Mixed Models for Discrete- and Grouped-Time Clustered Survival Data

Don Hedeker
Department of Public Health Sciences
Biological Sciences Division
University of Chicago

hedeker@uchicago.edu

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Modeling time until an event occurs

- initiation of smoking experimentation in adolescents
- time until school suspension in "problem" kids
- time until start (or end) of service use
- time until quit or relapse (smoking, alcohol, drugs, weight)
- time until death

analysis is called "survival" analysis, but why be so morbid?

$\Rightarrow$ it can be used for any time-to-event data

Metric of time

- Continuous time - event timing is known in fine detail
  – days until disease development (or recovery)

- Grouped time - event timing is known within intervals of time (also called interval-censored)
  – smoking initiation assessed yearly from 7th to 10th grades

- Discrete time - event timing is known, but discrete number of timepoints and no time intervals
  – person failed on the 5th question in a TV game show

Focus on grouped- and discrete-time, but continuous time can be modelled similarly (using, say, 10 quantiles for event-time intervals, see Liu & Huang, Statistics in Medicine, 2008)

Reading materials - no random effects

- Singer & Willett (2003) *Applied Longitudinal Data Analysis*, Oxford University Press

- Allison (1995) *Survival Analysis using the SAS System: A Practical Guide*

- Xie, McHugo, Drake, & Sengupta (2003). Using discrete-time survival analysis to examine patterns of remission from substance use disorder among persons with severe mental illness. *Mental Health Services Research, 5*, 55-64.

Reading materials and examples - with random effects

- Hedeker, Siddiqui, & Hu (2000). Random-effects regression analysis of correlated grouped-time survival data. *Statistical Methods in Medical Research*, **9**:161-179
  available via www.uic.edu\∼hedeker

- Hedeker & Mermelstein (2011). Multilevel analysis of ordinal outcomes related to survival data. *Handbook of Advanced Multilevel Analysis*, (pp. 115-136), Hoop & Roberts (eds.), Taylor and Francis.

- SuperMix www.ssicentral.com/supermix/downloads.html
  - www.ssicentral.com/supermix/examples/Survival.html
  - in Supermix (even the free student version), from Help menu, select "Contents," "Examples from SMIX manual," "Grouped- and discrete-time survival data"

Notation is our friend!

- $i = 1, \ldots, N$ level-2 units (clusters or subjects)
- $j = 1, \ldots, n_i$ level-1 units (subjects or multiple failure times)
- assessment time takes on discrete positive values $t = 1, 2, \ldots, m$ representing time points or intervals
- each ij unit is observed until time t_{ij}
  - an event occurs ($t_{ij} = t$ and $\delta_{ij} = 1$)
  - observation is censored ($t_{ij} = t$ and $\delta_{ij} = 0$)
- censoring: unit is observed at t_{ij} but not at $t_{ij} + 1$
- δ_{ij} is the censor/event indicator

$\Rightarrow$ Outcome is t_{ij} (which is either censored or not)

Failure, Survival, and Hazard probabilities

cumulative **Failure** probability, up to and including time t

$P(t_{ij}) = \Pr(t_{ij} \leq t)$

cumulative **Survival** probability beyond time t

$1 - P(t_{ij})$

Hazard = conditional probability that an event occurs at time t given that it has not already occurred

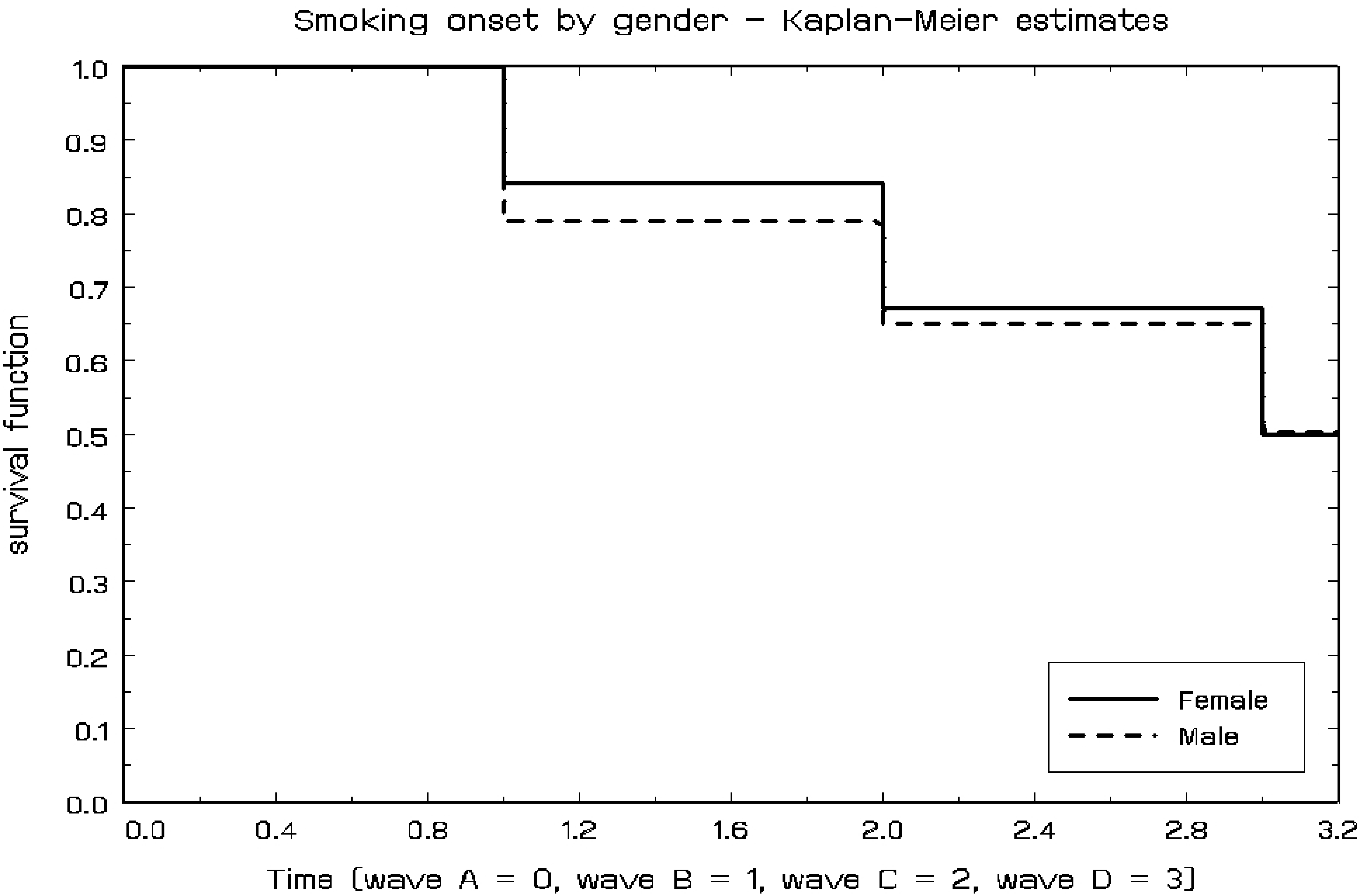
$p(t_{ij}) = \Pr(t_{ij} = t \mid t_{ij} \geq t) = (\#\text{ events at } t) \div (\#\text{ at risk at } t)$

$\Rightarrow$ " time-interval t" instead of "time t" for time-interval data

Kaplan-Meier Survival Function estimates

Initiation of smoking experimentation in adolescents

time	# censor	# event	hazard prob	interval survival prob	cumulative survival prob
Females (N=814)					
post-int	105	130	$\frac{130}{814} = .160$	.840	.840
year 1	154	117	$\frac{117}{814-235} = .202$	.798	$(.840)(.798) = .671$
year 2	229	79	$\frac{79}{814-235-271} = .257$	.744	$(.671)(.744) = .499$
Males (N=742)					
post-int	83	156	$\frac{156}{742} = .210$	.790	.790
year 1	134	89	$\frac{89}{742-239} = .177$	.823	$(.790)(.823) = .650$
year 2	217	63	$\frac{63}{742-239-223} = .225$	.775	$(.650)(.775) = .504$


Smoking onset by gender - Kaplan-Meier estimates
survival function
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
Time (wave A = 0, wave B = 1, wave C = 2, wave D = 3)
Female
Male

Categorical Regression Models - right-hand side

$$\gamma_t + \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \boldsymbol{z}'_{ij}\boldsymbol{v}_i$$

- γ_t represent baseline hazard
- $\boldsymbol{x}_{ij}$ are covariates
  - at level-1, level-2, or cross-level interactions
  - can include polynomials, dummy variables, interactions, ...
- $\boldsymbol{\beta}$ are the regression coefficients for the covariates
- $\boldsymbol{z}_{ij}$ are the random effect variable(s)
  - usually just an intercept for clustered data
  - often an intercept and time for longitudinal data
- $\boldsymbol{v}_i$ are the random effects $\sim$ N(0, $\boldsymbol{\Sigma}_v$)
  - how cluster i influences the observations within the cluster
  - how a subject starts and progresses across time

Discrete or Grouped Time?

Discrete time: events occur at discrete points in time

- repeated tasks, *e.g.*, Who wants to be a millionaire?

- logit link: discrete-time proportional odds model

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

- with no random effects, same as TIES=DISCRETE option in SAS PROC PHREG in terms of $\boldsymbol{\beta}$

- + in formulation means as $\beta \uparrow$ event occurs sooner (*i.e.*, hazard is increased)

Grouped time: events occur within continuous time intervals (also called interval-censored time)

- grades of school, *e.g.*, smoking initiation in past year

- complementary log-log link: underlying proportional hazards model in continuous time

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

- with no random effects, same as TIES=EXACT option in SAS PROC PHREG in terms of $\boldsymbol{\beta}$

- $+$ in formulation means as $\beta \uparrow$ event occurs sooner ($i.e.$, hazard is increased)

Logit or clog-log link?

- very similar results (so, in practice, it doesn't matter)
- logit yields odds ratio interpretation for $\exp \beta$
  - logit has proportional odds assumption
- clog-log yields hazards ratio interpretation for $\exp \beta$
  - clog-log has analogous proportional hazards assumption as continuous-time Cox model
- clog-log most useful for grouped-time
  - where time is really continuous, but measurement only occurs at discrete timepoints and captures event information about a time interval
- logit most common for discrete-time
  - no advantage for clog-log over logit for truly discrete-time

Initiation of smoking experimentation in adolescents

time	interval hazard p	interval survival $1 - p$	interval odds $p/(1-p)$	hazard ratio (M/F)	odds ratio (M/F)
Females (N=814)					
post-int	.160	.840	.190		
year 1	.202	.798	.253		
year 2	.257	.744	.345		
Males (N=742)					
post-int	.210	.790	.269	1.313	1.416
year 1	.177	.823	.215	.876	.850
year 2	.225	.775	.290	.875	.841

Hazard $\approx$ odds if p is small (rare event)

Two ways to structure the data and analyses

- Ordinal
  - ordinal representation of survival time
  - analysis using ordinal regression models
  - logit or clog-log in terms of $P(t_{ij})$ (cumulative failure)

- Binary
  - creation of "person period" indicator(s) for each observation to represent survival time
  - analysis using binary regression models
  - logit or clog-log in terms of $p(t_{ij})$ (hazard)

$\Rightarrow$ Ordinal is easier in terms of dataset structure, but binary is easier (and more general) in terms of analysis

Survival data as categorical outcomes

Ordinal: 2 (post-baseline) timepts with no intermittent censoring

- Outcome = 1 : died at T1 (interval between T0 and T1)

  ☹

- Outcome = 2 : died at T2 (interval between T1 and T2)

  😐

- Outcome = 3 : did not die at T2 (censored at T2)

  ☺

Dichot: 2 (post-baseline) timepts with no intermittent censoring

Create person-time indicators y_1 & y_2 (0=censor, 1=event)
# of records depends on timing of event "person-period dataset"

- y_1=1: died at T1 (interval between T0 and T1)

  ☹

- y_1=0 and y_2=1: died at T2 (interval between T1 and T2)

  ☺

  ☹

- y_1=0 and y_2=0: did not die at T2 (was censored at T2)

  ☺

  ☺

Three timepoints with censoring

	Ordinal		*Dichotomous*
outcome	ordinal dep var	event indicator	up to 3 records per person
Censor at T1	1	0	y_1=0
Event at T1	1	1	y_1=1
Censor at T2	2	0	y_1=0 y_2=0
Event at T2	2	1	y_1=0 y_2=1
Censor at T3	3	0	y_1=0 y_2=0 y_3=0
Event at T3	3	1	y_1=0 y_2=0 y_3=1

lower values of the ordinal dependent variable signify "worse" outcome

Dichotomous or Ordinal representation?

- Results are the same or similar
  - clog-log link: identical results for proportional hazards estimates (*i.e.*, effects that don't vary with time)
  - logit link: similar results

- Ordinal is more efficient in terms of dataset size, especially as number of timepoints is large

- Dichotomous more easily allows inclusion of time-dependent covariates and non-proportional hazards (or odds) models
  - each person has a record for each pertinent timept, so inclusion of time-dependent covariate is easy

e.g., for a subject with three timepoints of data:

outcome	time-invariant covariate	time-dependent covariate	time indicators	
y_1=0	sex	intentions_1	0	0
y_2=0	sex	intentions_2	1	0
y_3=0 or =1	sex	intentions_3	0	1

- values of intentions change across time
- adding covariate interactions with time indicators allow assessment of proportional hazards (odds) assumption
  - without interactions: proportional hazards (odds)
  - with interactions: non-proportional hazards (odds)

Decisions, decisions ..

	data representation	
link	dichotomous	ordinal
logit		
clog-log		

- don't sweat it, results are the same or very similar, which is why many prefer dichotomous & logit combination
- for grouped-time data, clog-log would seem to be best choice (in agreement with Cox proportional hazards model for continuous time)
- any interest in non-proportional effects or time-dependent covariates, then dichotomous representation is best

School-based Smoking Prevention Study

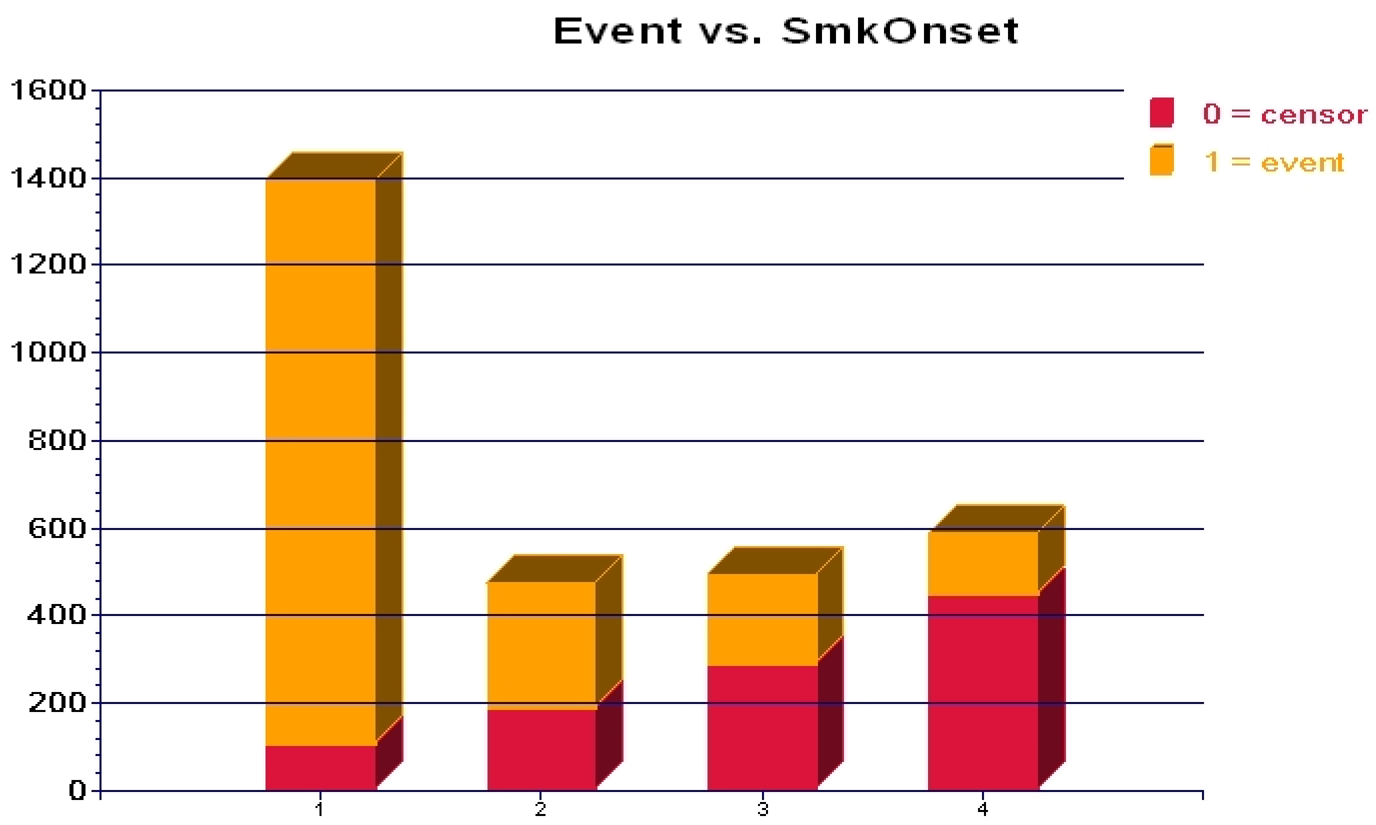
The Television School and Family Smoking Prevention and Cessation Project (Flay, *et al.*, 1988);

- *sample* - 2952 7th-graders - 135 classrooms - 28 schools in Los Angeles area
- *outcome*
  - "Have you ever tried a cigarette? (yes/no)"
- *timing* - students assessed at
  - *pre-intervention (1/86)* ($n = 1556$ never tried)
  - post-intervention (4/86)
  - 1 year follow-up (4/87)
  - 2 year follow-up (4/88)

- *design* - schools randomized to intervention conditions, interventions delivered in classrooms
  - a social-resistance classroom curriculum (CC)
  - a media (television) intervention (TV)
  - CC combined with TV
  - a no-treatment control group

Question of interest:

- Intervention effect on smoking initiation at post-intervention and 2 yearly follow-ups?


