the **E** check box for WEEK in the **Available** grid. Mark the **2** check box for Week in the **Available** grid to specify the random slope at level 2 of the model. After completion, the **Variables** screen should look as shown below.

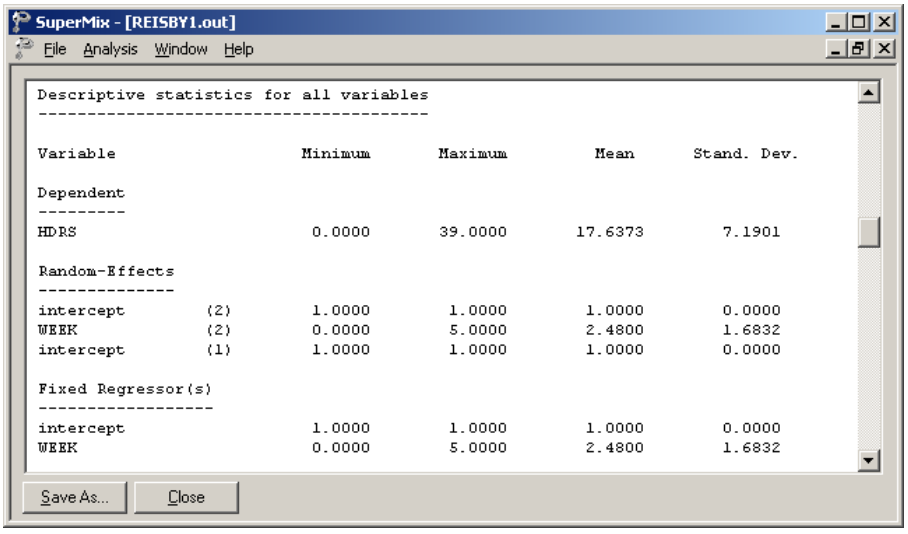


Before the analysis can be run, save the model specifications to **reisby1.mum**. Run the model to produce the output file **reisby1.out**.

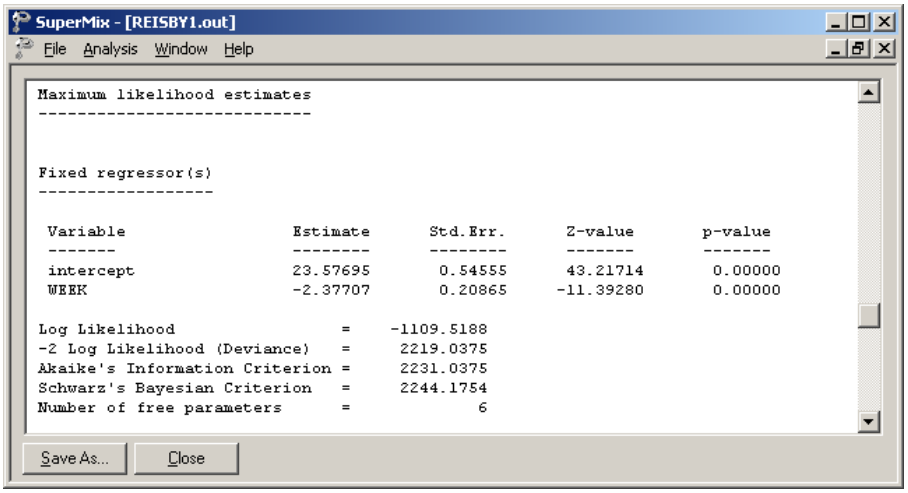
3.1.2.3 Discussion of results

Descriptive statistics

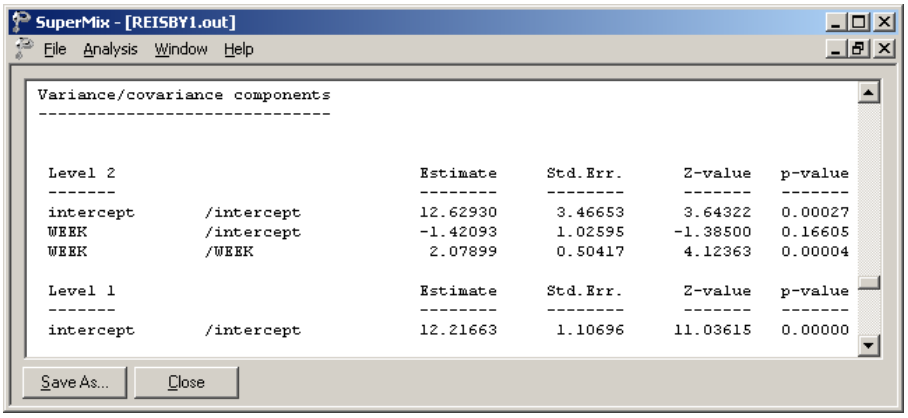
The section of the output file shown below contains the descriptive statistics for all variables in the current model specification. If all patients' data were complete, the average for the time variable WEEK would have been exactly 2.5; the value of 2.48 indicates that the number of patients with information at each time point fluctuates somewhat.



3.1.2.4 Interpreting the results



The summary of the hierarchical structure of the data shows how the 375 measurements are nested within the 66 patients. It also indicates that the number of repeated measurements per patient varies from 4 to 6 observations. The convergence is attained in 5 iterations. The output file contains the final estimates of the fixed and random coefficients included in the model, along with some goodness of fit measures as shown .



Fixed effects results

The results show a highly significant coefficient ($p < 0.00001$) for the time effect, as represented by the variable WEEK. At the beginning of the study, when WEEK = 0, the average expected HDRS score is 23.57695. For each subsequent week, a decrease of 2.37707 in average HDRS score is expected. At the end of the study period, the average expected HDRS score is 23.57695 – 5(2.37707) = 11.6916.

Random effects results

With the exception of the WEEK-intcept covariance, all variance components are highly significant, as shown in the *p*-value column. From the output above we have $\hat{\text{var}}(v_{i0})$ = 12.62930, $\hat{\text{var}}(v_{i1})$ = 2.07899, $\hat{\text{cov}}(v_{i0}, v_{i1})$ = –1.42093, and $\hat{\text{var}}(e_{ij})$ = 12.21663. Typically, one would expect most of the variation in HDRS scores at the measurement level, and thus would expect $\hat{\text{var}}(e_{ij})$ to be larger than any of the other variances/covariances. With these data, however, there is more variation in the random intercepts over patients than in the measurements nested within patients. Due to this, it may be of interest to take a closer look at the variation in HDRS scores at the two levels of the hierarchy.

Fit statistics and ICC

In the case of a model with only a random intercept, there are two variances of interest: the variation in the random intercept over the patients (the level-2 units), and the residual variation at level 1, over the measurements. By calculating the total variation in the HDRS score explained by such a model, obtained as $\hat{\text{var}}(e_{ij}) + \hat{\text{var}}(v_{i0})$, we can obtain an estimate of the intracluster correlation coefficient.

The intracluster coefficient is defined as

$$ICC = \frac{\hat{\text{var}}(v_{i0})}{\hat{\text{var}}(e_{ij}) + \hat{\text{var}}(v_{i0})}$$

and would, for a random intercept model for this data, represent the proportion of variation in HDRS scores between patients. The term intracluster correlation coefficient applies to random intercept models only; in more complicated models the focus is on explanation of variation in various coefficients.

In the current model, the situation is somewhat more complicated due to the inclusion of both random intercept and random slope. This implies a possible correlation between the level-2 random effects. When calculating an estimate of the total variation, the covariance(s) between random effects have to be taken into account in any attempt to estimate the proportion of variation in outcome at any level or for any random coefficient. In addition, the inclusion of a covariate such as ENDOG can affect the variance estimates.

