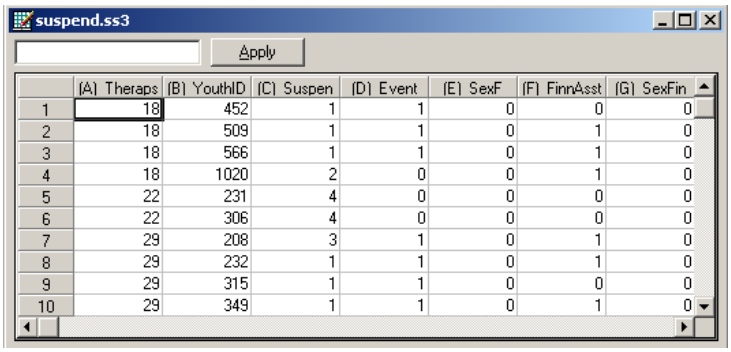
Two-level survival analysis models

The data

The data set for this example is taken from Schoenwald & Henggeler (2005). Children in the study were assigned to therapists and followed across time. At the child level, data were collected at baseline (pre-treatment, T_0), post-treatment (T_1), 6 months post-treatment (T_2), and 12 months post- treatment (T_3). The outcome of interest is whether a child was suspended in the current school year, assessed at T_0, T_1, T_2, or T_3. Specifically, here, we will focus on the time until the first school suspension as the "survival" outcome. As indicated in more detail later, this is indicated by a combination of the variables Event and Suspend: for example, if the student was suspended, the indicator Event is given the value 1 and Suspend will indicate the time period during which this occurred. However, there are also subjects who do not experience the event (*i.e.*, were not suspended), and who drop out of the study before its end. Such subjects are considered to be right-censored in the survival analysis literature, and for these subjects the Event variable is coded 0 and the Suspend variable indicated the last time period prior to their dropout from the study. For subjects who never experience the event and who never drop out, they receive Event codes of 0 and Suspend codes equal to the final time point. In addition to these data concerning school suspension, the gender of each student was also recorded, as well as whether or not the student's family was receiving financial assistance. The first 8 cases of the data set **suspend.ss3** are shown below.



	(A) Theraps	(B) YouthID	(C) Suspen	(D) Event	(E) SexF	(F) FinnAsst	(G) SexFin
1	18	452	1	1	0	0	0
2	18	509	1	1	0	1	0
3	18	566	1	1	0	1	0
4	18	1020	2	0	0	1	0
5	22	231	4	0	0	0	0
6	22	306	4	0	0	0	0
7	29	208	3	1	0	1	0
8	29	232	1	1	0	1	0
9	29	315	1	1	0	0	0
10	29	349	1	1	0	1	0

The variables of interest are:

- Therapst is the patient therapist ID (443 level-2 units).
- YouthID is the child's ID (1914 level-1 units).
- Suspend is an ordinal outcome variable that assumes values 1, 2, 3 or 4, corresponding to the time points T_0, T_1, T_2, and T_3.
- Event is the event indicator, where 1 indicates suspension took place and 0 that the observation was censored.
- SexF indicates the child's gender (1 = female; 0 = male).
- FinnAsst equals 1 if financial assistance is given to the student's family and 0 otherwise
- SexFin equals SexF × FinnAsst and therefore assumes values of 0 and 1.

The model

Let y_{ij} denote an ordinal outcome variable that takes on discrete positive values $t = 1, 2, \ldots, m$. In previous examples we assumed that y_{ij} has C categories. For example

- 1 = not depressed,
- 2 = mildly depressed,
- 3 = depressed and
- 4 = extremely depressed.

The subscript (i, j) denotes subject j, $j = 1, 2, \ldots n_i$ nested within level-2 unit i, $i = 1, 2, \ldots, N$. In the present context the level-1 units j indicates children and the level-2 unit i indicates therapists. Note, that as another example of this type of model, one could have multiple failure times nested within individuals.