Event vs. SmkOnset
1600
1400
1200
1000
800
600
400
200
0
1
2
3
4
0 = censor
1 = event

Four timepoints, but first is missing or excluded

Ordinal - c:\SuperMixEn Examples\Workshop\Survival\SmkCCLC.ss3

Dichotomous - c:\SuperMixEn Examples\Manual\Survival\SmkBCD2.ss3

	Ordinal		*Dichotomous* (up to 3 records per person)	
outcome	ordinal dep var	event indicator	dep var	time indicators
Censor at baseline	1	0	*not in dataset*	
Event at baseline	1	1	*not in dataset*	
Censor at post-int	2	0	y_1=0	0 0
Event at post-int	2	1	y_1=1	0 0
Censor at 1 yr	3	0	y_1=0 y_2=0	0 0 1 0
Event at 1 yr	3	1	y_1=0 y_2=1	0 0 1 0
Censor at 2 yr	4	0	y_1=0 y_2=0 y_3=0	0 0 1 0 0 1
Event at 2 yr	4	1	y_1=0 y_2=0 y_3=1	0 0 1 0 0 1

Grouped-Time Onset of Cigarette Experimentation in 1556 students
Proportional Hazards Model estimates (se)

	PROC PHREG	clog-log regression	
term	(ties=exact)	dichot	ordinal
intercept β_0		-1.652	-1.652
		(.091)	(.091)
intercept $\beta_0 + \gamma_2$		-1.613	-.939
		(.096)	(.083)
intercept $\beta_0 + \gamma_3$		-1.344	-.428
		(.106)	(.081)
Male β_1	.056	.056	.056
	(.080)	(.080)	(.080)
CC β_2	.041	.041	.041
	(.080)	(.080)	(.080)
TV β_3	.023	.023	.023
	(.080)	(.080)	(.080)
$-2 \log L$			
full model	3166.7	3187.4	3187.4
with $\beta_2 = \beta_3 = 0$	3167.0	3187.8	3187.8

Grouped-Time Onset of Cigarette Exp. - 1556 students in 28 schools
Mixed-effects Proportional Hazards estimates (se)

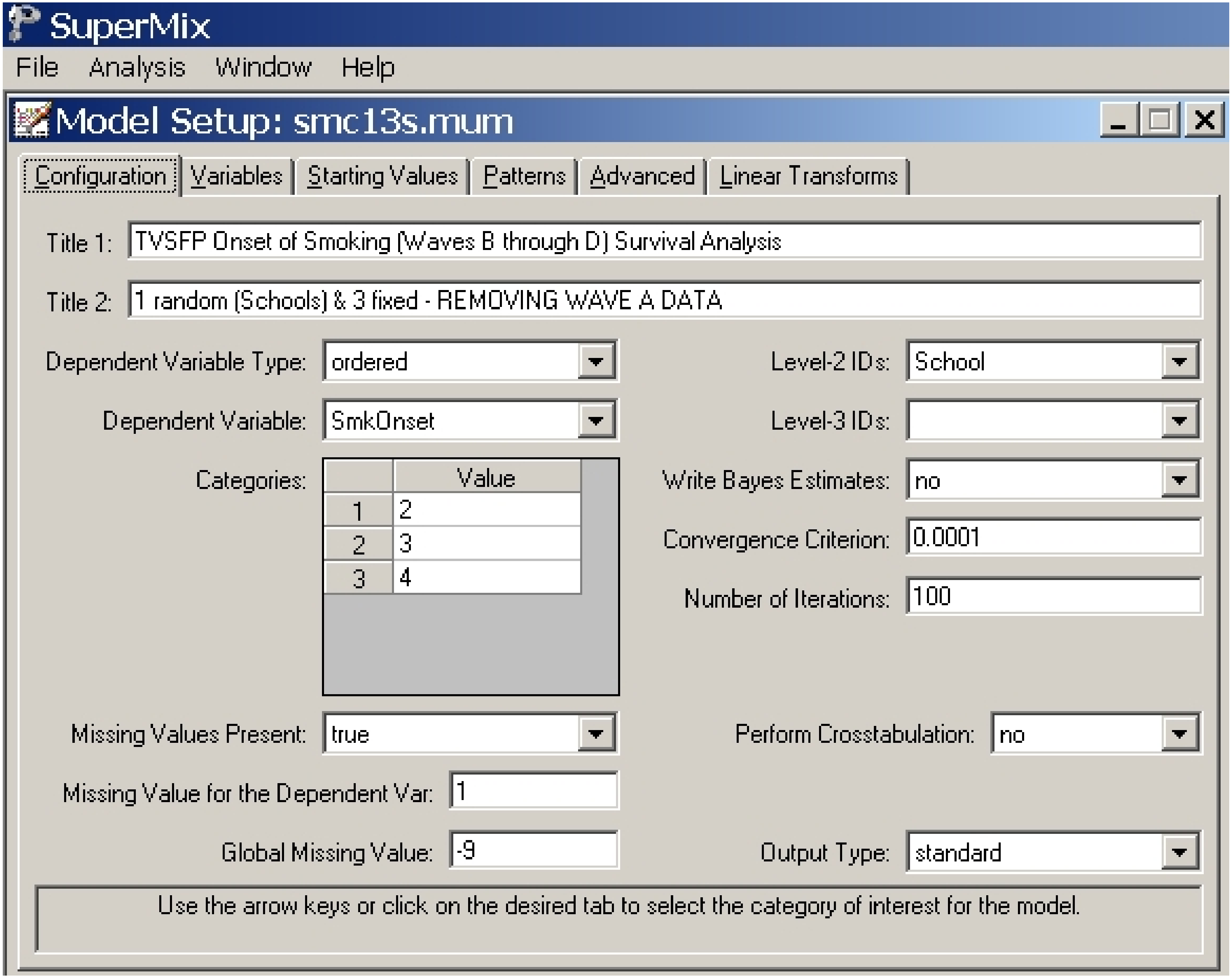
term	Dichot	Ordinal
intercept β_0	-1.657	-1.657
	(.095)	(.095)
intercept $\beta_0 + \gamma_2$	-1.617	-.944
	(.101)	(.087)
intercept $\beta_0 + \gamma_3$	-1.346	-.432
	(.111)	(.085)
Male β_1	.058	.058
	(.080)	(.080)
CC β_2	.045	.045
	(.084)	(.084)
TV β_3	.021	.021
	(.084)	(.084)
School variance σ_v^2	.0031	.0031
[$r = .002$]	(.011)	(.011)
$-2 \log L$		
full model	3187.4	3187.4
with $\beta_2 = \beta_3 = 0$	3187.7	3187.7

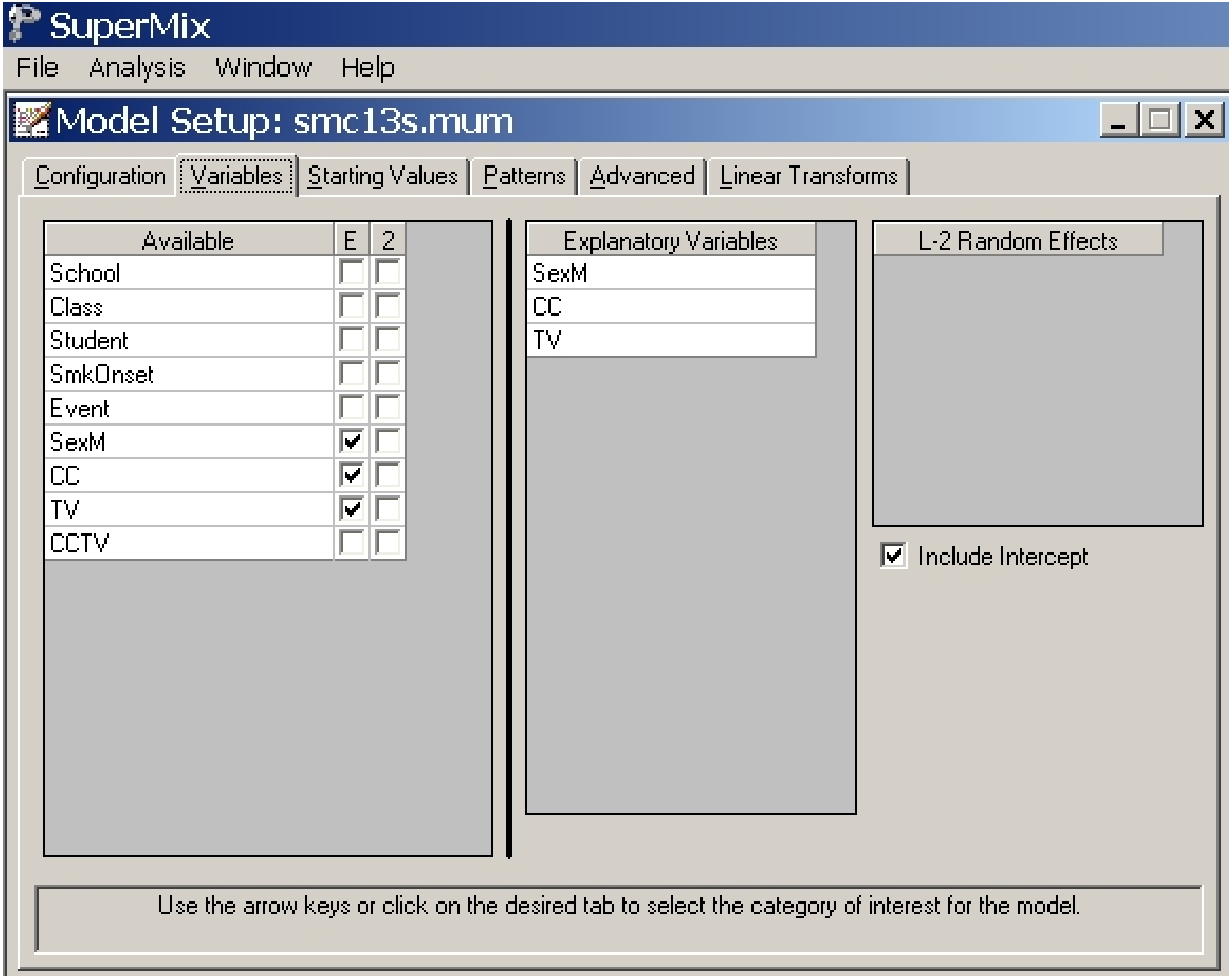
Ordinal representation - c:\SuperMixEn Examples\Workshop\Survival\SmkCCLC.ss3

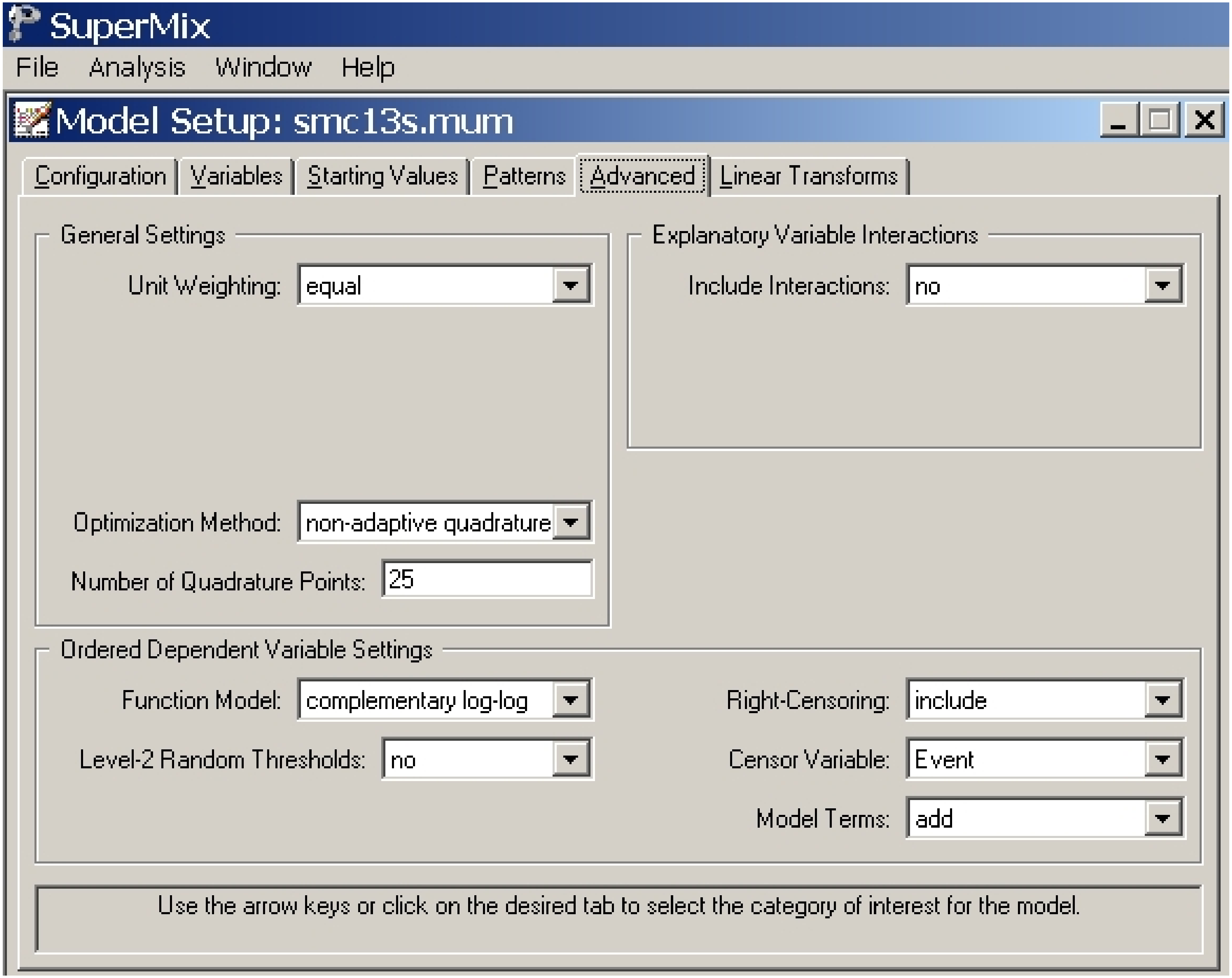
SuperMix - [SMKCCLC.ss3]

File Edit Window Help

	(A)_School	(B)_Class	(C)_Student	(D)_SmkOns	(E)_Event	(F)_SexM	(G)_CC	(H)_TV	(I)_CCTV
1	193	193101	193101103	1	1	0	0	0	0
2	193	193101	193101105	4	0	1	0	0	0
3	193	193101	193101108	4	0	0	0	0	0
4	193	193101	193101111	1	1	1	0	0	0
5	193	193101	193101113	2	1	1	0	0	0
6	193	193101	193101117	2	1	1	0	0	0
7	193	193101	193101121	4	0	1	0	0	0
8	193	193101	193101132	4	0	0	0	0	0
9	193	193101	193101201	4	1	0	0	0	0
10	193	193101	193101204	4	0	0	0	0	0
11	193	193101	193101207	1	1	1	0	0	0
12	193	193101	193101210	4	0	1	0	0	0
13	193	193101	193101212	4	0	1	0	0	0
14	193	193101	193101214	4	0	1	0	0	0
15	193	193101	193101218	1	1	1	0	0	0
16	193	193101	193101220	2	1	0	0	0	0
17	193	193101	193101224	4	0	0	0	0	0
18	193	193101	193101225	2	0	0	0	0	0
19	193	193101	193101302	4	0	0	0	0	0
20	193	193101	193101306	4	0	0	0	0	0
21	193	193101	193101309	1	1	1	0	0	0
22	193	193101	193101315	2	1	1	0	0	0
23	193	193101	193101316	1	1	1	0	0	0
24	193	193101	193101319	4	0	0	0	0	0
25	193	193101	193101322	4	0	1	0	0	0
26	193	193101	193101326	4	0	0	0	0	0


SuperMix
File
Analysis
Window
Help
Model Setup: smc13s.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1: TVSFP Onset of Smoking (Waves B through D) Survival Analysis
Title 2: 1 random (Schools) & 3 fixed - REMOVING WAVE A DATA
Dependent Variable Type: ordered
Dependent Variable: SmkOnset
Categories:
Value
1 2
2 3
3 4
Level-2 IDs: School
Level-3 IDs:
Write Bayes Estimates: no
Convergence Criterion: 0.0001
Number of Iterations: 100
Missing Values Present: true
Missing Value for the Dependent Var: 1
Global Missing Value: -9
Perform Crosstabulation: no
Output Type: standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File Analysis Window Help
Model Setup: smc13s.mum
Configuration Variables Starting Values Patterns Advanced Linear Transforms
Available E 2
School
Class
Student
SmkOnset
Event
SexM
CC
TV
CCTV
Explanatory Variables
SexM
CC
TV
L-2 Random Effects
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File Analysis Window Help
Model Setup: smc13s.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting: equal
Optimization Method: non-adaptive quadrature
Number of Quadrature Points: 25
Explanatory Variable Interactions
Include Interactions: no
Ordered Dependent Variable Settings
Function Model: complementary log-log
Level-2 Random Thresholds: no
Right-Censoring: include
Censor Variable: Event
Model Terms: add
Use the arrow keys or click on the desired tab to select the category of interest for the model.