The total variation in HDRS scores over patients is defined as

$$\text{Var(level 2)} = \text{var}(v_{i0}) + \text{var}(v_{i1})(\text{WEEK})_{ij}^2 + 2\left[\text{cov}(v_{i0}, v_{i1})\right](\text{WEEK})_{ij}$$

The total variation is a function of the value assumed by the predictor WEEK, which has a random slope. As such, the total variation at the beginning of the study is

$$\begin{aligned}\text{Var}(\text{level 2}) &= \text{var}(v_{i0}) + \text{var}(v_{i1})(0)^2 + 2\left[\text{cov}(v_{i0}, v_{i1})\right](0) \\ &= \text{var}(v_{i0})\end{aligned}$$

while at the end of the study we have

$$\begin{aligned}\text{Var}(\text{level 2}) &= \text{var}(v_{i0}) + \text{var}(v_{i1})(5)^2 + 2\left[\text{cov}(v_{i0}, v_{i1})\right](5) \\ &= \text{var}(v_{i0}) + 25\,\text{var}(v_{i1}) + 10\,\text{cov}(v_{i0}, v_{i1})\end{aligned}$$

An estimate of the total variation at this level can be obtained by using the estimates of the variances and covariance obtained under this model. By substituting $\hat{\text{var}}(v_{i0})$, $\hat{\text{var}}(v_{i1})$, and $\hat{\text{cov}}(v_{i0}, v_{i1})$ into the equations above, we obtain the estimated variation in HDRS scores over patients at different points during the study period.

At the beginning of the study, the estimated total variation in HDRS scores over patients is simply the estimated variation in the random intercept, *i.e.*, $\hat{\text{var}}(v_{i0})$ = 12.62930. At the end of the study, the total variation at level-2 is estimated as

$$\begin{aligned}\hat{\text{var}}(\textit{level 2}) &= \hat{\text{var}}(v_{i0}) + 25\,\hat{\text{var}}(v_{i1}) + 10\,\hat{\text{cov}}(v_{i0}, v_{i1}) \\ &= 12.62930 + 25(2.07899) + 10(-1.42093) \\ &= 50.39475.\end{aligned}$$

At the beginning of the study we obtain

$$\begin{aligned}\frac{\hat{\text{var}}(\text{level 2})}{\hat{\text{var}}(\text{level 2}) + \hat{\text{var}}(\text{level 1})} &= \frac{12.62930}{12.62930 + 12.21663} \\ &= 0.5083\end{aligned}$$

and thus conclude that 50.8% of the variation in HDRS scores at this time is over patients. At the end of the study, we find that

$$\begin{aligned}\frac{\hat{\text{var}}(\text{level 2})}{\hat{\text{var}}(\text{level 2}) + \hat{\text{var}}(\text{level 1})} &= \frac{50.39475}{50.39475 + 12.21663} \\ &= 0.8049,\end{aligned}$$

so that only 20% of the variation in HDRS scores are estimated to be at the measurement level, with 80% at the patient level. As mentioned before, the total variation in HDRS scores is a function of the time of measurement, as represented by the variable WEEK. The very different estimates of variation at a patient level show how the introduction of an important

predictor, in this case at the measurement level, can have an impact on variance estimates at a different level of the hierarchy. By the end of the study period, the residual variation over measurements has been dramatically reduced, this being explained to a large extent by the inclusion of the time effect. Most of the remaining unexplained variation is at the patient level.

As a result of this finding and in the light of our original research question, whether the initial depression classification of a patient is also related to the HDRS scores over the time in which medication is administered, the model will be extended to include the covariate ENDOG. This dichotomous variable assumes a value of 1 when endogenous depression was diagnosed, and 0 if not. In addition, we will provide for a possible interaction between depression classification and measurement occasion by including the interaction term WxENDOG in the model. While WxENDOG can be viewed as a cross-level interaction, as WEEK is a measurement-level variable and ENDOG a patient-level variable, the inclusion of the patient-level variable ENDOG may enable us to explain more of the remaining variation in the random intercepts and slopes at the patient level.

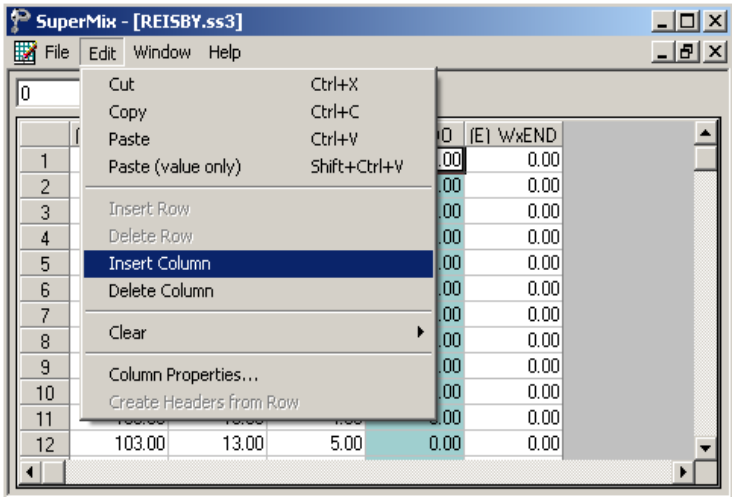
3.1.3 A 2-level random intercept-and-slope model with centered predictor

In the previous example, the time variable WEEK is coded from 0 to 5 and indicates the number of weekly follow-ups. The estimated average intercept of 23.577 obtained for this model represented the expected average HDRS score at the beginning of the study, *i.e.* WEEK = 0. An alternative formulation of the model that can be considered is one in which the estimated average intercept represents the expected average HDRS score midway through the study period. This linear transformation of the predictor variable WEEK, in which the grand mean of the variable is subtracted from each observed WEEK value, is referred to as grand mean centering. While the model based on the "raw" data and the model utilizing grand mean centered variables can be shown to be mathematically equivalent, the coefficients in these models have very different meanings.

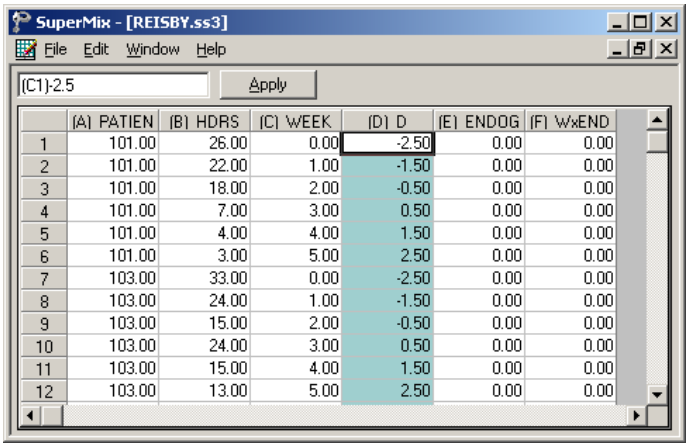
3.1.3.1 Preparing the data

Recall that the descriptive statistics in the previous model indicated a mean value over all level-1 observations of WEEK equal to 2.48. This is the true observed mean, compared to the value of 2.5 that would have been obtained if all patients had complete data over the course of the study. Here, we opt to use the value of 2.5 to center the WEEK variable.

To grand mean center the predictor WEEK, proceed as follows. Open the **reisby.ss3** in the SuperMix spreadsheet, then highlight the column WEEK. Select the **Insert Column** option on the **Edit** menu as shown below to insert a blank column named D after WEEK.