Let δ_{ij} denote the censor/event indicator, then $\delta_{ij}=1$ if the event occurs and $\delta_{ij}=0$ if an observation is censored. In survival analysis each ij is observed until time t_{ij} and if an event occurs $t_{ij}=t$ and $\delta_{ij}=1$. If the observation is censored at $t_{ij}=t$ then $\delta_{ij}=0$.

In the case of censoring it is assumed that a unit is observed at t_{ij} but not at t_{ij+1}. Hedeker, Siddiqui & Hu (2000) showed that if events occur within continuous time intervals (*i.e.*, grouped-time), for example, a student is suspended in the past year, use of the complementary log-log link for an ordinal outcome is equivalent to a proportional hazards model in continuous time. Therefore, the grouped-time proportional hazards mixed model can be written as:

$$\log\left[-\log\left(1-P\left(t_{ij}\right)\right)\right]=\gamma_t+\mathbf{w}'_{ij}\boldsymbol{\alpha}+\mathbf{x}'_{ij}\boldsymbol{\beta}_i$$

where $\mathbf{w}_{ij}$ is a vector of explanatory variables and $\mathbf{x}_{ij}$ a vector of fixed effects. Typically, the elements of $\mathbf{x}_{ij}$ are a subset of $\mathbf{w}_{ij}$. For example, the elements of $\mathbf{x}_{ij}$ might correspond to the intercept and age, whereas $\mathbf{w}_{ij}$ would include these two terms plus any additional model covariates. It is assumed that the random effects $\boldsymbol{\beta}_i$ are from a normal distribution with mean zero and covariance matrix $\boldsymbol{\Phi}$.

$P\left(t_{ij}\right)$ denotes the probability that an event takes place in the interval designated at time t_{ij}. γ_t represent threshold values, and in the present context these reflect the baseline hazard (*i.e.*, the hazard when all covariates equal 0). The plus sign following γ_t means that a positive $\boldsymbol{\alpha}$ indicates an increased hazard (*i.e.*, the event occurs sooner) as values of the covariate increase.

Survival data as ordinal outcomes

Assume 4 time points with no intermittent censoring and let y denote the outcome variable. Let us first consider subjects who were suspended at some point in the study. For these subjects, the variable Event will be coded as 1 and the coding of the Suspend variable will be as follows.

Suspend:

$y_{ij}=1$: Student first suspended at T_0.

$y_{ij}=2$: Student not suspended at T_0, but first suspended at T_1.

$y_{ij}=3$: Student not suspended at T_0 or T_1, but first suspended at T_2.

$y_{ij} = 4$: Student not suspended at T_0, T_1 or T_2, but first suspended at T_3.

Similarly, subjects who were never censored would have the variable Event coded as 0, and the following codes for the Suspend variable.

Suspend:

$y_{ij} = 1$: Student not suspended at T_0 and no data beyond T_0.

$y_{ij} = 2$: Student not suspended at T_0 or T_1, and no data beyond T_1.

$y_{ij} = 3$: Student not suspended at T_0, T_1, or T_2, and no data beyond T_2 (*i.e.*, no data at T_3).

$y_{ij} = 4$: Student not suspended at T_0, T_1, T_2, or T_3.

Table 3.10 shows how values are assigned to y_{ij}, and the relationship between the y_{ij} outcomes and the event indicator.

Table 3.10: Four time points with censoring

Outcome	Ordinal dep. Variable	Event indicator
Censor at T_1	1	0
Event at T_1	1	1
Censor at T_2	2	0
Event at T_2	2	1
Censor at T_3	3	0
Event at T_3	3	1
Censor at T_4	4	0
Event at T_4	4	1