SuperMix - [smc13s.out]

File Analysis Window Help

```
o==============================================================o
| TVSFP Onset of Smoking (Waves B through D) Survival Analysis |
| 1 random (Schools) & 3 fixed - REMOVING WAVE A DATA          |
o==============================================================o


           Model and Data Descriptions

   Sampling Distribution                    = Multinomial
   Link Function                            = Cumulative CLL
   Number of Level-2 Units                    28
   Number of Level-1 Units                    1556
   Number of Level-1 Units per Level-2 Unit =
    21     74     24     13     29     70     18     17     25     27     19     31
    40     51     27     23     79     39     52    106     74    142     51    104
    81     74     94    151



       o===========================================================o
       | Descriptive statistics for all the variables in the model |
       o===========================================================o
                                                             Standard
   Variable             Minimum      Maximum         Mean    Deviation
   --------             -------      -------         ----    ---------
   SmkOnset1             0.0000       1.0000       0.3046       0.4604
   SmkOnset2             0.0000       1.0000       0.3175       0.4656
   SmkOnset3             0.0000       1.0000       0.3779       0.4850
   SexM                  0.0000       1.0000       0.4769       0.4996
   CC                    0.0000       1.0000       0.4788       0.4997
   TV                    0.0000       1.0000       0.4904       0.5001



       o=================================================o
       | Results for the model without any random effects |
       o=================================================o

                      Goodness of fit statistics

   Statistic                                    Value          DF           Ratio
   ---------                                    -----          --           -----
   Likelihood Ratio Chi-square              4194.6047        1550          2.7062
   Pearson Chi-square                       6386.1749        1550          4.1201
```

Save As... Close

SuperMix - [smc13s.out]

File Analysis Window Help

```
 o============================================o
 | Optimization Method: Non-Adaptive Quadrature |
 o============================================o

Number of quadrature points =              25
Number of free parameters =                 7
Number of iterations used =                 5

-2lnL (deviance statistic) =       3187.38945
Akaike Information Criterion       3201.38945
Schwarz Criterion                  3238.83857


                    Estimated regression weights

                                          Standard
Parameter              Estimate           Error        z Value      P Value
---------              --------           ---------    -------      -------
Threshold1              -1.6568            0.0951     -17.4289       0.0000
Threshold2              -0.9435            0.0870     -10.8481       0.0000
Threshold3              -0.4316            0.0850      -5.0802       0.0000
SexM                     0.0575            0.0798       0.7201       0.4714
CC                       0.0452            0.0844       0.5358       0.5921
TV                       0.0212            0.0837       0.2532       0.8001


Alternative Parameterization, setting Threshold1= 0

                    Estimated regression weights

                                          Standard
Parameter              Estimate           Error        z Value      P Value
---------              --------           ---------    -------      -------
intcept                 -1.6568            0.0951     -17.4289       0.0000
Threshold2               0.7134            0.0467      15.2638       0.0000
Threshold3               1.2252            0.0581      21.1000       0.0000


               Estimated level 2 variances and covariances

                                               Standard
Parameter                       Estimate       Error         z Value   P Value
---------                       ---------      ---------     -------   -------
intercept/intercept               0.0031         0.0113       0.2790    0.7803
```

Save As... Close

Testing of proportional hazards assumption

Relatively easy in dichotomous formulation by including interactions with time indicators, *e.g.*, for a subject with three timepoints:

outcome	covariate	time indicators		time interactions	
y_1=0	sex	0	0	sex × 0	sex × 0
y_2=0	sex	1	0	sex × 1	sex × 0
y_3=0 or y_3=1	sex	0	1	sex × 0	sex × 1

Likelihood ratio test: compare deviances (-2 log L) from two models, where one is nested within the other. Smaller deviance values are better, and the difference can be compared to a χ^2 distribution with q df (q = # of additional parameters in larger model)

In present case:

term	likelihood-ratio χ^2	df	$p <$
intervention (CC & TV)	4.1	4	ns
sex	8.0	2	.02

From model with sex by time interaction terms:

term	estimate	std error	z-statistic	$p <$
Male at Post-Int	.306	.119	2.57	.011
Male by Year 1	-.452	.184	-2.46	.015
Male by Year 2	-.458	.207	-2.21	.028
Male at Year 1	-.146	.141	-1.03	ns
Male at Year 2	-.152	.170	-.89	ns

Grouped-Time Onset of Cig. Exp. - 1556 students in 28 schools
Mixed-effects Partial Proportional Hazards estimates (se)

term	estimate	std error	$p <$
Intercept	-1.784	.108	.001
Year 1	.260	.128	.042
Year 2	.536	.143	.001
Sex (f=0; m=1)	.306	.119	.011
CC (no=0; yes=1)	.047	.084	.576
TV (no=0; yes=1)	.021	.083	.805
Sex × Year 1	-.452	.184	.015
Sex × Year 2	-.458	.207	.028
School variance	.0029	.011	.788

Binary representation

c:\SuperMixEn Examples\Manual\Survival\SmkBCD2.ss3

SuperMix - [SMKBCD2.ss3]

File Edit Window Help

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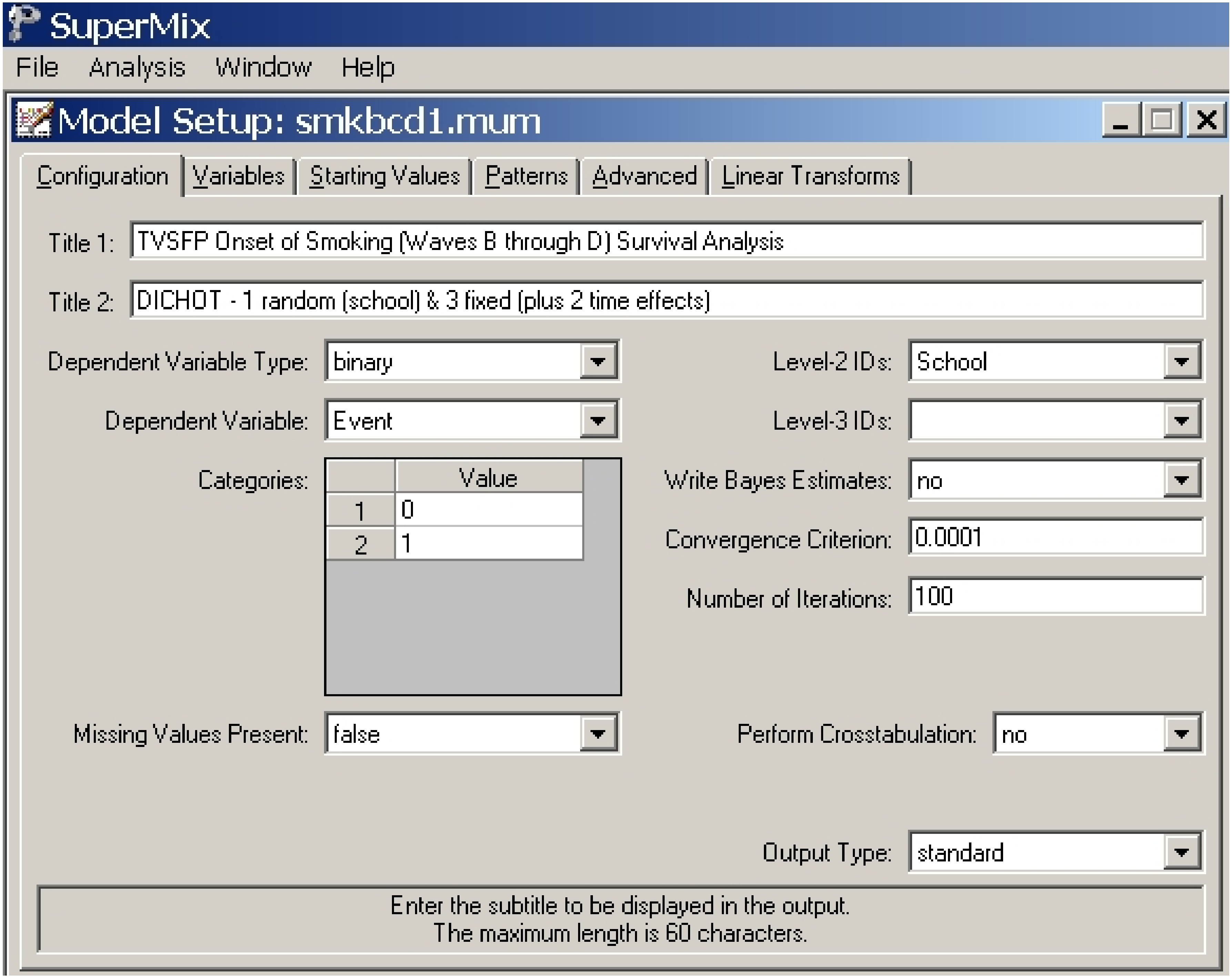
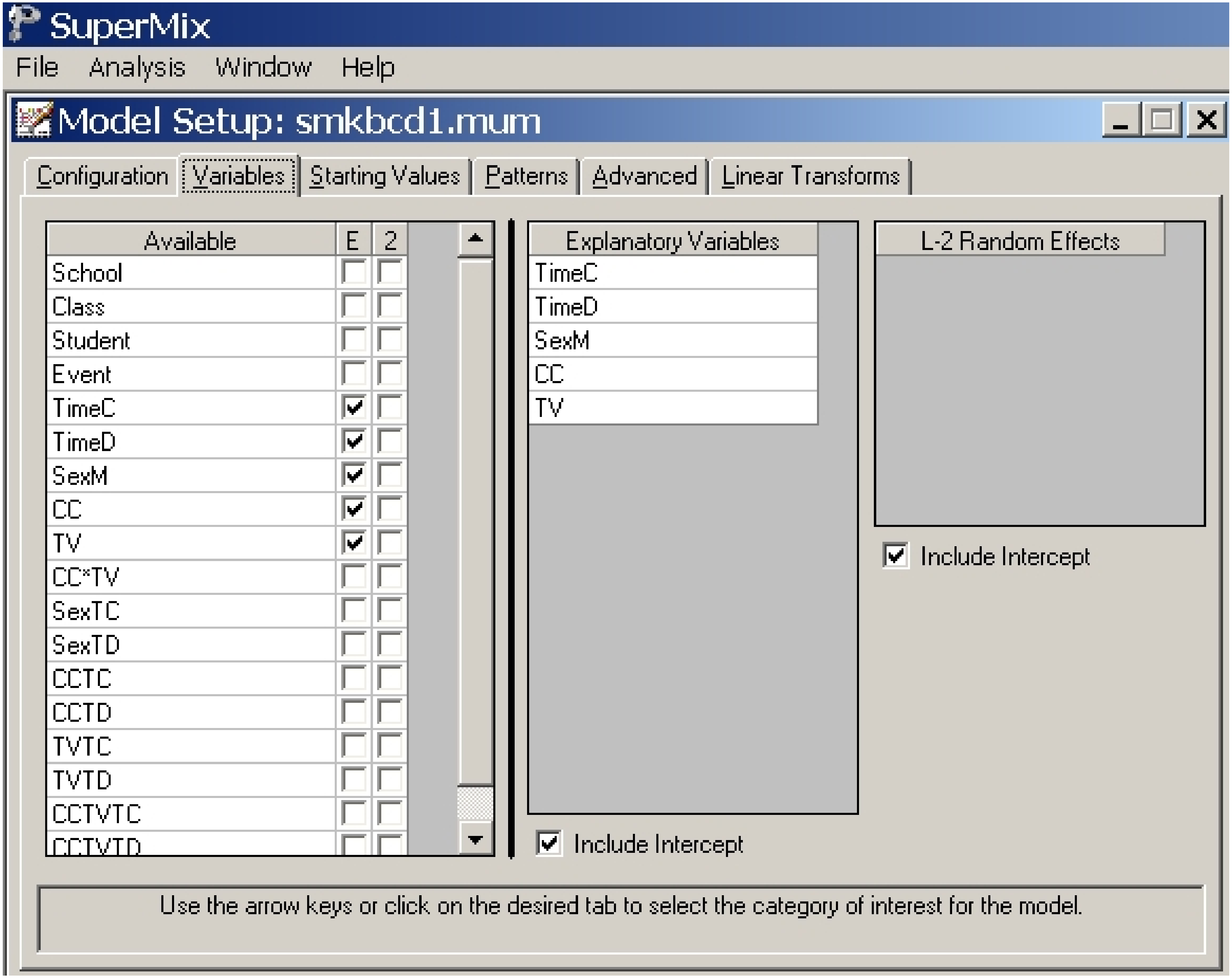
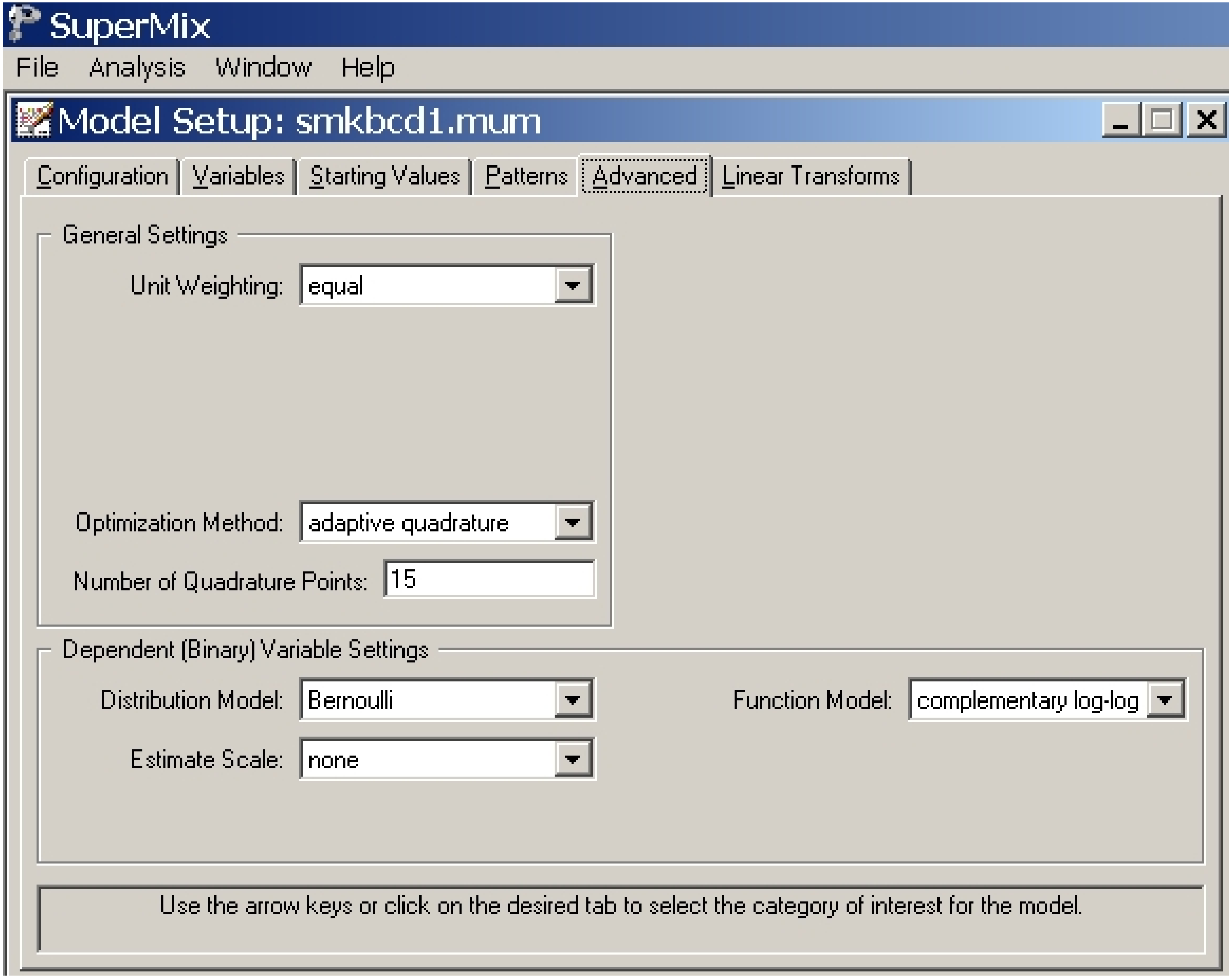
	(A)_School	(B)_Class	(C)_Student	(D)_Event	(E)_TimeC	(F)_TimeD	(G)_SexM	(H)_CC	(I)_TV	(J)_CC*TV	(K)_SexTC	(L)_SexTD
1	193	193101	193101105	0	0	0	1	0	0	0	0	0
2	193	193101	193101105	0	1	0	1	0	0	0	1	0
3	193	193101	193101105	0	0	1	1	0	0	0	0	1
4	193	193101	193101108	0	0	0	0	0	0	0	0	0
5	193	193101	193101108	0	1	0	0	0	0	0	0	0
6	193	193101	193101108	0	0	1	0	0	0	0	0	0
7	193	193101	193101113	1	0	0	1	0	0	0	0	0
8	193	193101	193101117	1	0	0	1	0	0	0	0	0
9	193	193101	193101121	0	0	0	1	0	0	0	0	0
10	193	193101	193101121	0	1	0	1	0	0	0	1	0
11	193	193101	193101121	0	0	1	1	0	0	0	0	1
12	193	193101	193101132	0	0	0	0	0	0	0	0	0
13	193	193101	193101132	0	1	0	0	0	0	0	0	0
14	193	193101	193101132	0	0	1	0	0	0	0	0	0
15	193	193101	193101201	0	0	0	0	0	0	0	0	0
16	193	193101	193101201	0	1	0	0	0	0	0	0	0
17	193	193101	193101201	1	0	1	0	0	0	0	0	0
18	193	193101	193101204	0	0	0	0	0	0	0	0	0
19	193	193101	193101204	0	1	0	0	0	0	0	0	0
20	193	193101	193101204	0	0	1	0	0	0	0	0	0
21	193	193101	193101210	0	0	0	1	0	0	0	0	0
22	193	193101	193101210	0	1	0	1	0	0	0	1	0
23	193	193101	193101210	0	0	1	1	0	0	0	0	1
24	193	193101	193101212	0	0	0	1	0	0	0	0	0
25	193	193101	193101212	0	1	0	1	0	0	0	1	0
26	193	193101	193101212	0	0	1	1	0	0	0	0	1