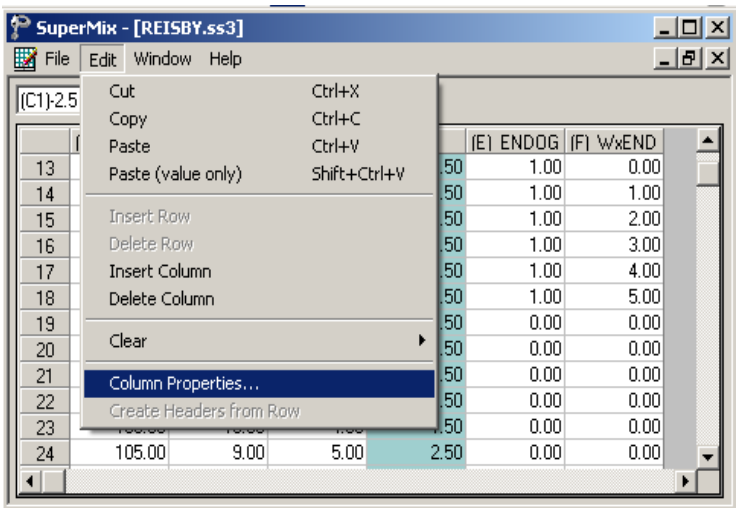


Keep the column D highlighted, type the formula (C1)–2.5 in the string field of the top-left corner and click on the **Apply** button to produce the following screen.

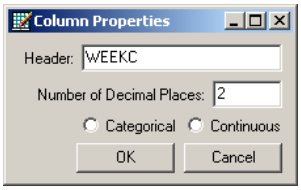


	(A) PATIEN	(B) HDRS	(C) WEEK	(D) D	(E) ENDOG	(F) WxEND
1	101.00	26.00	0.00	-2.50	0.00	0.00
2	101.00	22.00	1.00	-1.50	0.00	0.00
3	101.00	18.00	2.00	-0.50	0.00	0.00
4	101.00	7.00	3.00	0.50	0.00	0.00
5	101.00	4.00	4.00	1.50	0.00	0.00
6	101.00	3.00	5.00	2.50	0.00	0.00
7	103.00	33.00	0.00	-2.50	0.00	0.00
8	103.00	24.00	1.00	-1.50	0.00	0.00
9	103.00	15.00	2.00	-0.50	0.00	0.00
10	103.00	24.00	3.00	0.50	0.00	0.00
11	103.00	15.00	4.00	1.50	0.00	0.00
12	103.00	13.00	5.00	2.50	0.00	0.00

Rename the newly created variable to WEEKC by first highlighting the column, then selecting the **Column Properties** option on the **Edit** menu as shown below.



Input the desired variable name, *e.g.* WEEKC, in the **Header** string field as shown below and click on the **OK** button. By default, all variables are assumed to be continuous.



Save the changes to **reisby.ss3** by selecting the **Save** option on the **File** menu.

3.1.3.2 The model

The revised random intercept-and-slope model for the response variable HDRS may be expressed as

$$\text{HDRS}_{ij} = \beta_0 + \beta_1 \times \left(\text{WEEKC}\right)_{ij} + v_{i0} + v_{i1}\left(\text{WEEKC}\right)_{ij} + e_{ij}$$

or, alternatively, as

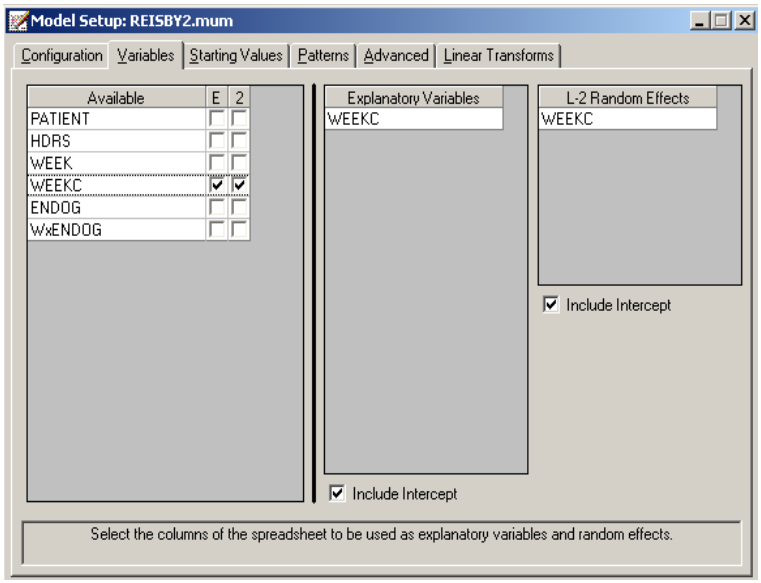
$$\text{HDRS}_{ij} = \beta_0 + \beta_1 \times \left[\left(\text{WEEK}\right)_{ij} - \overline{\text{WEEK}}\right] + v_{i0} + v_{i1}\left[\left(\text{WEEK}\right)_{ij} - \overline{\text{WEEK}}\right] + e_{ij}$$

where $\overline{\text{WEEK}} = 2.5$.

3.1.3.3 Setting up the analysis

Open the previous model setup for **reisby1.mum**. Save the file as **reisby2.mum** by using the **Save As** option on the **File** menu. Change the title on the **Configuration** tab if desired.

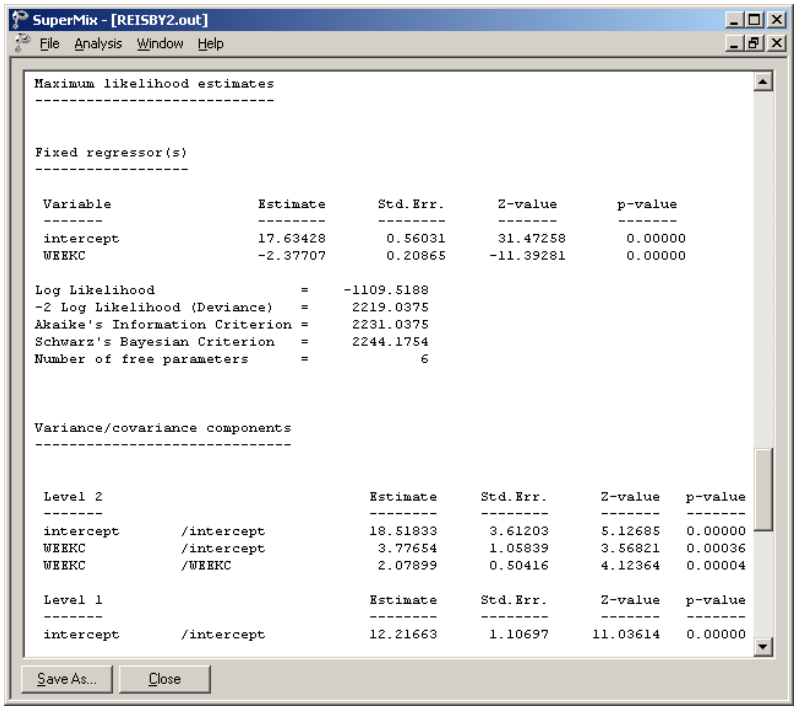
Click on the **Variables** tab and select WEEKC both as **Explanatory Variable** and **L-2 Random Effects** instead of WEEK as shown below.



Save the changes to the file **reisby2.mum**. Select the **Run** option on the **Analysis** menu to produce the output file **reisby2.out**. Use the **Analysis**, **View Output** option to open the output file.