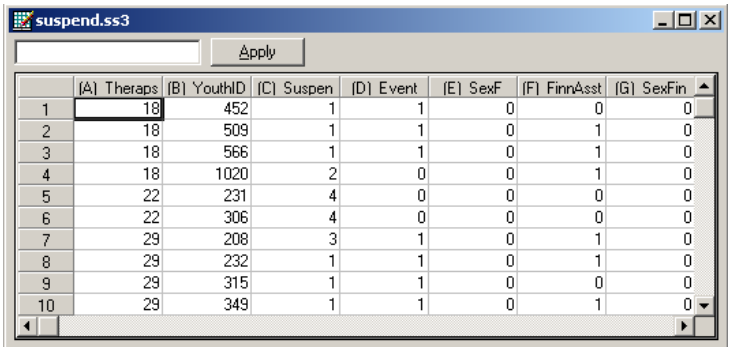
It should be noted that one could also fit grouped-time survival models using dichotomous indicators of event/censoring across the study time points. This approach, which is described in Singer and Willett (1993), can also be done in SuperMix, though additional data setup and

manipulation is required. The advantage of representing the survival data as ordinal outcomes is that there is no need to include time indicators since the thresholds take care of this. The ordinal presentation is also more efficient in terms of data set size, especially when the number of time points is large. More information on these two different approaches can be found in Hedeker, Siddiqui & Hu (2000).

Example

The model is fitted to the data in **suspend.ss3** as follows. The first step is to create the **ss3** file shown above from the Excel file **suspend.xls**. This is accomplished as follows:

- Use the **Import Data File** option on the **File** menu to load the **Open** dialog box.
- Browse for the file **suspend.xls** in the **Examples**, **Survival** folder.
- Select the file and click on the **Open** button to open the following SuperMix spreadsheet window for **suspend.ss3**.



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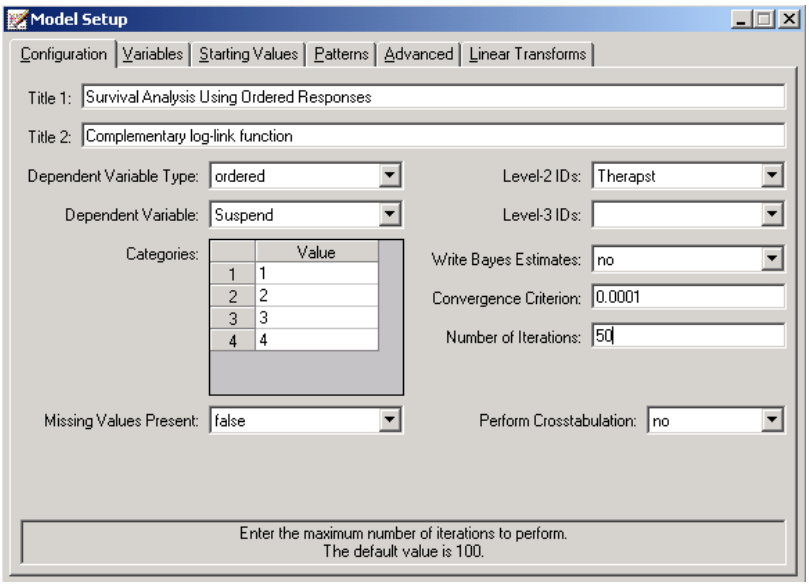
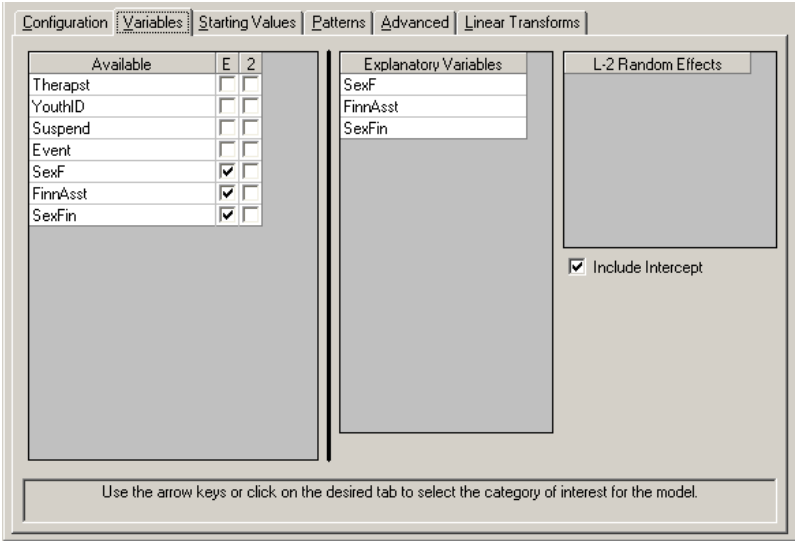
Setting up the analysis