SuperMix
File Analysis Window Help
Model Setup: smkbcd1.mum
Configuration Variables Starting Values Patterns Advanced Linear Transforms
Title 1: TVSFP Onset of Smoking (Waves B through D) Survival Analysis
Title 2: DICHOT - 1 random (school) & 3 fixed (plus 2 time effects)
Dependent Variable Type: binary
Dependent Variable: Event
Categories:
Value
1 0
2 1
Level-2 IDs: School
Level-3 IDs:
Write Bayes Estimates: no
Convergence Criterion: 0.0001
Number of Iterations: 100
Missing Values Present: false
Perform Crosstabulation: no
Output Type: standard
Enter the subtitle to be displayed in the output.
The maximum length is 60 characters.


SuperMix
File
Analysis
Window
Help
Model Setup: smkbcd1.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
School
Class
Student
Event
TimeC
TimeD
SexM
CC
TV
CC*TV
SexTC
SexTD
CCTC
CCTD
TVTC
TVTD
CCTVTC
CCTVTD
Explanatory Variables
TimeC
TimeD
SexM
CC
TV
Include Intercept
L-2 Random Effects
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File
Analysis
Window
Help
Model Setup: smkbcd1.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
adaptive quadrature
Number of Quadrature Points:
15
Dependent (Binary) Variable Settings
Distribution Model:
Bernoulli
Function Model:
complementary log-log
Estimate Scale:
none
Use the arrow keys or click on the desired tab to select the category of interest for the model.

SuperMix - [smkbcd1.out]

File Analysis Window Help

```
| TVSFP Onset of Smoking (Waves B through D) Survival Analysis |
| DICHOT - 1 random (school) & 3 fixed (plus 2 time effects)    |
o=============================================================o


          Model and Data Descriptions

   Sampling Distribution                    = Bernoulli
   Link Function                            = Complementary Log-Log (CLL)
   PROB(Success)= 1.0-EXP[-EXP(ETA)]

   Number of Level-2 Units                    28
   Number of Level-1 Units                    3226
   Number of Level-1 Units per Level-2 Unit =
    51   163    57    30    59   153    34    42    62    56    42    64
    86    99    54    46   175    82   123   200   155   264   117   194
   202   150   172   294



    o============================================================o
    | Descriptive statistics for all the variables in the model |
    o============================================================o
                                                             Standard
   Variable              Minimum      Maximum         Mean  Deviation
   --------              -------      -------         ----  ---------
   Event1                 0.0000       1.0000       0.8035     0.3974
   Event2                 0.0000       1.0000       0.1965     0.3974
   intercept              1.0000       1.0000       1.0000     0.0000
   TimeC                  0.0000       1.0000       0.3354     0.4722
   TimeD                  0.0000       1.0000       0.1823     0.3861
   SexM                   0.0000       1.0000       0.4727     0.4993
   CC                     0.0000       1.0000       0.4823     0.4998
   TV                     0.0000       1.0000       0.4771     0.4996



    o===================================================o
    | Results for the model without any random effects |
    o===================================================o

                        Goodness of fit statistics

   Statistic                                Value         DF          Ratio
   ---------                                -----         --          -----
```

Save As... Close

SuperMix - [smkbcd1.out]

File Analysis Window Help

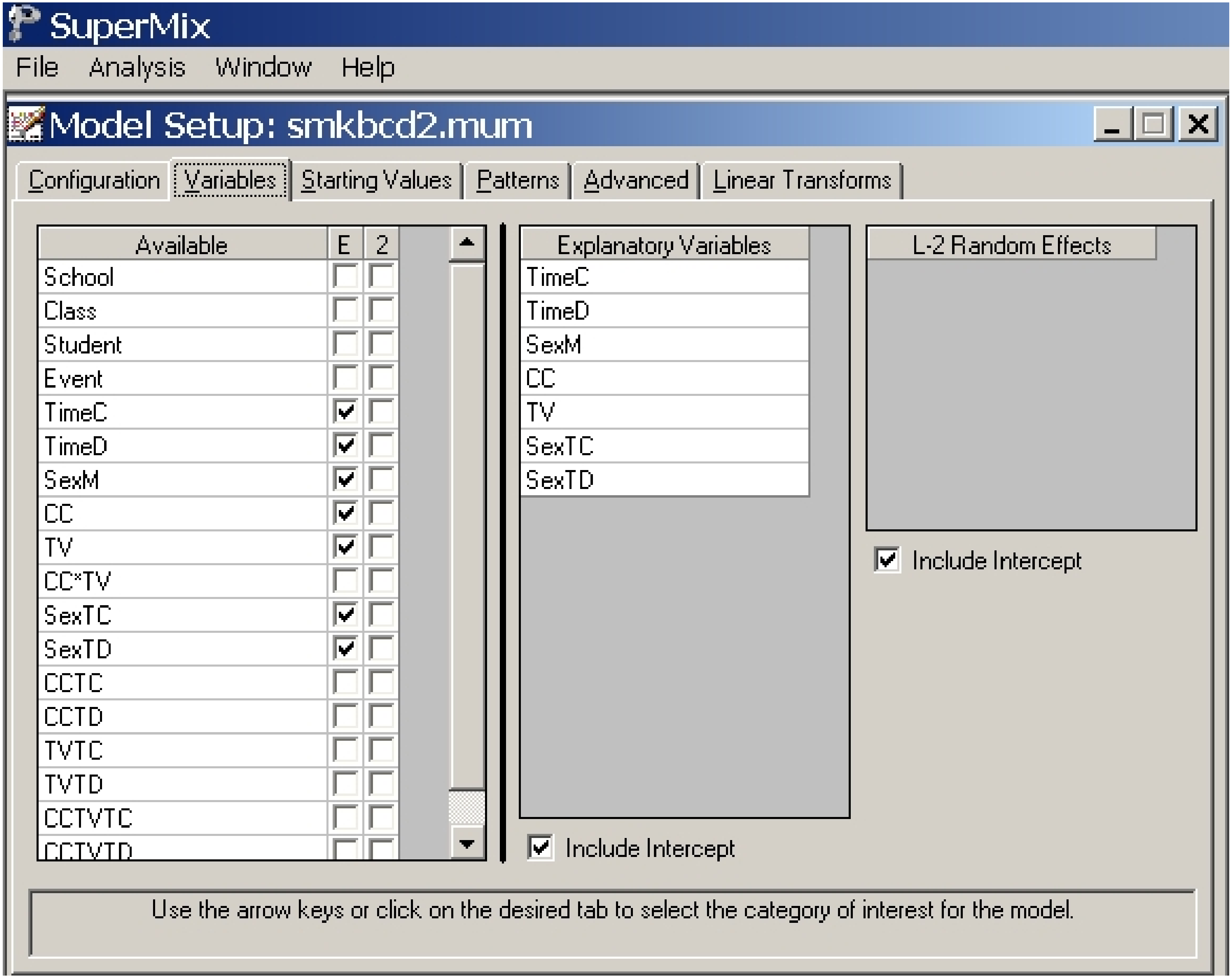
```
o===========================================o
| Optimization Method: Adaptive Quadrature |
o===========================================o

Number of quadrature points =              15
Number of free parameters =                 7
Number of iterations used =                 5

-2lnL (deviance statistic) =       3187.38945
Akaike Information Criterion       3201.38945
Schwarz Criterion                  3243.94244
```

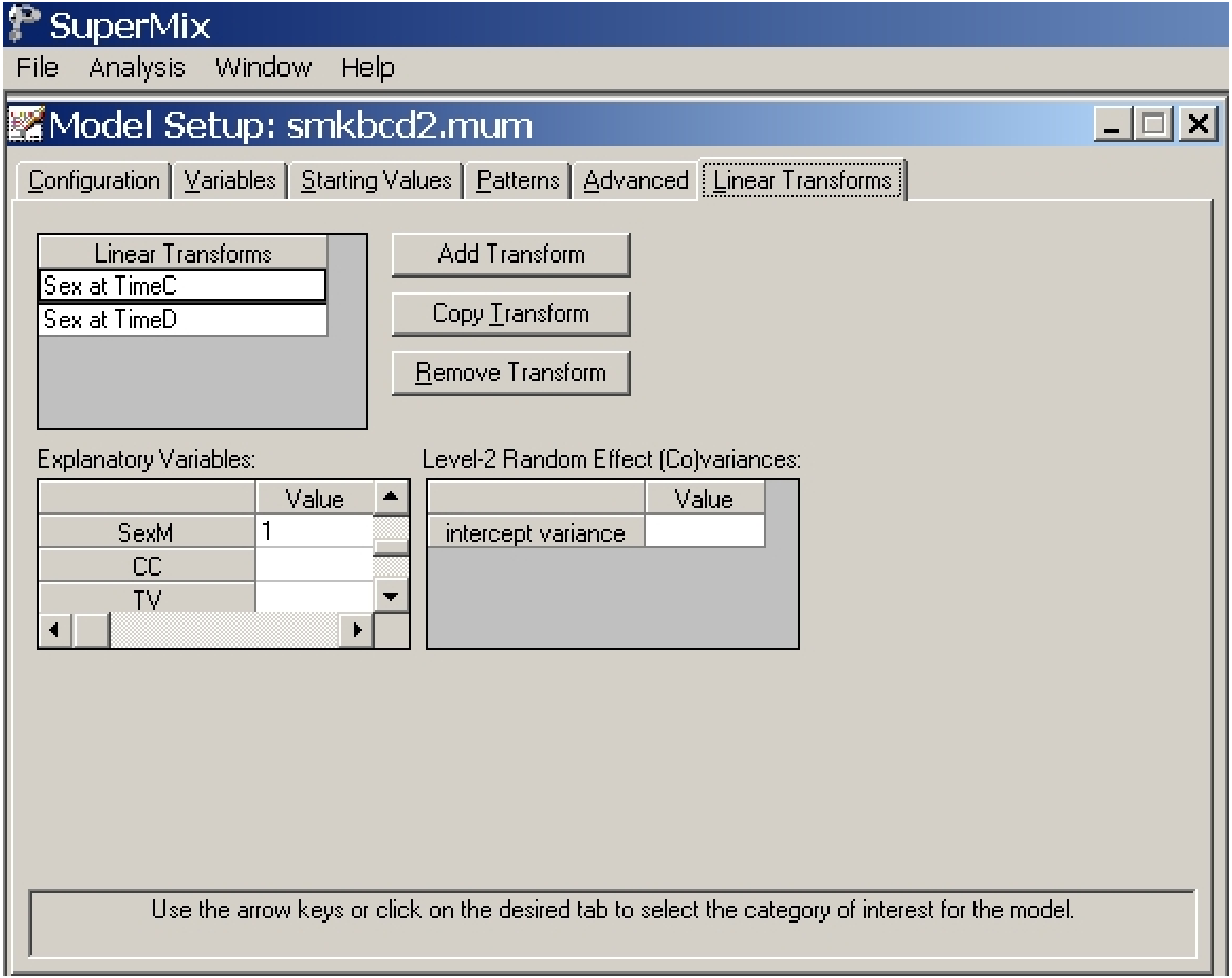
Estimated regression weights

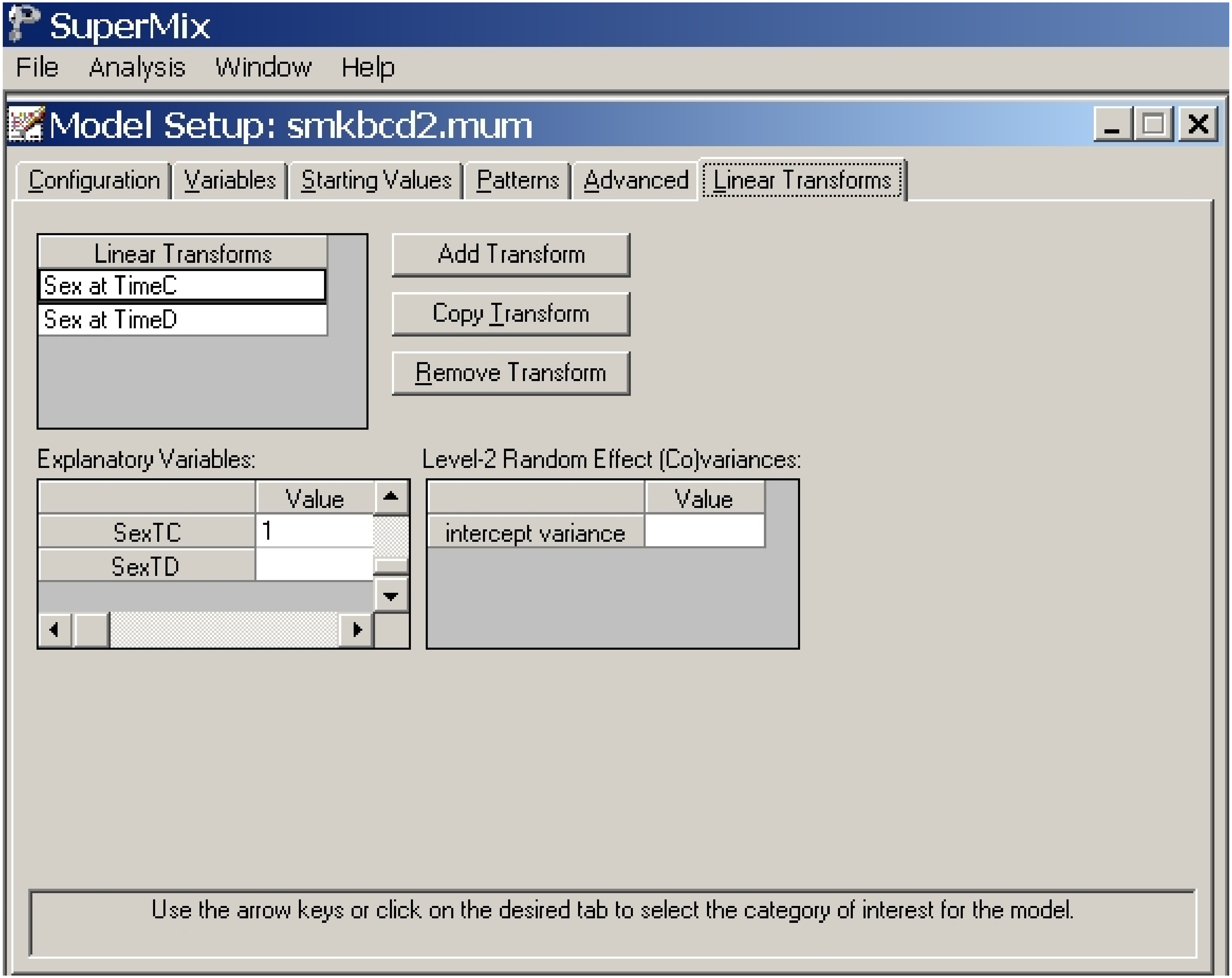
Parameter	Estimate	Standard Error	z Value	P Value
intercept	-1.6568	0.0951	-17.4289	0.0000
TimeC	0.0400	0.0916	0.4367	0.6623
TimeD	0.3105	0.1035	3.0010	0.0027
SexM	0.0575	0.0798	0.7201	0.4714
CC	0.0452	0.0844	0.5358	0.5921
TV	0.0212	0.0837	0.2532	0.8001