3.1.3.4 Discussion of results

The output file contains the final estimates of the fixed and random coefficients included in the model, along with some goodness of fit measures as given below. Note that the use of grand mean centering of the time variable has no effect on the fit statistics.



3.1.3.5 Interpreting the results

Comparison of models

Table 3.3: Estimates and standard errors for two models

Coefficient	Level-2 model	
	WEEK = 0 ~ 5	WEEKC = –2.5 ~ 2.5
β_0	23.57695	17.63428
	(0.54555)	(0.56031)
β_1	–2.37707	–2.37707
	(0.20865)	(0.20865)
$\sigma^2_{v_0}$	12.6293	18.51833
	(3.46653)	(3.61203)
$\sigma_{v_0 v_1}$	–1.42093	3.77654
	(1.02595)	(1.05839)
$\sigma^2_{v_1}$	2.07899	2.07899
	(0.50417)	(0.50416)
σ^2_e	12.21663	12.21663
	(1.10697)	(1.10697)

Table 3.3 contains the estimates and standard errors of the above two analyses. The coefficient for WEEKC is the same as for the uncentered variable WEEK. However, the variance of the random intercept ($\sigma^2_{v_0}$) and the covariance term $\sigma_{v_0v_1}$ have changed. The covariance between the intercept and the WEEKC slope is now significant.

Table 3.3: Estimates and standard errors for two models (continued)

Deviance	2219.0375	2219.0375
AIC	2231.0375	2231.0375
SBC	2244.1754	2244.1754
Number of free parameters	6	6

As shown above, the estimates of the slope and its variance are the same. This is because the scale of WEEK was not changed; only its location changed. The estimated intercept decreased from 23.58 to 17.63, which corresponds to the average HDRS score at week 2.5 instead of week 0. Similarly, the $\sigma^2_{v_0}$ of intercept increased to 18.52, which shows the increase of the individual variance at week 2.5. The change of $\sigma_{v_0v_1}$ is interesting: not only the value changed, but also the sign. The covariance of the first analysis tells us that the higher the variance of intercept, the lower the variance of slope. Or say, at week 1, the HDRS score decreases at a faster rate for those patients who started with higher HDRS. However, at week 2.5, the patients with higher HDRS tend to improve less.

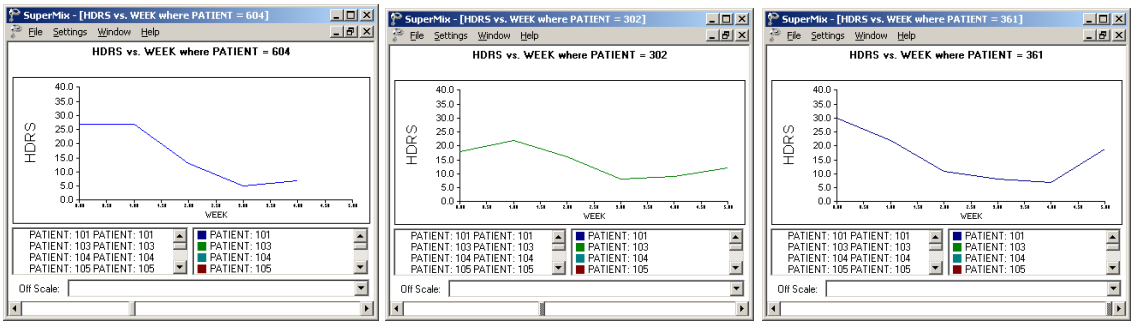


Figure 3.8: Changes in covariance over time

When looking at the three HDRS versus WEEK plots for patient 604, 302 and 361, we can see why this could happen. The graphs show the change of $\sigma_{v_0v_1}$ from week 0 to week 2.5.

3.1.4 A random intercept-and-slope with a covariate and an interaction term

The type of depression a patient was diagnosed with was recorded as part of the study and information on this patient characteristic is represented by the variable ENDOG, which assumes a value of 1 for patients with endogeneous depression and 0 otherwise. Including this variable in the model allows us to explore the potential relationship between a patient's HDRS score and the type of depression the patient was diagnosed with. Moreover, it is possible that the trend in HDRS scores over the study period may differ for the two ENDOG groups. Including an interaction term between the time of measurement and the type of depression in the model will allow us to evaluate this potential relationship as well.

3.1.4.1 The model

We now include ENDOG and WxENDOG in the level-1 model. ENDOG is a dummy variable representing the type of depression a patient was diagnosed with, and WxENDOG represents the interaction between WEEK and ENDOG. The model shows changes at both levels: at level 2, the covariate ENDOG is now included, while at level 1 the interaction between WEEK and ENDOG, which can potentially change from week to week, is added. The revised model for the response variable HDRS may be expressed as

Level-1 model:

$$\mathrm{HDRS}_{ij} = b_{0i} + b_{1i} \times \left(\mathrm{WEEK}\right)_{ij} + b_{2i} \times \left(\mathrm{WxENDOG}\right)_{ij} + e_{ij}$$

Level-2 model:

$$\begin{aligned} b_{0i} &= \beta_0 + \beta_3 \times \left(\mathrm{ENDOG}\right)_i + v_{0i} \\ b_{1i} &= \beta_1 + v_{1i} \\ b_{2i} &= \beta_2 \end{aligned}$$

or, in mixed model formulation, as

$$\begin{aligned} \mathrm{HDRS}_{ij} = \beta_0 + \beta_1 \times \left(\mathrm{WEEK}\right)_{ij} + \beta_2 \times \left(\mathrm{WxENDOG}\right)_{ij} + \beta_3 \times \left(\mathrm{ENDOG}\right)_i \\ + v_{0i} + v_{1i} \times \left(\mathrm{WEEK}\right)_{ij} + e_{ij} \end{aligned}$$

where β_0 denotes the average HDRS level at week 0 for the non-endogenous depression patients (ENDOG=0), β_1 refers to the weekly improvement for the non-endogenous group, β_2 indicates the expected change in HDRS score for a unit change in the value of the interaction term WxENDOG, and β_3 refers to the average expected change in HDRS level for endogenous patients. v_{0i} is the individual deviation from the average intercept. v_{1i} denotes the average deviation from the slope, or say, average improvement of the HDRS.

We can also write the model in terms of our original variables (WEEK and ENDOG) as:

Level-1 model:

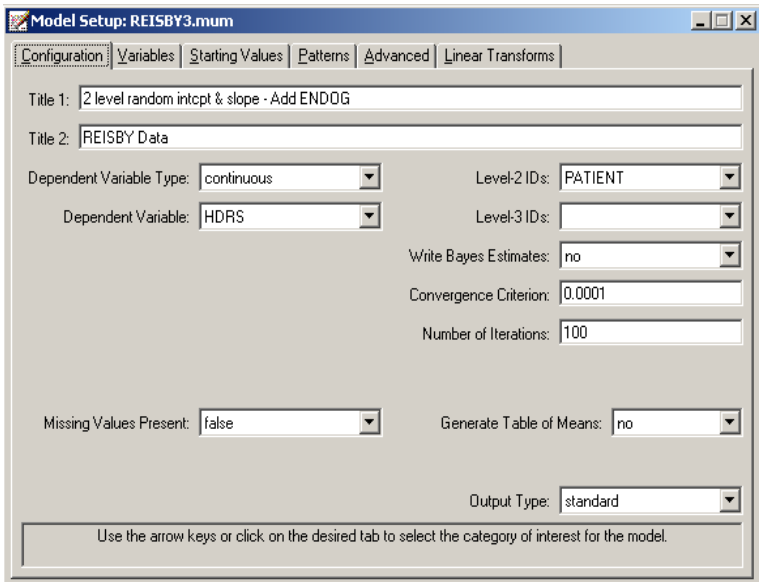
$$\mathrm{HDRS}_{ij} = b_{0i} + b_{1i} \times \left(\mathrm{WEEK}\right)_{ij} + b_{2i} \times \left(\mathrm{WxENDOG}\right)_{ij} + e_{ij}$$