We start by selecting the **New Model Setup** option on the **File** menu to load the **Model Setup** window.

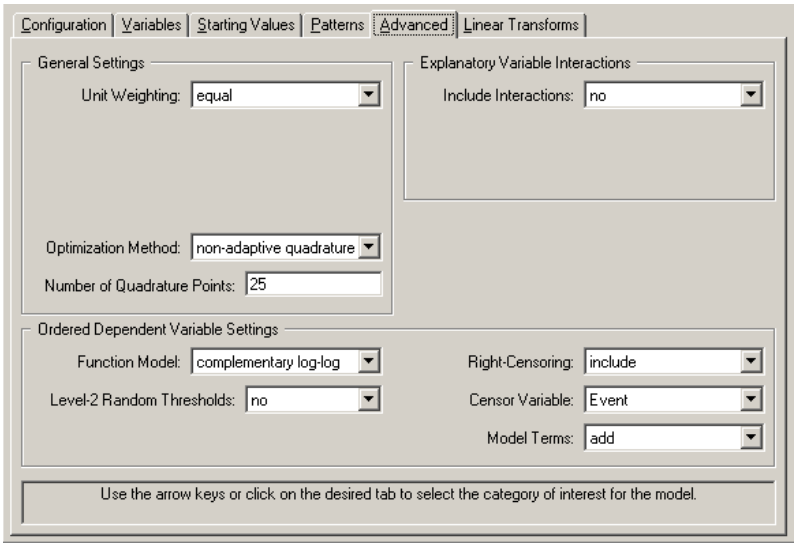


First, enter the titles Survival Analysis Using Ordered Responses and Complementary log-log link function in the **Title 1** and **Title 2** text boxes respectively. Select the ordinal outcome variable Suspend from the **Dependent Variable** drop-down list box. The variable Therapst, which defines the levels of the hierarchy, is selected as the Level-2 ID from the **Level-2 IDs** drop-down list box. Also set the number of iterations to 50.

Next, click on the **Variables** tab of the **Model Setup** window. SexF, FinnAsst, and SexFin are specified as the predictors (explanatory variables) of the fixed part of the model by checking the corresponding boxes in the **E** column of the **Available** grid on the **Variables** screen. These actions will produce the following screen.



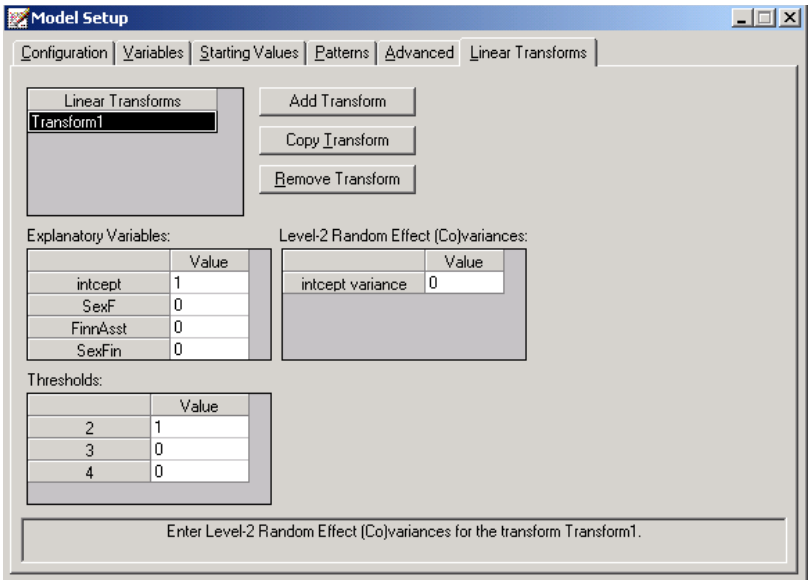
To specify the number of quadrature points and link function (**Function Model**), we proceed to the **Advanced** screen by clicking on the **Advanced** tab. Change **Model Terms** from **subtract** to **add** and select **complementary log-log** as the **Function Model**. Select non-adaptive quadrature as Optimization Method, and request 25 quadrature points. Finally, set the Right-censoring field to include, and select the variable Event as Censor Variable.