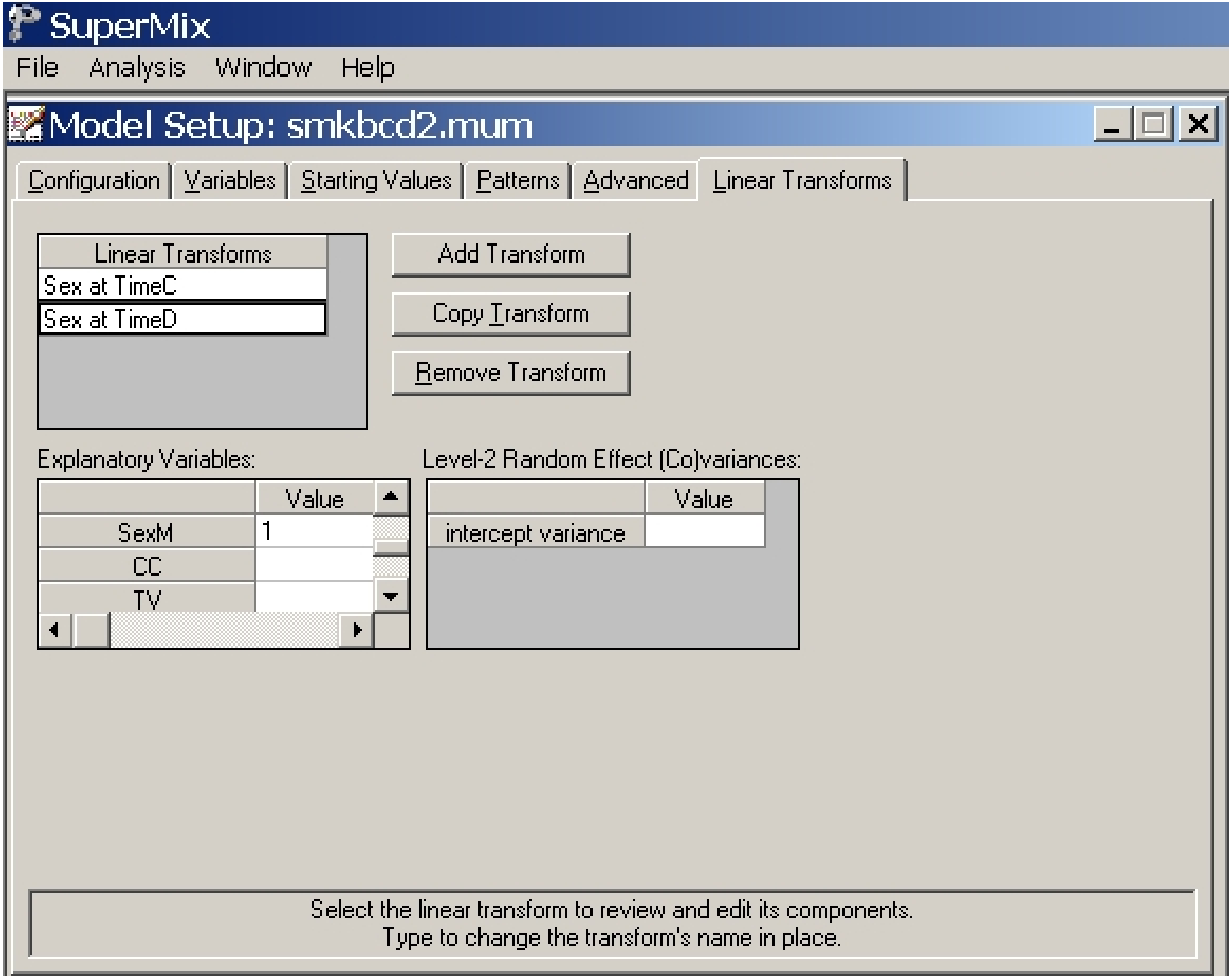
Estimated level 2 variances and covariances

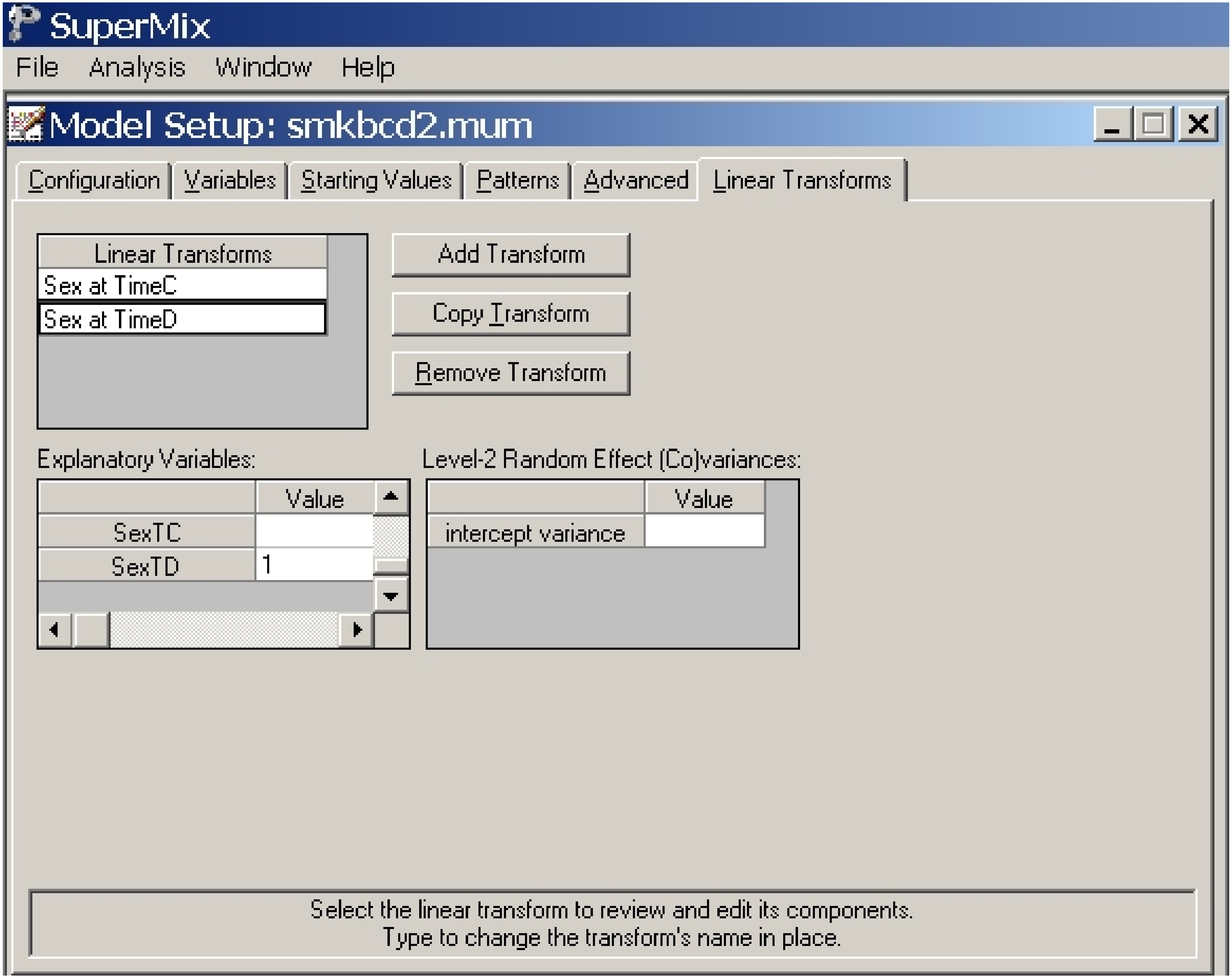
Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.0031	0.0113	0.2790	0.7803


SuperMix
File
Analysis
Window
Help
Model Setup: smkbcd2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
School
Class
Student
Event
TimeC
TimeD
SexM
CC
TV
CC*TV
SexTC
SexTD
CCTC
CCTD
TVTC
TVTD
CCTVTC
CCTVTD
Explanatory Variables
TimeC
TimeD
SexM
CC
TV
SexTC
SexTD
Include Intercept
L-2 Random Effects
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File
Analysis
Window
Help
Model Setup: smkbcd2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Linear Transforms
Sex at TimeC
Sex at TimeD
Add Transform
Copy Transform
Remove Transform
Explanatory Variables:
Value
SexM
1
CC
TV
Level-2 Random Effect (Co)variances:
Value
intercept variance
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File Analysis Window Help
Model Setup: smkbcd2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Linear Transforms
Sex at TimeC
Sex at TimeD
Add Transform
Copy Transform
Remove Transform
Explanatory Variables:
Value
SexTC
1
SexTD
Level-2 Random Effect (Co)variances:
Value
intercept variance
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File Analysis Window Help
Model Setup: smkbcd2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Linear Transforms
Sex at TimeC
Sex at TimeD
Add Transform
Copy Transform
Remove Transform
Explanatory Variables:
Value
SexM
1
CC
TV
Level-2 Random Effect (Co)variances:
Value
intercept variance
Select the linear transform to review and edit its components.
Type to change the transform's name in place.


SuperMix
File Analysis Window Help
Model Setup: smkbcd2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Linear Transforms
Sex at TimeC
Sex at TimeD
Add Transform
Copy Transform
Remove Transform
Explanatory Variables:
Value
SexTC
SexTD
1
Level-2 Random Effect (Co)variances:
Value
intercept variance
Select the linear transform to review and edit its components.
Type to change the transform's name in place.

SuperMix - [smkbcd2.out]

File Analysis Window Help

```
o========================================o
| Optimization Method: Adaptive Quadrature |
o========================================o

Number of quadrature points =              15
Number of free parameters =                 9
Number of iterations used =                 5

-2lnL (deviance statistic) =       3179.37812
Akaike Information Criterion       3197.37812
Schwarz Criterion                  3252.08910
```

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
intercept	-1.7849	0.1082	-16.4995	0.0000
TimeC	0.2606	0.1277	2.0408	0.0413
TimeD	0.5361	0.1434	3.7399	0.0002
SexM	0.3059	0.1190	2.5699	0.0102
CC	0.0471	0.0841	0.5599	0.5755
TV	0.0207	0.0833	0.2480	0.8041
SexTC	-0.4517	0.1844	-2.4493	0.0143
SexTD	-0.4576	0.2071	-2.2093	0.0272

Estimated level 2 variances and covariances

Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.0029	0.0106	0.2700	0.7872

SuperMix - [smkbcd2.out]

File Analysis Window Help

```
                    intercept

  intercept          1.000000


Calculation of the intracluster correlation
-------------------------------------------
residual variance = pi*pi / 6 (assumed)
cluster  variance =     0.0029

intracluster correlation =     0.0029 / (    0.0029 + (pi*pi/6)) = 0.002


           |---------------------------------------|
           |         TESTING OF TRANSFORMS         |
           |  (General Linear Hypothesis Testing)  |
           |---------------------------------------|


 ----------------------------------------------------------------------------------
   Coefficients                                      Estimate    Transform No.
                                                                       1         2
 ----------------------------------------------------------------------------------
    1 intercept                                      -1.78487    0.0000    0.0000
    2 TimeC                                           0.26058    0.0000    0.0000
    3 TimeD                                           0.53614    0.0000    0.0000
    4 SexM                                            0.30590    1.0000    1.0000
    5 CC                                              0.04710    0.0000    0.0000
    6 TV                                              0.02066    0.0000    0.0000
    7 SexTC                                          -0.45172    1.0000    0.0000
    8 SexTD                                          -0.45757    0.0000    1.0000
    9 Var(intercept)                                  0.00286    0.0000    0.0000

   Transform Estimate                                           -0.1458   -0.1517
   Standard Error                                                0.1410    0.1696
   Z-Statistic                                                  -1.0340   -0.8942
   Exceedence Pobability                                         0.3011    0.3712



    o=================================o
    | SuperMix used 0.66 seconds CPU |
    o=================================o
```

Save As... Close

Gender effect - estimated hazard ratios

- post-intervention: $\exp(.3059) = 1.36 \quad \Rightarrow$ Males hazard of smoking is significantly increased (an increase of about 36%)
- year 1: $\exp(-.1458) = .86 \quad \Rightarrow$ Males hazard of smoking is reduced (about 14%), but not significant
- year 2: $\exp(-.1517) = .86 \quad \Rightarrow$ Males hazard of smoking is reduced (about 14%), but not significant

note: these estimates are conditional estimates accounting for school, CC, and TV effects

Kaplan-Meier Survival Function estimates

Initiation of smoking experimentation in adolescents

time	# censor	# event	hazard prob	interval survival prob	cumulative survival prob
Females (N=814)					
post-int	105	130	$\frac{130}{814} = .160$	.840	.840
year 1	154	117	$\frac{117}{814-235} = .202$	.798	$(.840)(.798) = .671$
year 2	229	79	$\frac{79}{814-235-271} = .257$	.744	$(.671)(.744) = .499$
Males (N=742)					
post-int	83	156	$\frac{156}{742} = .210$	.790	.790
year 1	134	89	$\frac{89}{742-239} = .177$	.823	$(.790)(.823) = .650$
year 2	217	63	$\frac{63}{742-239-223} = .225$	.775	$(.650)(.775) = .504$

Model fit of response proportions

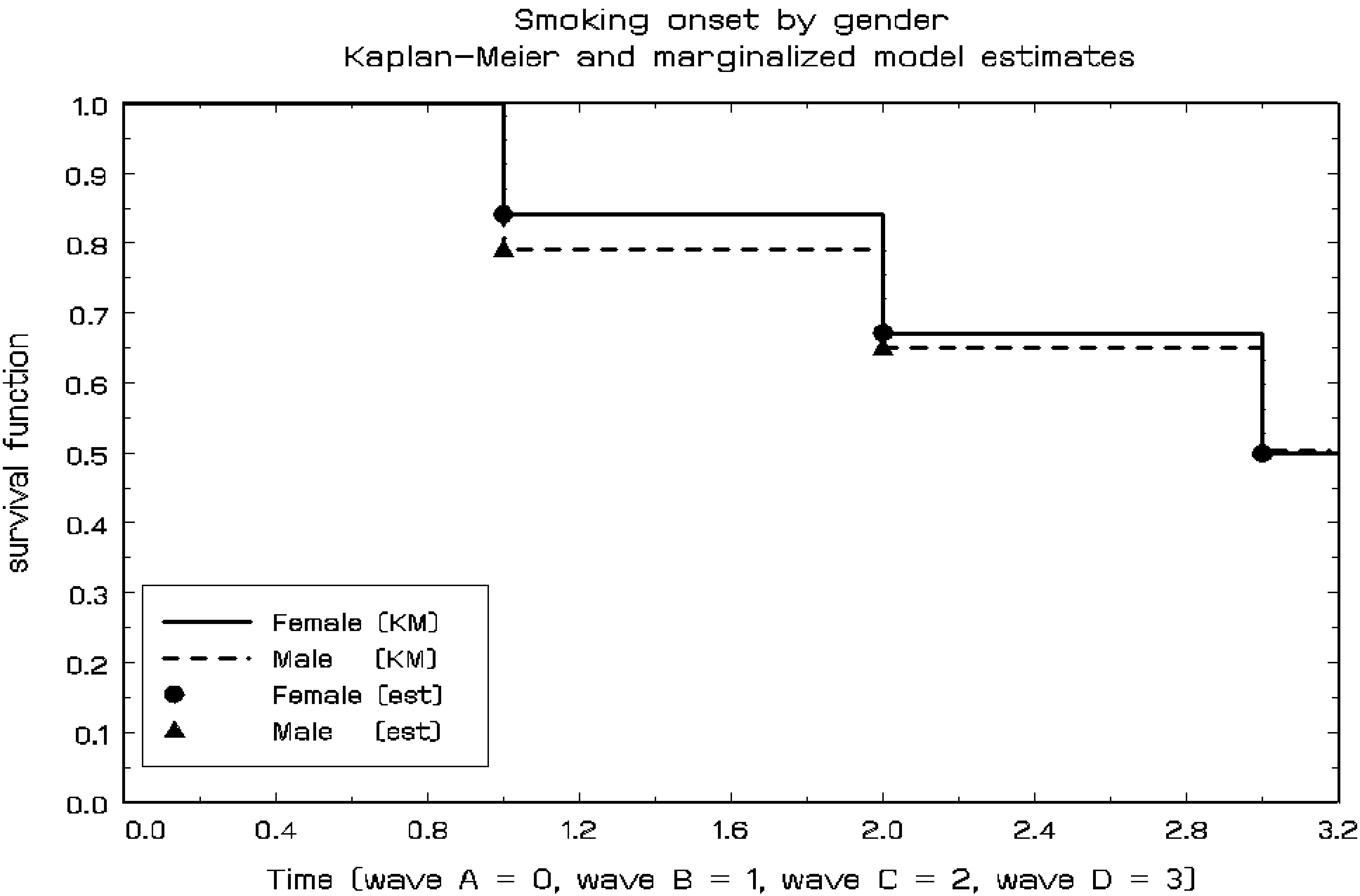
Partial Proportional Hazards (random schools) model - Dichotomous