Level-2 model:

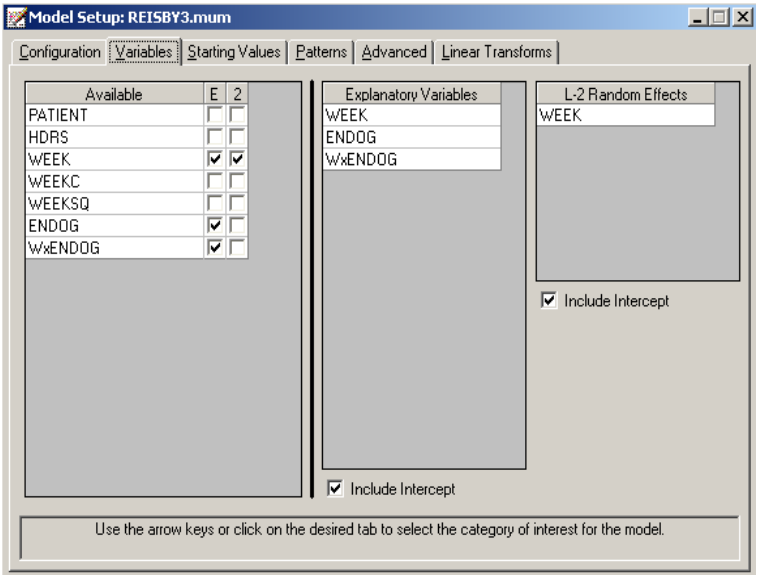
$$b_{0i} = \beta_0 + \beta_2 \times \left(\mathrm{ENDOG}\right)_i + v_{0i}$$
$$b_{1i} = \beta_1 + \beta_4 \times \left(\mathrm{ENDOG}\right)_i + v_{1i}$$

3.1.4.2 Setting up the analysis

To create the model specifications for this model, we start by opening **reisby.ss3** in a SuperMix spreadsheet window. Then we use the **Open Existing Model Setup** option on the **File** menu to load the **Model Setup** window for **reisby1.mum**. Save the file as **reisby3.mum** by using the **Save As** option on the **File** menu. Change the string in the **Title 1** text box on the **Configuration** screen to reflect the new model, thereby producing the following dialog box.



Next, click on the **Variables** tab to proceed to the **Variables** screen of the **Model Setup** window.



The two covariates are specified by checking the **E** check boxes for ENDOG and WxENDOG respectively in the **Available** grid respectively to produce the following **Variables** tab.

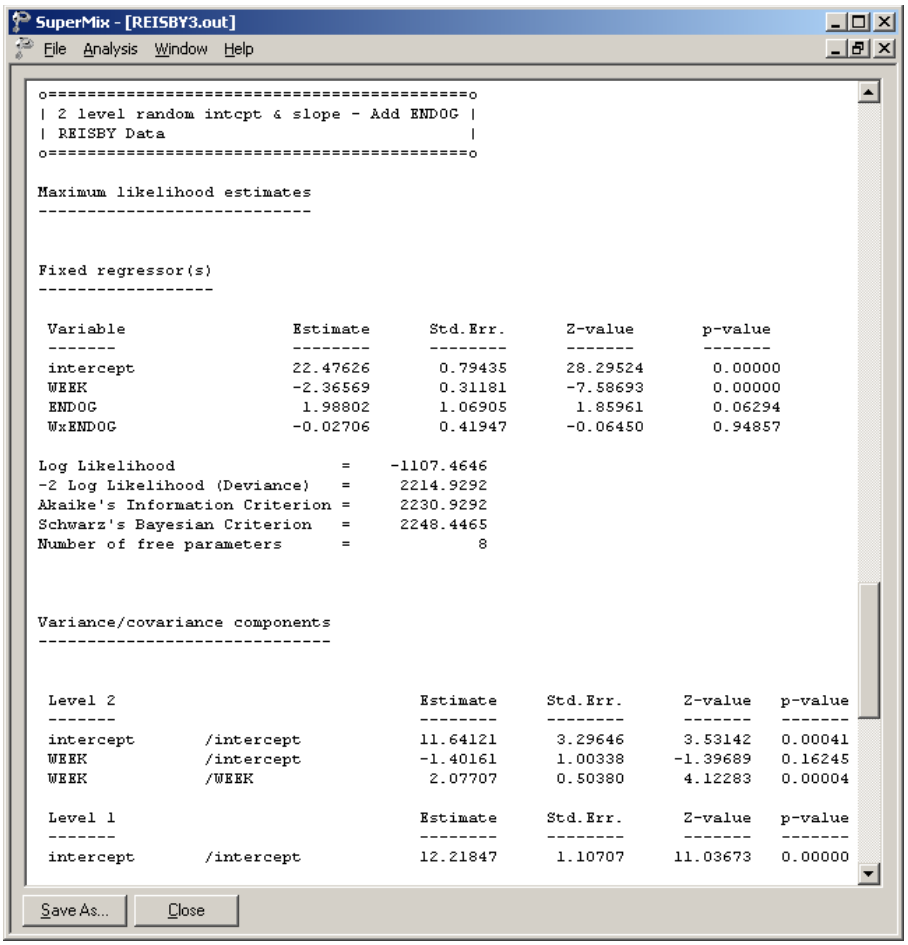
Save the changes to the file **reisby3.mum**. To fit the revised model to the data, select the **Run** option on the **Analysis** menu to produce the output file **reisby3.out**.

3.1.4.3 Interpreting the results

Fixed effects results

A portion of the output file **reisby3.out** is shown below.

The interaction WxENDOG between the time variable WEEK and the depression classification variable ENDOG, is not significant. Given this, we can take a closer look at the estimated coefficients for the main effects WEEK and ENDOG respectively. Note, however, that the *p*-value for the ENDOG coefficient is larger than 0.05, and thus can only be considered significant at a 10% level of significance. The effect of time, on the other hand, is found to be highly significant. While the average HDRS score is predicted to decrease by –2.37 score scale units each week, patients classified as having endogenous depression (*i.e.*, ENDOG = 1) are predicted to have a HDRS score of 2 units higher at all occasions.