To complete the model setup, we will illustrate use of the **Linear Transforms** option. In the current model specification, the baseline hazard is a function of the model intercept and thresholds. Specifically, the baseline hazard estimate at the first time point equals the estimated model intercept, the baseline hazard estimate at the second time point is the sum of the model intercept and the first estimated threshold, the baseline hazard at the third time point is the sum of the model intercept and the second estimated threshold, and the baseline hazard estimate at the final time point is a sum of the estimated intercept and the third estimated threshold. Thus, three of these baseline hazard estimates involve sums of the estimated parameters. To obtain these linear transforms of the model estimates, click on the **Linear Transforms** tab. The three linear transforms are specified as follows:

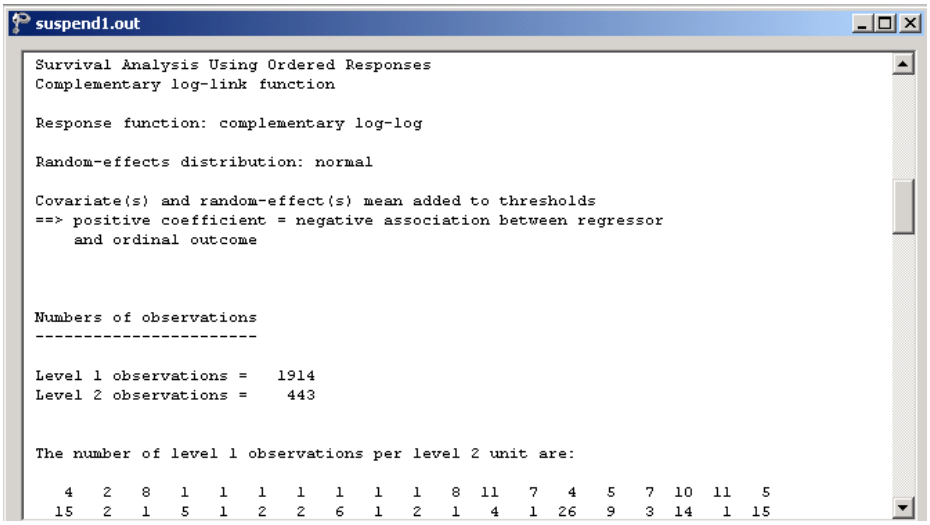
Intercpt	SexF	FinnAsst	SexFin	Random Intercpt (L-2)	Threshold 1	Threshold 2	Threshold 3
1	0	0	0	0	1	0	0
1	0	0	0	0	0	1	0
1	0	0	0	0	0	0	1

The screen below shows the values entered for the first transform.