Sex	clog-log $\Psi(z) = 1 - \exp(-\exp(z))$	est.
Hazard probability at Post-Int		
F	$\Psi((-1.785 + .47 \times .047 + .48 \times .021)/\sqrt{\hat{d}})$	.159
M	$\Psi((-1.785 + .306 + .47 \times .047 + .48 \times .021)/\sqrt{\hat{d}})$	.210
Hazard probability at Year 1		
F	$\Psi((-1.785 + .261 + .47 \times .047 + .48 \times .021)/\sqrt{\hat{d}})$	.202
M	$\Psi((-1.785 + .306 + .261 - .452 + .47 \times .047 + .48 \times .021)/\sqrt{\hat{d}})$	.176
Hazard probability at Year 2		
F	$\Psi((-1.785 + .536 + .47 \times .047 + .48 \times .021)/\sqrt{\hat{d}})$	.257
M	$\Psi((-1.785 + .306 + .536 - .458 + .47 \times .047 + .48 \times .021)/\sqrt{\hat{d}})$	.225

d = design effect $= (\sigma_v^2 + \sigma^2)/\sigma^2$ $\quad \hat{d} = (.0029 + \pi^2/6)/(\pi^2/6)$

.47 = CC mean, .48 = TV mean

Model Fit



Smoking onset by gender
Kaplan-Meier and marginalized model estimates
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
survival function
Female (KM)
Male (KM)
Female (est)
Male (est)
0.0
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
Time (wave A = 0, wave B = 1, wave C = 2, wave D = 3)

Youth within therapists example

Schoenwald, S.K. (2008). Toward evidence-based transport of evidence-based treatments: MST as an example. *Journal of Child and Adolescent Substance Abuse*, 17(3), 69-91.

"has child been suspended in the current school year"

	visit 1	visit 2	visit 3	visit 4
no	1089	1122	1074	1046
yes	783	611	445	335

visit 1 = baseline, visit 2 = post-int, visit 3 = 6-months, visit 4 = 12-months

outcome of interest: time until first school suspension
covariates: child gender, family financial assistance

- 1914 youth nested within 443 therapists

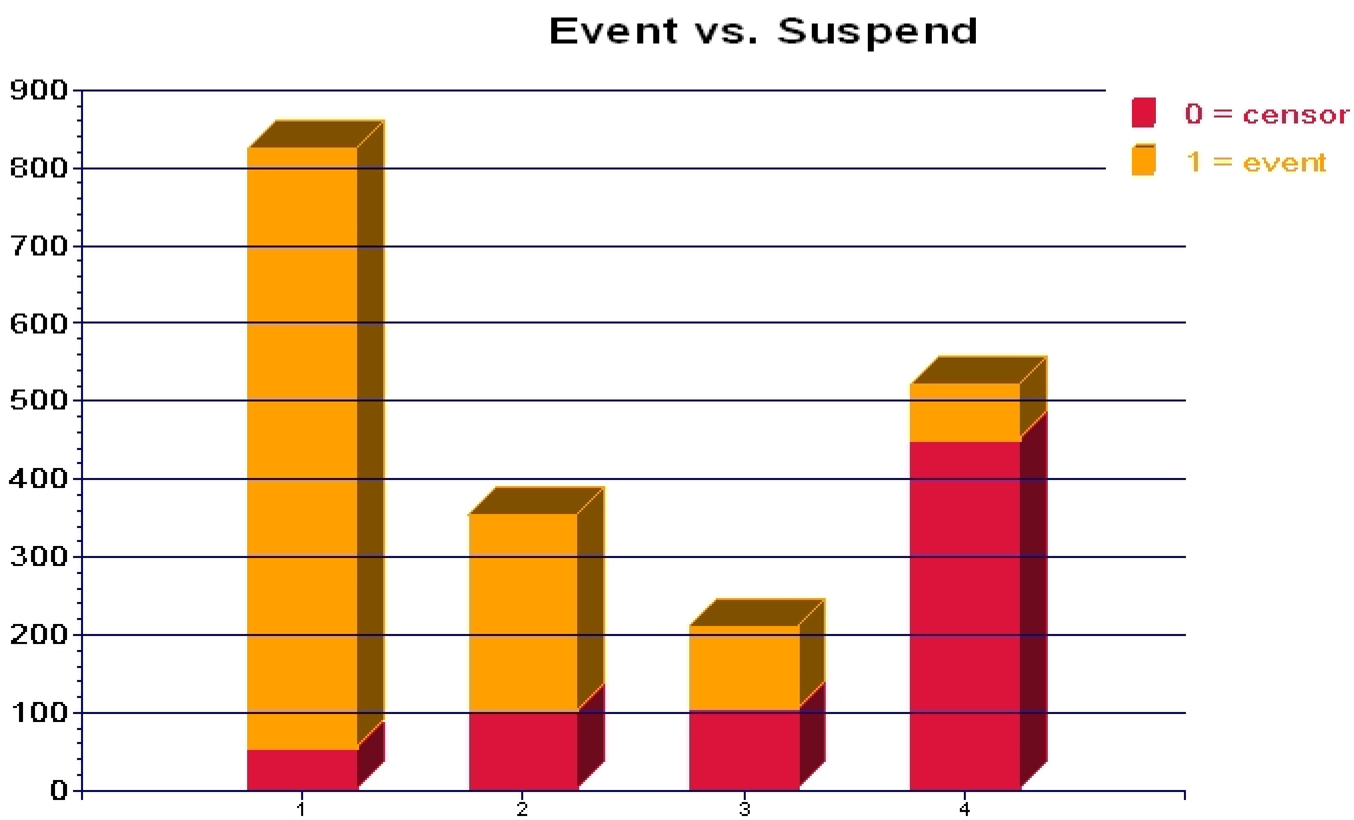
n	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	107	24.15	107	24.15
2	85	19.19	192	43.34
3	51	11.51	243	54.85
4	43	9.71	286	64.56
5	35	7.90	321	72.46
6	27	6.09	348	78.56
7	26	5.87	374	84.42
8	14	3.16	388	87.58
9	10	2.26	398	89.84
10	6	1.35	404	91.20
11	10	2.26	414	93.45
12	6	1.35	420	94.81
13	6	1.35	426	96.16
14	7	1.58	433	97.74
15	4	0.90	437	98.65
16	2	0.45	439	99.10
17	1	0.23	440	99.32
19	2	0.45	442	99.77
26	1	0.23	443	100.00

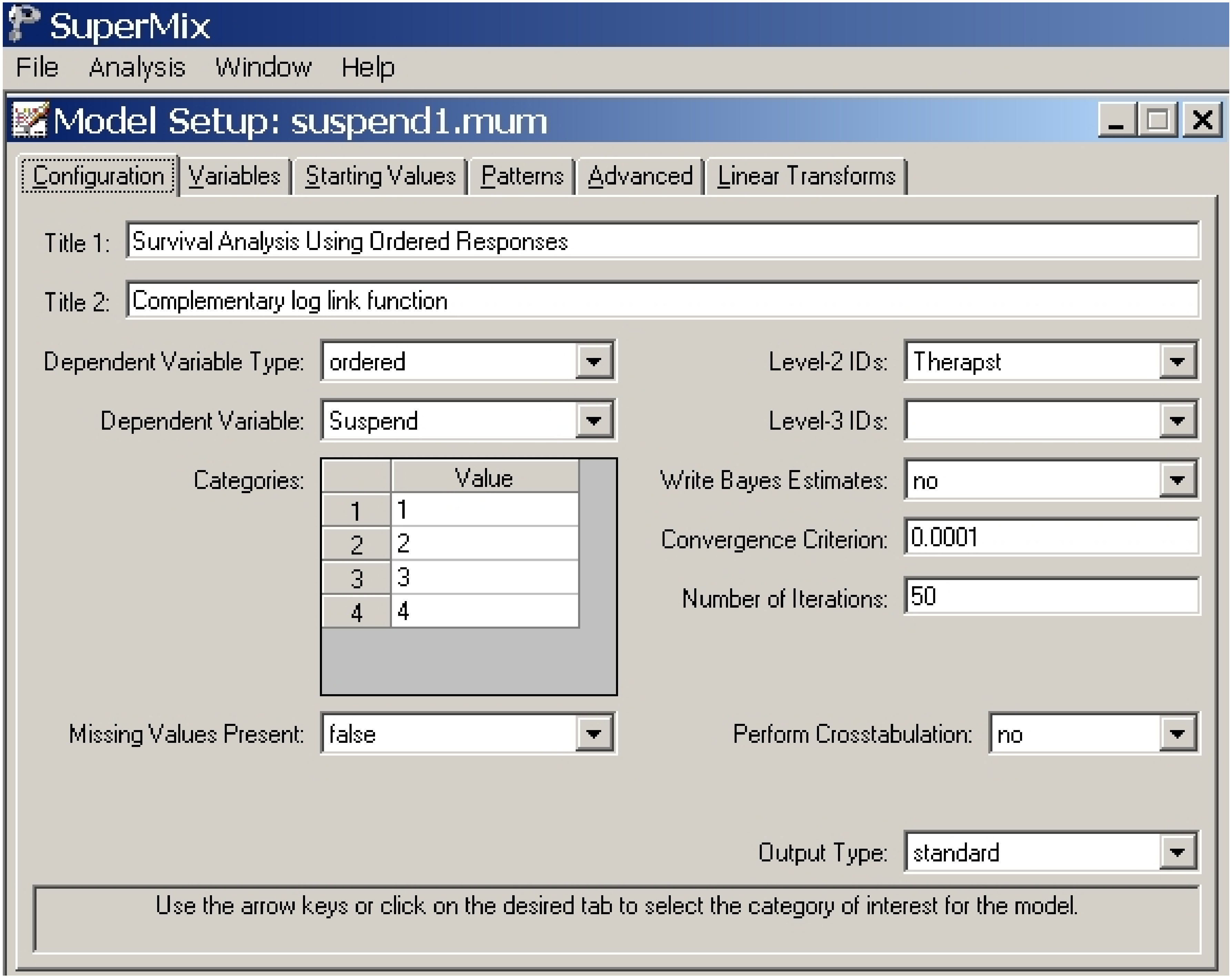
c:\SuperMixEn Examples\Primer\Survival\Suspend.ss3

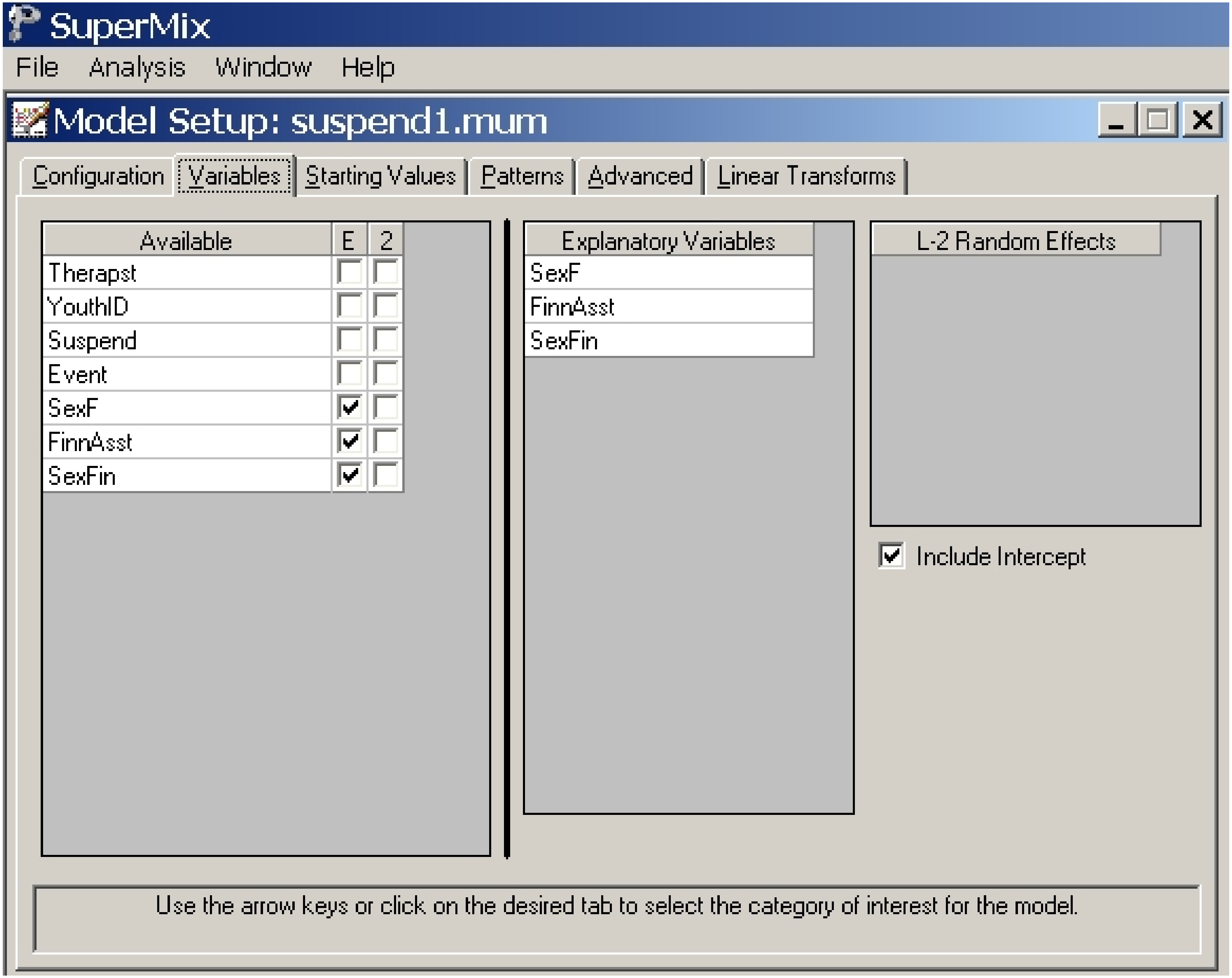
SuperMix - [suspend.ss3]