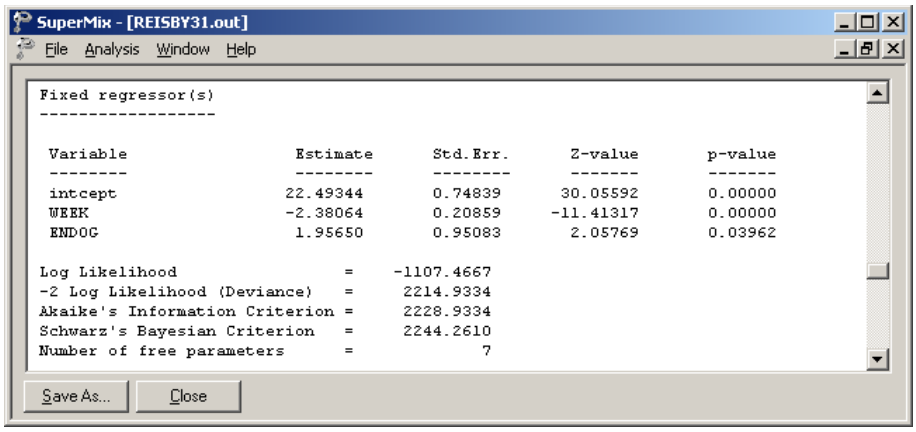


To obtain the predicted average HDRS scores, the estimates obtained from the output are used:

$$\hat{y} = \hat{\beta}_0 + \hat{\beta}_1(\text{WEEK}) + \hat{\beta}_2(\text{ENDOG}) + \hat{\beta}_3(\text{WxENDOG})$$
$$= 22.47626 - 2.36569(\text{WEEK}) + 1.98802(\text{ENDOG}) - 0.02706(\text{WxENDOG})$$

Model comparison

A question that arises from inspection of the results obtained thus far is whether the interaction term contributes overall to the explanation of the variation in the HDRS scores. To test this, we can fit a model without the interaction term and use the deviance reported in the output to compare results for the model with interaction and the model without this term. The relevant output from an analysis without the interaction term is shown below. We note that the deviance obtained for the simpler model is almost identical to that of the model considered in this section. Based on this, we conclude that a model without the interaction WxENDOG would fit the data as well as the one with the interaction term included.



In addition, we can test the hypothesis that the model with covariate (ENDOG) fits the data better than the random intercept and slope model considered previously. To test this hypothesis, we calculate the difference between the –2 log likelihood value obtained for the previous model and the –2 log likelihood value for the current model. It can be shown that this difference of 2219.04 – 2214.93 = 4.11 has a χ^2 distribution with associated degrees of freedom equal to the difference in the number of parameters estimated in the two examples, *i.e.*, 8 – 7 = 1 degrees of freedom. Since the *p*-value for this test statistic is less than 0.05, it is concluded that the random intercept-and-slope model with ENDOG as a covariate provides a better description of the data than the original random intercept-and-slope model. This finding is supported by the fact that the *p*-value for ENDOG when the interaction effect between WEEK and ENDOG is excluded equals 0.04.

3.1.5 A random intercept-and-slope quadratic model

3.1.5.1 The model

In this section we include an additional predictor and a random term to examine a possible quadratic response trend in HDRS scores over time. Keeping the level-2 model the same as before, the corresponding model for the response variable HDRS may be expressed as

Level-1 model:

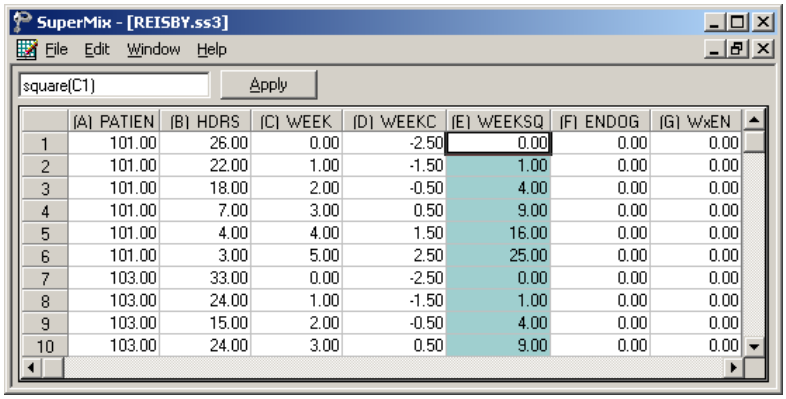
$$\mathrm{HDRS}_{ij} = b_{0i} + b_{1i} \times \left(\mathrm{WEEK}\right)_{ij} + b_{2i} \times \left(\mathrm{WEEK}^2\right)_{ij} + e_{ij}$$

Level-2 model:

$$b_{0i} = \beta_0 + v_{0i}$$
$$b_{1i} = \beta_1 + v_{1i}$$
$$b_{2i} = \beta_2 + v_{2i}$$

3.1.5.2 Preparing the data

Create a new blank variable named WEEKSQ as shown in section 2.5.1. Highlight the column WEEKSQ, type the formula SQUARE(C1) where C = WEEK in the string field and click on the **Apply** button to produce the following screen. Save the change to **reisby.ss3**.

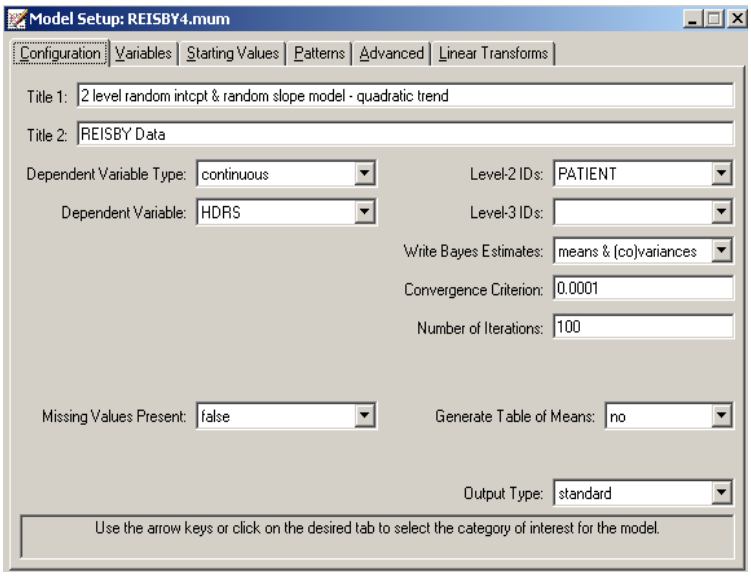


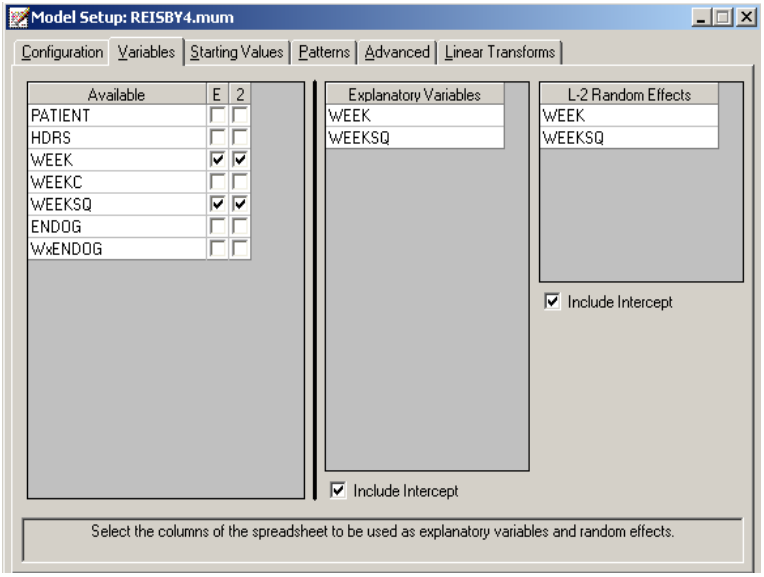
	(A) PATIEN	(B) HDRS	(C) WEEK	(D) WEEKC	(E) WEEKSQ	(F) ENDOG	(G) WxEN
1	101.00	26.00	0.00	-2.50	0.00	0.00	0.00
2	101.00	22.00	1.00	-1.50	1.00	0.00	0.00
3	101.00	18.00	2.00	-0.50	4.00	0.00	0.00
4	101.00	7.00	3.00	0.50	9.00	0.00	0.00
5	101.00	4.00	4.00	1.50	16.00	0.00	0.00
6	101.00	3.00	5.00	2.50	25.00	0.00	0.00
7	103.00	33.00	0.00	-2.50	0.00	0.00	0.00
8	103.00	24.00	1.00	-1.50	1.00	0.00	0.00
9	103.00	15.00	2.00	-0.50	4.00	0.00	0.00
10	103.00	24.00	3.00	0.50	9.00	0.00	0.00

3.1.5.3 Setting up the analysis

Again, we can modify the model setup file of **reisby1.mum** by first opening it, then saving the file as **reisby4.mum**. Change the title on the **Configuration** tab and request Bayes estimates by selecting the **means & (co)variances** option from the **Write Bayes Estimates** drop-down list.