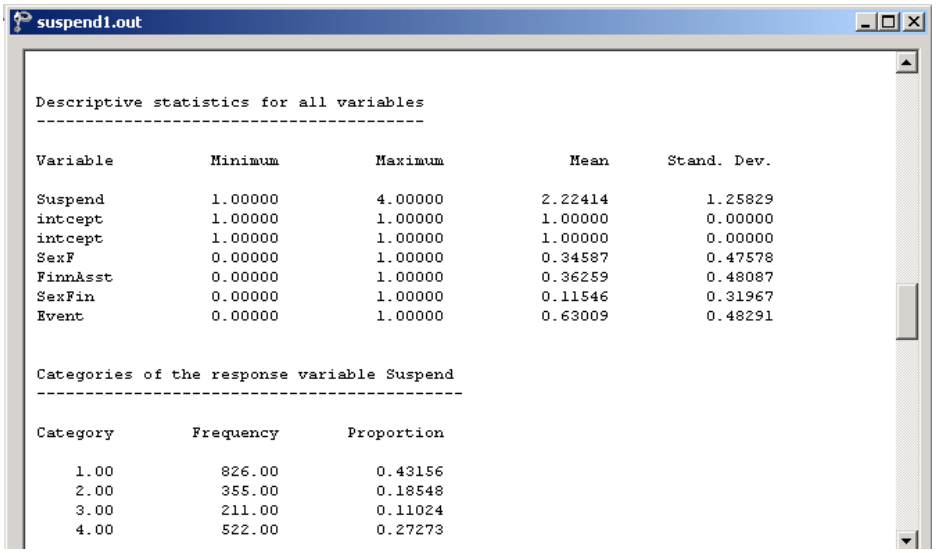
For the second transform, values of 0, 1, 0 are assigned for the thresholds. The third transform contains values of 0, 0, 1 for the three thresholds. This step completes the model set-up. Use the **File**, **Save** option to save the model setup to a file named **suspend1.mum**. Next, use the **Analysis**, **Run** option on the main menu bar to run the analysis.

Discussion of results



The portion of the output file shown below indicates that there are 443 therapists. Nested within these level-2 units are 1914 subjects. A summary of the number of level-1 observations per level-2 unit (only first two lines shown) is also given.

This part of the output is followed by descriptive statistics for all the variables. The variable Suspend has four categories with values 1, 2, 3 and 4. Except for the intercept term, the remaining variables are all dichotomous.

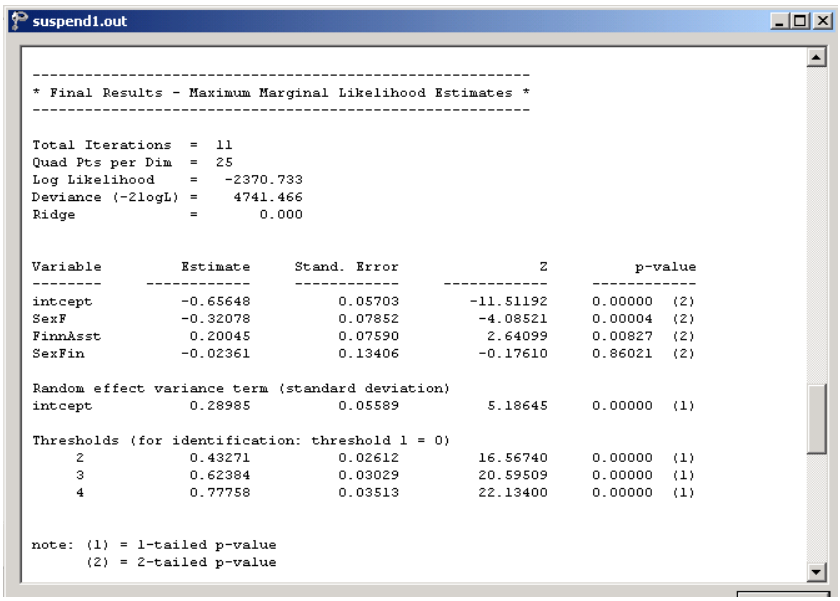


The proportions of subjects assigned a value of 1, 2, 3 or 4 are 0.432, 0.185, 0.110 and 0.273 respectively. A crosstabulation of Suspend by Event is given in Table 3.11. It follows that, for example, 773 students out of the 1914 in the study were suspended prior to treatment (T_0). For 53 children, we only know that they were not suspended at T_0, thereafter they are missing and treated as right-censored.