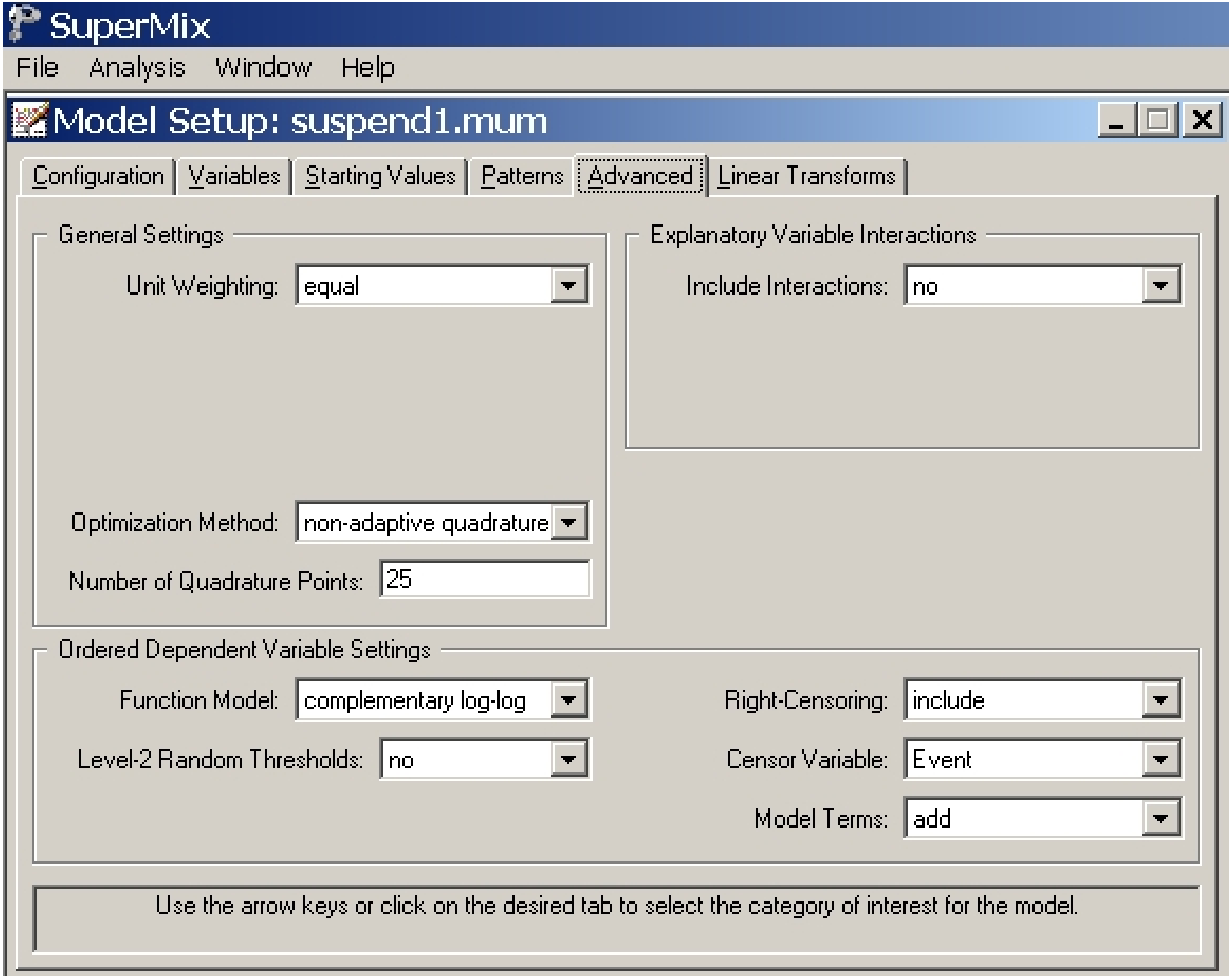
File Edit Window Help

	(A)_Therapst	(B)_YouthID	(C)_Suspend	(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
11	29	414	1	1	0	1	0
12	29	423	3	0	1	0	0
13	29	1059	1	1	0	0	0
14	29	1980	3	0	1	0	0
15	30	294	4	0	0	0	0
16	32	1542	3	1	1	1	1
17	43	1129	2	0	1	1	1
18	44	2009	1	1	0	1	0
19	46	287	1	1	0	0	0
20	51	995	4	0	1	0	0
21	57	1070	4	0	1	1	1
22	59	222	4	0	1	0	0
23	59	543	1	1	0	0	0
24	59	544	1	1	0	0	0
25	59	790	4	0	0	0	0
26	59	1022	4	0	0	0	0
27	59	1331	1	1	0	0	0
28	59	1738	4	0	0	0	0
29	59	2177	3	1	1	0	0


Event vs. Suspend
900
800
700
600
500
400
300
200
100
0
1
2
3
4
0 = censor
1 = event


SuperMix
File Analysis Window Help
Model Setup: suspend1.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1: Survival Analysis Using Ordered Responses
Title 2: Complementary log link function
Dependent Variable Type: ordered
Dependent Variable: Suspend
Categories:
Value
1 1
2 2
3 3
4 4
Level-2 IDs: Therapst
Level-3 IDs:
Write Bayes Estimates: no
Convergence Criterion: 0.0001
Number of Iterations: 50
Missing Values Present: false
Perform Crosstabulation: no
Output Type: standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File
Analysis
Window
Help
Model Setup: suspend1.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
Therapst
YouthID
Suspend
Event
SexF
FinnAsst
SexFin
Explanatory Variables
SexF
FinnAsst
SexFin
L-2 Random Effects
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.


SuperMix
File Analysis Window Help
Model Setup: suspend1.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
General Settings
Unit Weighting:
equal
Optimization Method:
non-adaptive quadrature
Number of Quadrature Points:
25
Explanatory Variable Interactions
Include Interactions:
no
Ordered Dependent Variable Settings
Function Model:
complementary log-log
Level-2 Random Thresholds:
no
Right-Censoring:
include
Censor Variable:
Event
Model Terms:
add
Use the arrow keys or click on the desired tab to select the category of interest for the model.

SuperMix - [suspend1.out]

File Analysis Window Help

```
o==========================================o
| Survival Analysis Using Ordered Responses |
| Complementary log link function           |
o==========================================o



            Model and Data Descriptions

   Sampling Distribution                    = Multinomial
   Link Function                            = Cumulative CLL
   Number of Level-2 Units                    443
   Number of Level-1 Units                    1914
   Number of Level-1 Units per Level-2 Unit =
```

4	2	8	1	1	1	1	1	1	1	8	11
7	4	5	7	10	11	5	15	2	1	5	1
2	2	6	1	2	1	4	1	26	9	3	14
1	15	1	5	4	1	14	2	3	1	7	3
7	8	7	14	1	6	1	6	13	17	8	13
3	1	2	10	6	8	2	4	2	5	5	4
6	5	4	4	2	1	2	4	6	4	2	7
1	15	10	2	9	1	1	7	11	5	5	3
1	6	3	9	3	14	5	6	9	2	3	1
4	4	2	11	4	4	14	7	8	7	2	2
4	2	16	9	6	3	2	4	4	2	8	2
3	14	1	7	5	2	6	12	5	2	8	8
6	1	2	2	1	19	2	11	3	6	13	3
1	2	11	1	2	12	12	1	3	3	3	6
1	2	2	14	9	3	4	7	1	5	9	2
1	3	5	1	2	5	12	2	1	13	4	1
7	16	3	4	19	1	4	6	11	3	3	12
7	1	1	3	2	8	1	1	3	4	5	11
4	3	7	3	2	1	8	7	1	2	1	4
6	1	10	9	1	7	4	5	1	3	5	13
1	6	1	8	7	1	2	1	5	2	4	5
2	6	10	5	5	11	1	10	1	1	1	11
5	1	9	5	1	5	2	7	7	7	7	1
5	3	2	5	7	1	5	3	4	1	3	2
2	2	2	3	12	6	6	5	2	6	1	2
1	7	2	5	3	1	8	9	1	7	2	1
7	13	15	4	8	6	1	2	3	1	2	2
5	3	3	2	4	3	4	3	3	6	4	6
1	2	5	1	2	4	1	6	5	2	5	2
4	6	1	2	1	1	3	7	4	1	1	6
1	1	2	2	1	2	2	4	2	2	1	3
2	3	4	4	2	3	2	1	1	2	3	1
4	3	4	1	3	4	1	2	1	3	5	2

Save As... Close

SuperMix - [suspend1.out]

File Analysis Window Help

```
o=============================================o
| Optimization Method: Non-Adaptive Quadrature |
o=============================================o

Number of quadrature points =              25
Number of free parameters =                 8
Number of iterations used =                 3

-2lnL (deviance statistic) =       4741.46612
Akaike Information Criterion       4757.46612
Schwarz Criterion                  4801.92172
```

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
Threshold1	-0.6561	0.0549	-11.9533	0.0000
Threshold2	-0.2235	0.0517	-4.3188	0.0000
Threshold3	-0.0324	0.0511	-0.6338	0.5262
Threshold4	0.1213	0.0511	2.3721	0.0177
SexF	-0.3207	0.0818	-3.9203	0.0001
FinnAsst	0.2004	0.0742	2.7014	0.0069
SexFin	-0.0237	0.1345	-0.1760	0.8603

Alternative Parameterization, setting Threshold1= 0

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
intcept	-0.6561	0.0549	-11.9533	0.0000
Threshold2	0.4326	0.0258	16.7671	0.0000
Threshold3	0.6237	0.0306	20.3592	0.0000
Threshold4	0.7775	0.0344	22.6048	0.0000

Estimated level 2 variances and covariances

Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.0834	0.0303	2.7503	0.0060

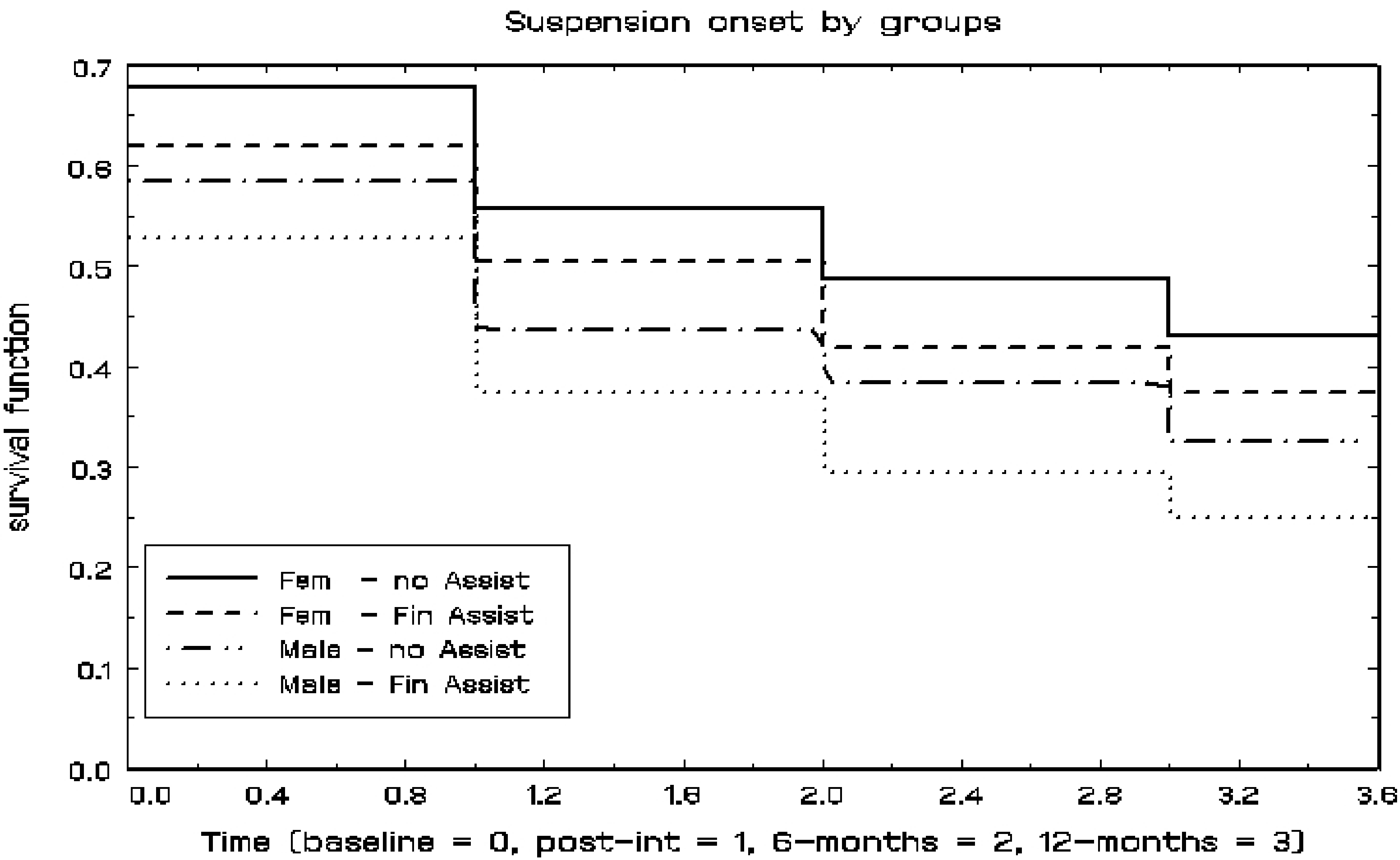
Save As... Close

Kaplan-Meier Survival Function estimates

Time to first school suspension

time	# censor	# event	hazard prob	interval surv prob	cumulative survival prob
Males with financial assistance (N=473)					
baseline	14	223	$\frac{223}{473} = .471$	.529	.529
post-int	26	69	$\frac{69}{(473-237)} = .292$	.708	$(.529)(.708) = .374$
6-months	13	30	$\frac{30}{(473-237-95)} = .213$	.787	$(.374)(.787) = .294$
12-months	83	15	$\frac{15}{(473-237-95-43)} = .153$	.847	$(.294)(.153) = .249$

$\Rightarrow$ Similar calculations for other groups (males without assistance, females with assistance, females without assistance)



Suspension onset by groups
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
survival function
0.0
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
Time (baseline = 0, post-int = 1, 6-months = 2, 12-months = 3)
Fem - no Assist
Fem - Fin Assist
Male - no Assist
Male - Fin Assist

Model fit - Males with financial assistance

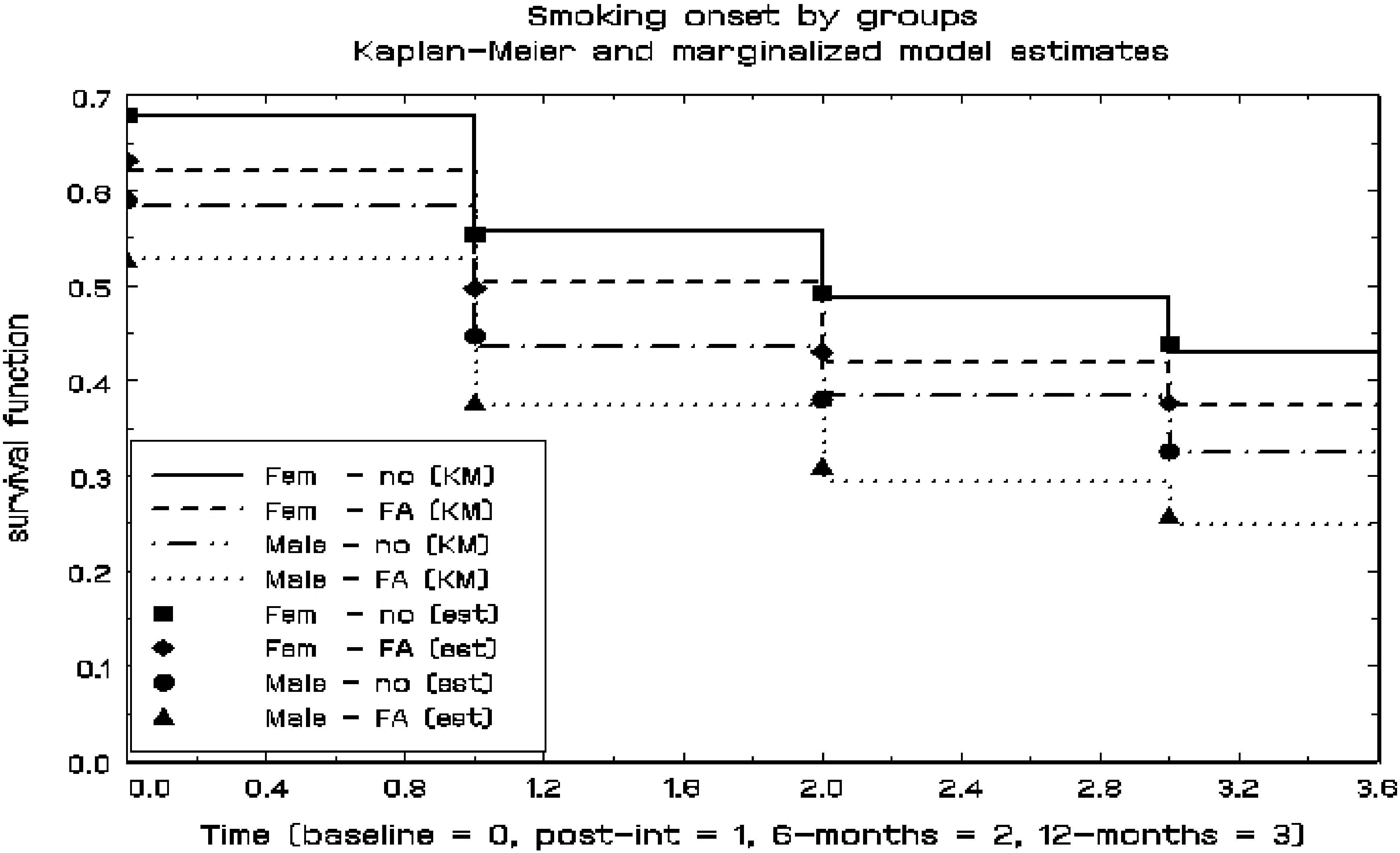
Proportional Hazards (random therapists) model - Ordinal

clog-log $\Psi(z) = 1 - \exp(-\exp(z))$	estimate	(1 - estimate)*
Probability of Category 1 response: Failure at Baseline		
$\Psi((-.656 + .200)/\sqrt{\hat{d}})$ =	.470	.530
Prob of Category 1 or 2 response: Cumulative Failure at Post-Int		
$\Psi((-.224 + .200)/\sqrt{\hat{d}})$ =	.624	.376
Prob of Category 1, 2, or 3 response: Cum Failure at 6-months		
$\Psi((-.032 + .200)/\sqrt{\hat{d}})$ =	.694	.306
Prob of Category 1, 2, 3, or 4 response: Cum Failure at 12-months		
$\Psi((.121 + .200)/\sqrt{\hat{d}})$ =	.748	.252

d = design effect = $(\sigma_v^2 + \sigma^2)/\sigma^2$ $\quad \hat{d} = (.0834 + \pi^2/6)/(\pi^2/6)$