Next, click on the **Variables** tab to proceed to the **Variables** screen of the **Model Setup** window. The two covariates are specified by checking the **E** and **2** check boxes for WEEKSQ in the **Available** grid to produce the **Variables** screen shown below.





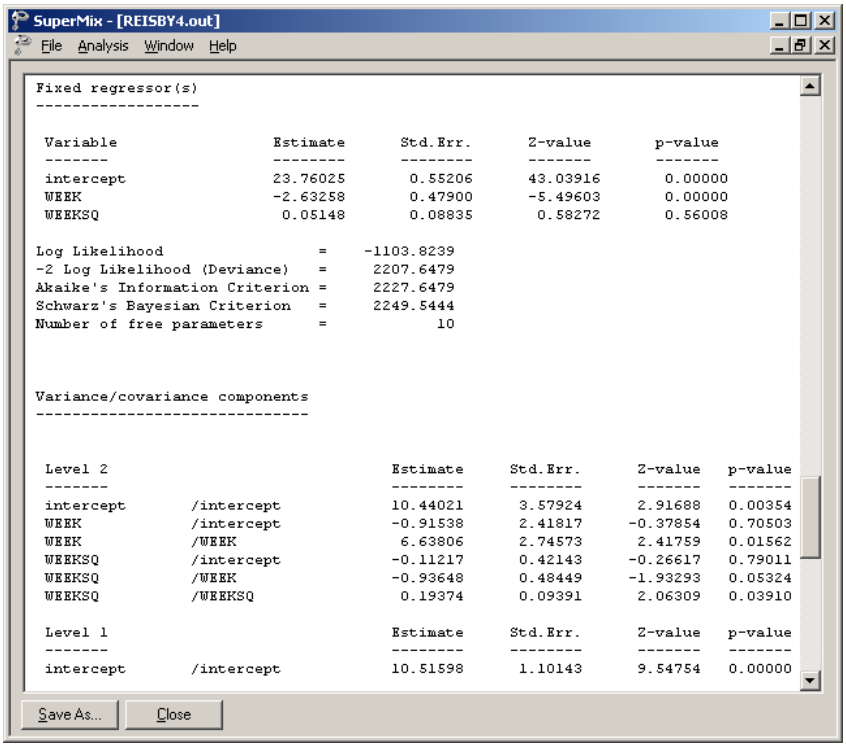
Save the changes to the file **reisby4.mum** and run the model.

3.1.5.4 Interpreting the results

A portion of the output file **reisby4.out** is shown below.

Fixed effects results

The level-1 estimate of the WEEKSQ coefficient is 0.05, which turns out not to be significant (p = 0.56). On the other hand, the WEEKSQ random effect is significant at a 5% level (p = 0.04). Comparing the present results with those reported in **reisby1.out**, we see that the deviance difference of 2219.04 – 2207.65 = 11.19 with 10 – 7 = 3 degrees of freedom, indicating an improved overall model fit at a 5% significance level. These results imply that, although the mean trend of HDRS scores over time is linear, some of the individuals' trajectories are quadratic.

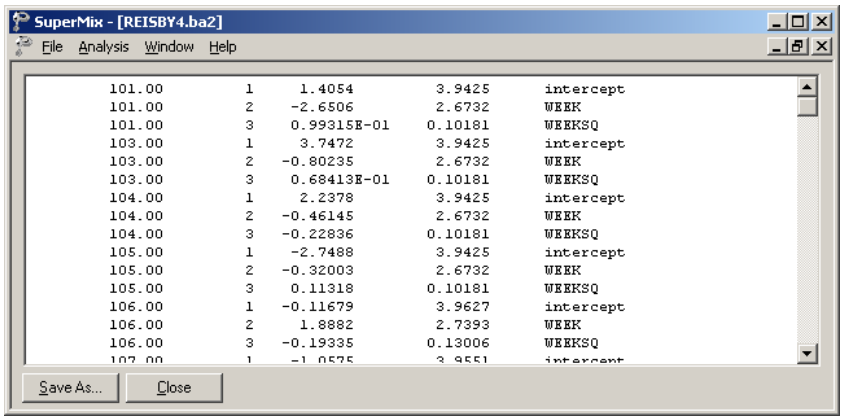


3.1.5.5 Residuals

Level 2 Bayes results

Up to this point, we have considered results averaged over all patients. We now turn our attention to the residual file **reisby4.ba2**, which offers the opportunity to take a closer look at the results by individual patient. After running the above model, select the **Analysis**, **View L-2 Bayes Results** option to open the image below. The contents of this file are displayed for the first 5 patients. Three lines of information are given for each patient, containing, in order of appearance,

- the number of the patient in the data set,
- the number of the empirical Bayes coefficient,
- the empirical Bayes estimate,
- the estimated variance of the Bayes coefficient, and
- the name of the associated coefficient as used in the model.



To obtain patient-specific predicted HDRS scores, the empirical Bayes estimate for each patient have to be taken into account, as these estimates indicate the extent to which the random intercept or slope for that patient deviates from the intercept and slope over all patients. Patient-specific predicted HDRS scores are calculated as

$$\hat{y}_{ij} \mid \hat{\beta} = 23.76025\text{-}2.63258 \times \text{WEEK}_{ij} + 0.05148 \times \text{WEEK}^2_{ij} + \hat{v}_{0i} + \hat{v}_{1i} \times \text{WEEK}_{ij} + \hat{v}_{2i} \times \text{WEEK}^2_{ij}$$

For the first patient shown in the residual file above, we have $\hat{v}_{i0}$ = 1.4054, $\hat{v}_{i1}$ = –2.6506 and $\hat{v}_{i2}$ = 0.099315. From this information, we can already tell that the intercept for the patient is higher than average, but that the WEEK slope for this patient is lower than average. The positive value of the quadratic term indicates that the decreasing rate slows down more quickly than average with an increase in time. The predicted HDRS score for this patient (PATIENT = 101) is found to be

$$\hat{y}_{ij} \mid \hat{\beta} = 23.76025\text{-}2.63258 \times \text{WEEK}_{ij} + 0.05148 \times \text{WEEK}^2_{ij} + 1.4054\text{-}2.6506 \times \text{WEEK}_{ij} + 0.099315 \times \text{WEEK}^2_{ij}.$$

Substituting the WEEK with values 0, 1, …, 5, we get the predicted HDRS scores for Patient 101, and similarly, for all the other patients. Table 3.4 and the graphical display below give the predicted HDRS for the first 5 patients.