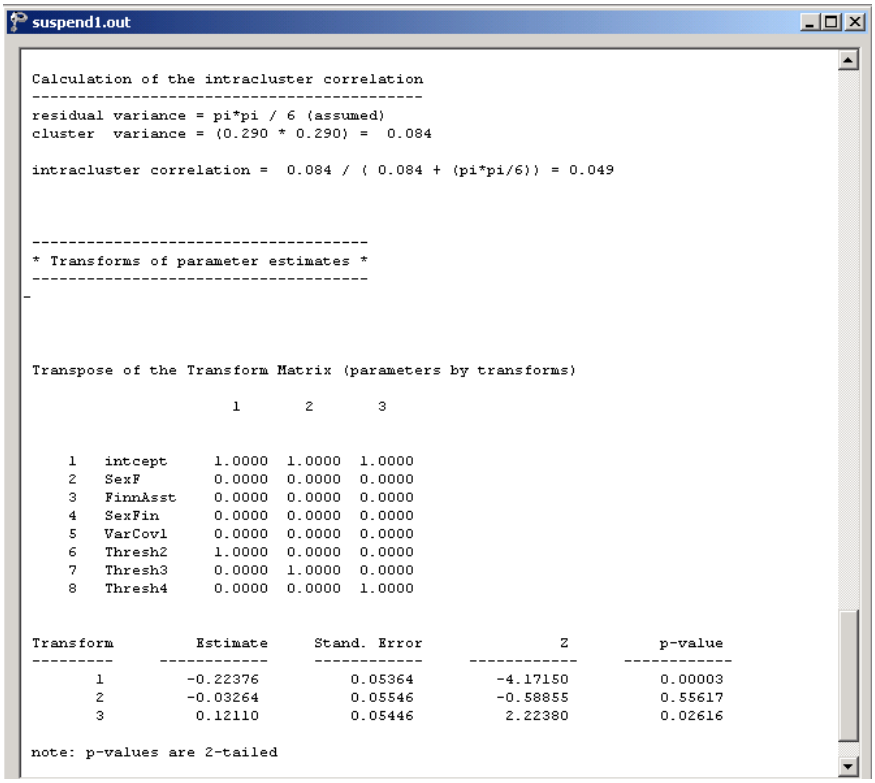
Table 3.11: Crosstabulation of Suspend by Event

T_0	T_1	T_2	T_3
773	255	106	72
53	100	105	450

Parameter estimates are given in the next part of the output. We conclude that there is no gender-financial assistance interaction and that all the remaining parameter estimates are significant. The effect of SexF is negative indicating that girls have a significantly decreased hazard (*i.e.*, a longer time to the first suspension), relative to boys. The FinnAsst estimate is positive indicating an increased hazard (shorter time to first suspension) for children from families receiving financial assistance, relative to children from families not receiving this assistance.



The last part of the output contains an estimate of the intracluster correlation. Although this estimate indicates a modest therapist effect, the random effect variance term is highly significant. From this we conclude that the time until suspension does vary significantly across therapists.



A summary of the transforms (given in transposed form) is given followed by a significance test for each transform. In combination with the intercept estimate, these provide the estimates of the baseline hazard (*i.e.*, the hazard when all covariates equal 0). Specifically, the baseline hazard estimates for the four study time points are -0.65649, -0.22377, -0.03265, and 0.12110. These can be converted to the probability scale using the inverse of the complementary log-log function, namely,

$$P(z) = 1 - \exp[-\exp(z)]$$

This yields probability estimates of the baseline hazard for the first school suspension as .405, .550, .620, and .677 across these four study time points. Note that these are conditional estimates, conditional on the therapist effects. In other words, they are estimates controlling for the effect of therapist on the individual student outcomes.