Table 3.4: Predicted HDRS values for selected patients

	Patient 101	Patient 103	Patient 104	Patient 105	Patient 106	Population Avg.
Week 0	25.166	27.507	25.998	21.011	23.643	23.760
Week 1	20.033	24.192	22.727	18.224	22.757	21.179
Week 2	15.202	21.117	19.102	15.765	21.587	18.701
Week 3	10.673	18.282	15.124	13.636	20.133	16.326
Week 4	6.446	15.686	10.792	11.836	18.396	14.054
Week 5	2.520	13.330	6.106	10.365	16.375	11.884

We find that Patient 101 had a higher initial HDRS score, but over time obtained a lower than average score. For Patient 103, a higher than average predicted HDRS score is obtained at each time point. In contrast, Patient 105 scored lower at each time point. The quadratic term doesn't affect much of the population average; however the effect is obvious for Patients 105 and 106.

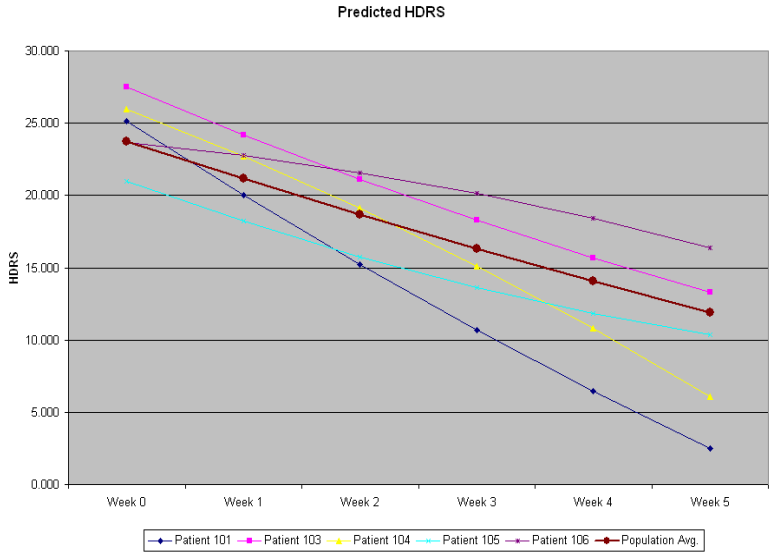


Figure 3.9: Predicted HDRS for selected patients

Model-based graphs

Residual plot

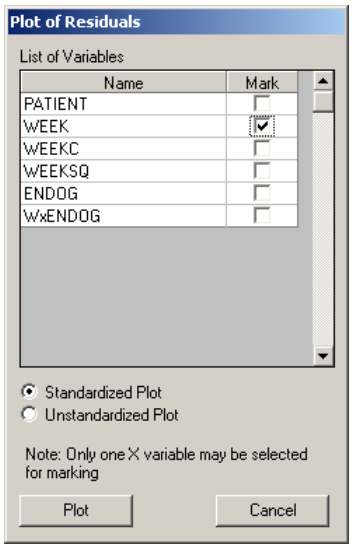
Level-1 residuals can also be obtained, either for a typical or specific patient, by using the empirical Bayes estimates. The residuals for a typical patient are obtained as

$$\begin{aligned}\text{Patient residual} &= \text{Observed HDRS score} - \hat{y} \mid \beta \\ &= \text{Observed HDRS score} - [23.76025\text{-}2.63258 \times \text{WEEK}_{ij} \\ &\quad + 0.05148 \times \text{WEEK}^2_{ij}\end{aligned}$$

The residuals for a specific patient use the additional information given by the empirical Bayes residuals and have the form

$$\begin{aligned}\text{Patient-specific residual} &= \text{Observed HDRS score} - \hat{y} \mid \beta \\ &= \text{Observed HDRS score} - [23.76025\text{-}2.63258 \times \text{WEEK}_{ij} \\ &\quad + 0.05148 \times \text{WEEK}^2_{ij} + \hat{v}_{0i} + \hat{v}_{10} \times \text{WEEK}_{ij} + \hat{v}_{20} \times \text{WEEK}^2_{ij}]\end{aligned}$$

Select the **Residuals** option on the **File**, **Model-based Graphs** menu to activate the **Plot of Residuals** dialog box. Check the **Mark** check box for WEEK as shown below, then click on the **Plot** button.



The graph obtained, as shown below, shows that, in general, the range of the level-1 residuals is $(-5; 5)$.

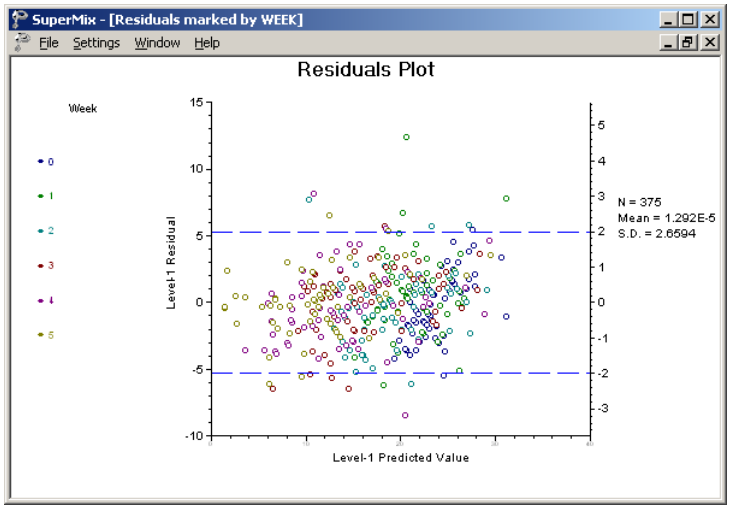
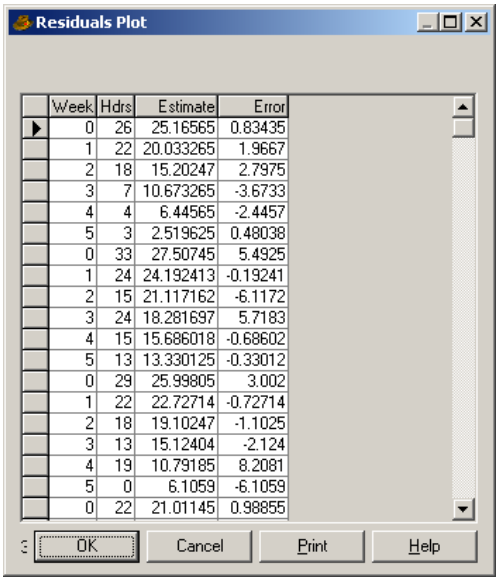


Figure 3.10: Plot of level-1 residuals vs. predicted values

Inspection of these residuals can be useful in examining the distributional assumptions for the level-1 data, in this case at the measurement level. For the current example, residuals for a typical patient have a mean of 0.000 with standard error of 2.66. Double-click on the middle of the graph to open an additional window that shows the detailed residual data for each observation.

We note that the estimate for Patient 101 at the beginning of the study was 25.166, and 2.520 at the end of the study. On both occasions, the residuals associated with these estimates were positive, indicating that the estimates are above estimated average.



Week	Hdrs	Estimate	Error
0	26	25.16565	0.83435
1	22	20.033265	1.9667
2	18	15.20247	2.7975
3	7	10.673265	-3.6733
4	4	6.44565	-2.4457
5	3	2.519625	0.48038
0	33	27.50745	5.4925
1	24	24.192413	-0.19241
2	15	21.117162	-6.1172
3	24	18.281697	5.7183
4	15	15.686018	-0.68602
5	13	13.330125	-0.33012
0	29	25.99805	3.002
1	22	22.72714	-0.72714
2	18	19.10247	-1.1025
3	13	15.12404	-2.124
4	19	10.79185	8.2081
5	0	6.1059	-6.1059
0	22	21.01145	0.98855