* (cumulative) survival = 1 - cumulative failure estimates

Model Fit



Smoking onset by groups
Kaplan-Meier and marginalized model estimates
survival function
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
Time (baseline = 0, post-int = 1, 6-months = 2, 12-months = 3)
Fem - no (KM)
Fem - FA (KM)
Male - no (KM)
Male - FA (KM)
Fem - no (est)
Fem - FA (est)
Male - no (est)
Male - FA (est)

Model without Sex by Financial Assistance

comparing models with and without interaction, via likelihood-ratio test, $\chi_1^2 = 4741.49696 - 4741.46612 = .03$

variable	estimate	std error	z-value	p-value
SexF	-0.3293	0.0654	-5.0362	0.0000
FinAsst	0.1933	0.0621	3.1109	0.0019

$\exp(-.3293) = .719 \quad \Rightarrow$ Females hazard of school suspension is significantly reduced (a reduction of about 28% relative to males)

$\exp(.1933) = 1.213 \quad \Rightarrow$ Financial assistance kids have significantly increased hazard (an increase of about 21%)

note: these estimates are conditional estimates, accounting for the therapist effects

Conditional vs Marginal effects

- In a mixed model, the regression coefficients and the random therapist effects are jointly estimated
- regressor effects are obtained controlling for, or adjusted for, or conditional on the therapist effects
  - comparing the populations of boys versus girls, controlling for therapists (*i.e.*, how different are the populations of boys and girls who have the same therapist)
- marginal effects or unconditional effects are sometimes of (greater) interest (*i.e.*, population-averaged effects)
  - comparing the populations of boys versus girls
- in linear mixed models, conditional = marginal effects, but this is not true, in general, in non-linear mixed models (*i.e.*, mixed models for non-normal outcomes)

Expressing conditional as marginal effects

In a random intercept model, $\beta^M = \beta^C \,/\, \sqrt{d}$

- β^M and β^C are the marginal and conditional effects
- d is the design effect $= (\sigma_\upsilon^2 + \sigma^2)/\sigma^2$

in current example, $d = (.0834 + \pi^2/6)/(\pi^2/6) = 1.0507$

$$
\begin{array}{rcrl}
-.3293/\sqrt{1.0507} & = & -.3213 & \text{marginal sex effect} \\
.1933/\sqrt{1.0507} & = & .1886 & \text{marginal financial assistance effect}
\end{array}
$$

$\exp(-.3213) = .725 \;\;\Rightarrow$ Females hazard of school suspension is significantly reduced (a reduction of about 27% relative to males)

$\exp(.1886) = 1.208 \;\;\Rightarrow$ Financial assistance kids have significantly increased hazard (an increase of about 21%)

Degree of clustering attributable to therapists

```
Calculation of the intracluster correlation
----------------------------------------------------------------------
residual variance        = pi*pi / 6 (assumed)
cluster variance         = 0.0834
intracluster correlation = 0.0834 / ( 0.0834 + (pi*pi/6)) = 0.048
```

⇒ fair degree of clustering within therapists

- suggests that some therapists have positive effect on time to school suspension, others have negative effect

Empirical Bayes estimates of random effects

$$\log\left[-\log(1 - P(t_{ij}))\right] = \gamma_t + \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \upsilon_i \qquad \text{where } \upsilon_i \sim N(0, \sigma^2_\upsilon)$$

- Random effects υ_i are also estimated
- can be of interest to indicate how particular clusters (*i.e.*, therapists) are doing
- can be used to rank or compare clusters, or indicate unusual clusters
- SuperMix provides these under "Analysis," "View level-2 Bayes results" (also saved as a file with .ba2 extension)
- graph them under "File," "Model-based Graphs," "Confidence Intervals"

SuperMix - [suspend1.ba2]

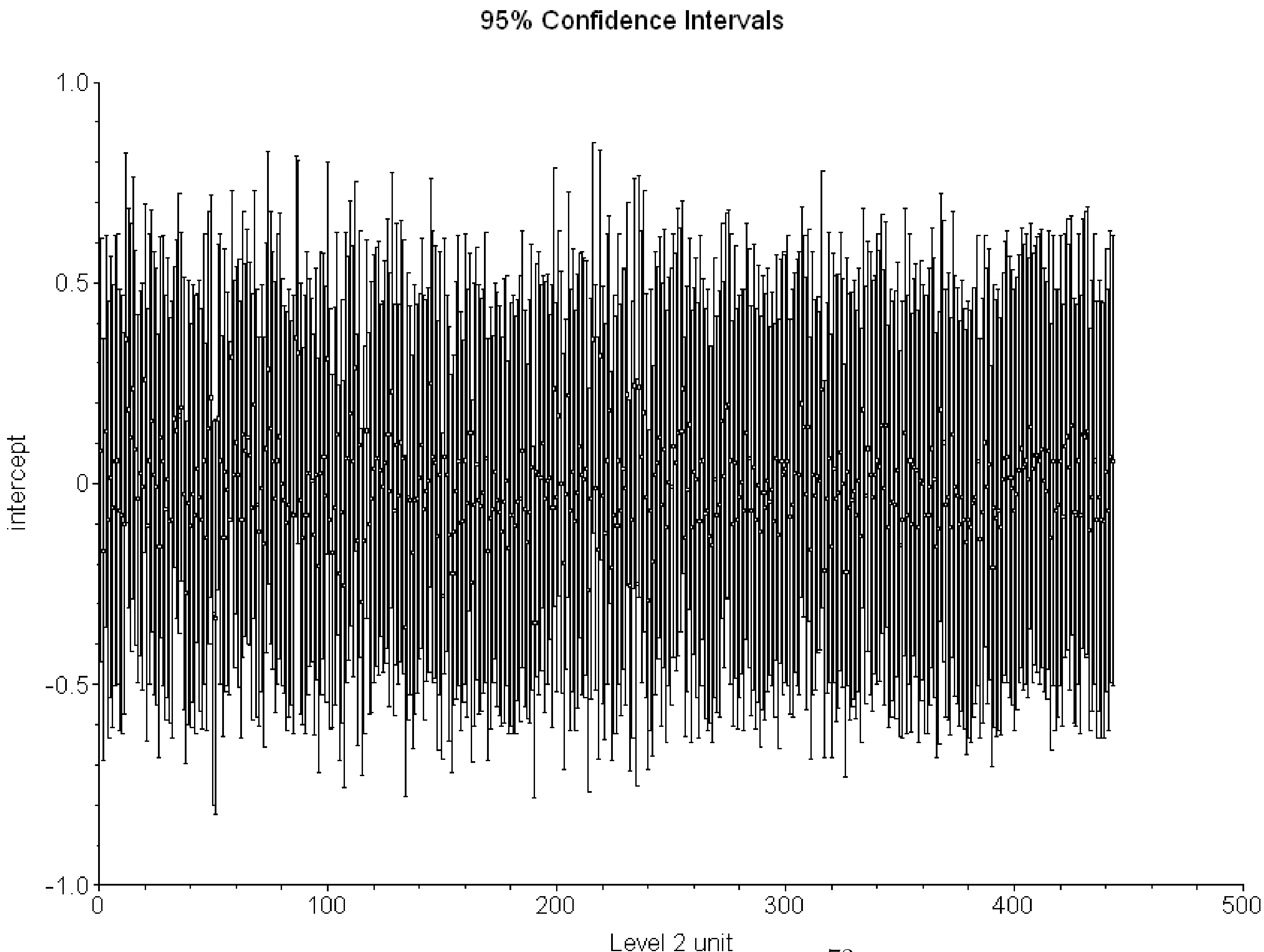
File Analysis Window Help

18.00	1	0.0847254	0.0721942	intercept
22.00	1	-0.1648145	0.0716857	intercept
29.00	1	0.1303024	0.0616695	intercept
30.00	1	-0.0889056	0.0766830	intercept
32.00	1	0.0166572	0.0782806	intercept
43.00	1	-0.0563505	0.0790462	intercept
44.00	1	0.0579273	0.0816773	intercept
46.00	1	0.0619980	0.0819204	intercept
51.00	1	-0.0660614	0.0783262	intercept
57.00	1	-0.0778757	0.0774677	intercept
59.00	1	-0.0994690	0.0584513	intercept
61.00	1	0.3626713	0.0551956	intercept
62.00	1	0.1870216	0.0644151	intercept
63.00	1	0.1158601	0.0738833	intercept
64.00	1	0.2382228	0.0715629	intercept
65.00	1	0.0885906	0.0630860	intercept
66.00	1	-0.0367840	0.0546296	intercept
67.00	1	0.0260429	0.0538858	intercept
69.00	1	-0.0070501	0.0667565	intercept
70.00	1	0.2627573	0.0488251	intercept
71.00	1	-0.1024032	0.0757441	intercept
72.00	1	0.0619980	0.0819204	intercept
74.00	1	0.1562897	0.0715860	intercept
75.00	1	0.0259039	0.0789987	intercept
76.00	1	-0.0068054	0.0767206	intercept
78.00	1	-0.1552735	0.0722777	intercept
80.00	1	0.1160785	0.0646016	intercept
81.00	1	0.0579273	0.0816773	intercept
82.00	1	-0.0608002	0.0730036	intercept
87.00	1	0.0141358	0.0781492	intercept
88.00	1	-0.0911188	0.0665233	intercept
90.00	1	-0.0889056	0.0766830	intercept
93.00	1	0.1643157	0.0364191	intercept
94.00	1	0.1354260	0.0580098	intercept
97.00	1	0.1746658	0.0783138	intercept
98.00	1	0.1926879	0.0490523	intercept
102.00	1	-0.0238433	0.0754248	intercept
103.00	1	-0.2703161	0.0472772	intercept
104.00	1	-0.0476530	0.0797024	intercept
105.00	1	-0.1033370	0.0658267	intercept
106.00	1	-0.0245574	0.0701926	intercept
109.00	1	-0.0778757	0.0774677	intercept
110.00	1	0.0386340	0.0492344	intercept
112.00	1	-0.0305314	0.0750780	intercept
113.00	1	-0.0887597	0.0713304	intercept
114.00	1	0.0619980	0.0819204	intercept

Save As... Close

ID, random effect number, random effect estimate (standardized $\theta_i = \upsilon_i/\sigma_\upsilon$), (posterior) variance, random effect label

$$\hat{\theta}_i \pm 1.96\sqrt{\text{therapist's posterior variance}}$$



SAS for reading in Empirical Bayes estimates

```
DATA one;
INFILE 'c:\SuperMixEn Examples\Primer\Survival\Suspend1.ba2';
INPUT id r1 TherInt TherPrec intercpt $;
PROC SORT; BY TherInt;
PROC PRINT; VAR id TherInt TherPrec;
RUN;
```

```
 Obs   id   TherInt TherPrec
   1  265  -0.35481 0.047210
   2  354  -0.34406 0.049831
   3  123  -0.33236 0.062671
   4  122  -0.32261 0.059428
   .    .         .        .
   .    .         .        .
 440  175   0.32769 0.059300
 441  400   0.36221 0.061400
 442   61   0.36267 0.055196
 443  173   0.36696 0.052603
```

And the winner is ...

Therapst	YouthID	Suspend	Event	SexF	FinnAsst	SexFin
265	422	1	0	0	0	0
265	510	4	0	1	0	0
265	572	3	0	0	0	0
265	594	4	0	0	0	0
265	640	1	1	0	1	0
265	747	1	1	0	1	0
265	1101	3	0	0	0	0
265	1340	2	1	0	1	0
265	1505	3	1	0	1	0
265	1667	4	0	0	1	0
265	1863	3	0	0	0	0
265	1926	4	0	0	0	0
265	2011	4	0	0	1	0
265	2016	3	1	0	1	0

mostly censored observations with higher times to first suspension

And the loser is ....

Therapst	YouthID	Suspend	Event	SexF	FinnAsst	SexFin
173	200	1	1	0	0	0
173	279	1	1	0	0	0
173	382	2	0	1	1	1
173	477	2	1	1	0	0
173	523	1	1	0	0	0
173	760	1	1	0	1	0
173	923	1	1	0	0	0
173	1242	1	1	0	1	0
173	1610	1	1	0	0	0
173	1646	1	1	0	0	0
173	1725	2	0	1	0	0
173	1795	1	1	1	1	1
173	1991	4	0	1	0	0
173	2013	1	1	0	0	0
173	2250	1	1	0	0	0

mostly event observations with lower times to first suspension

Second thoughts

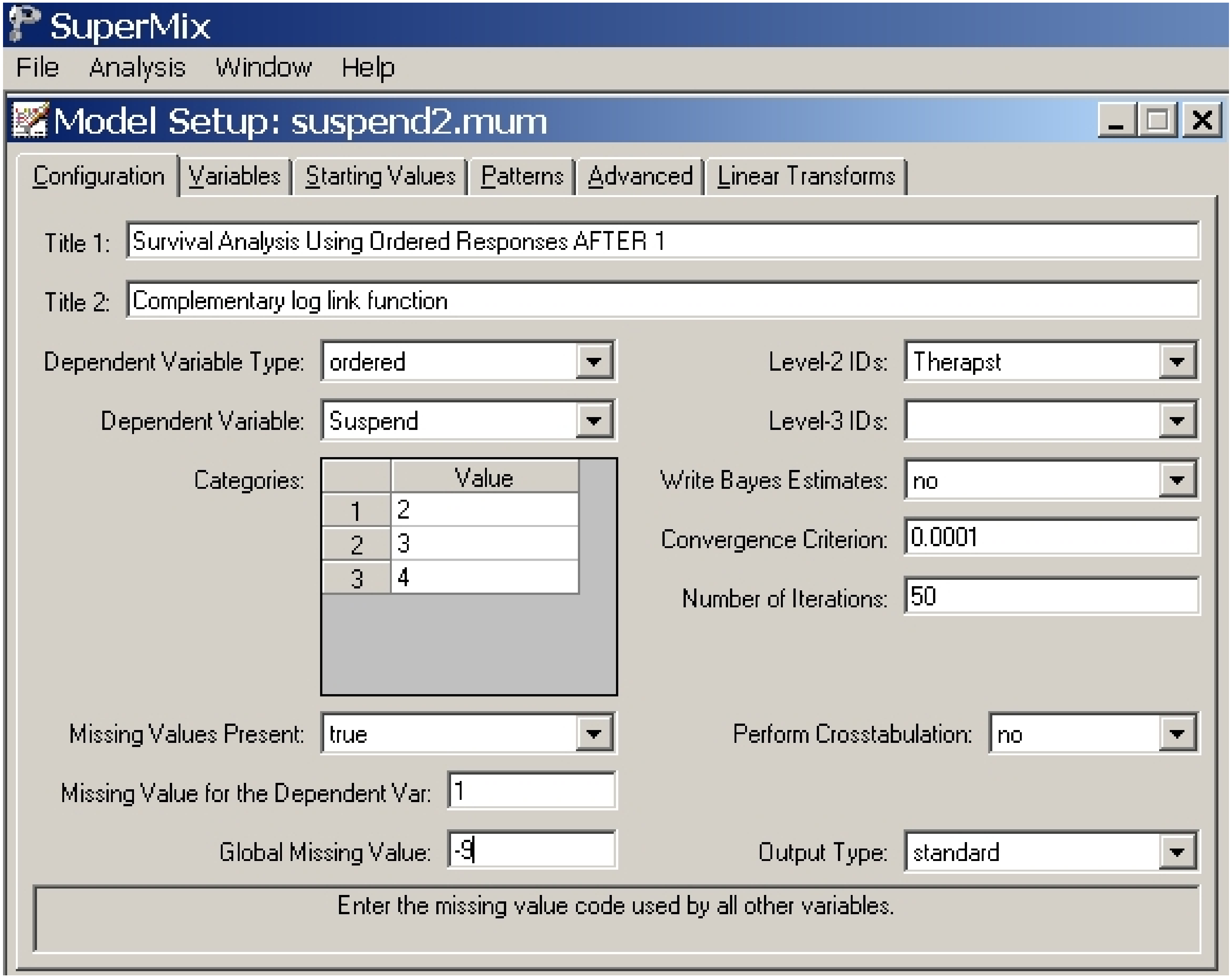
- Assessing effects of therapists including baseline seems problematic

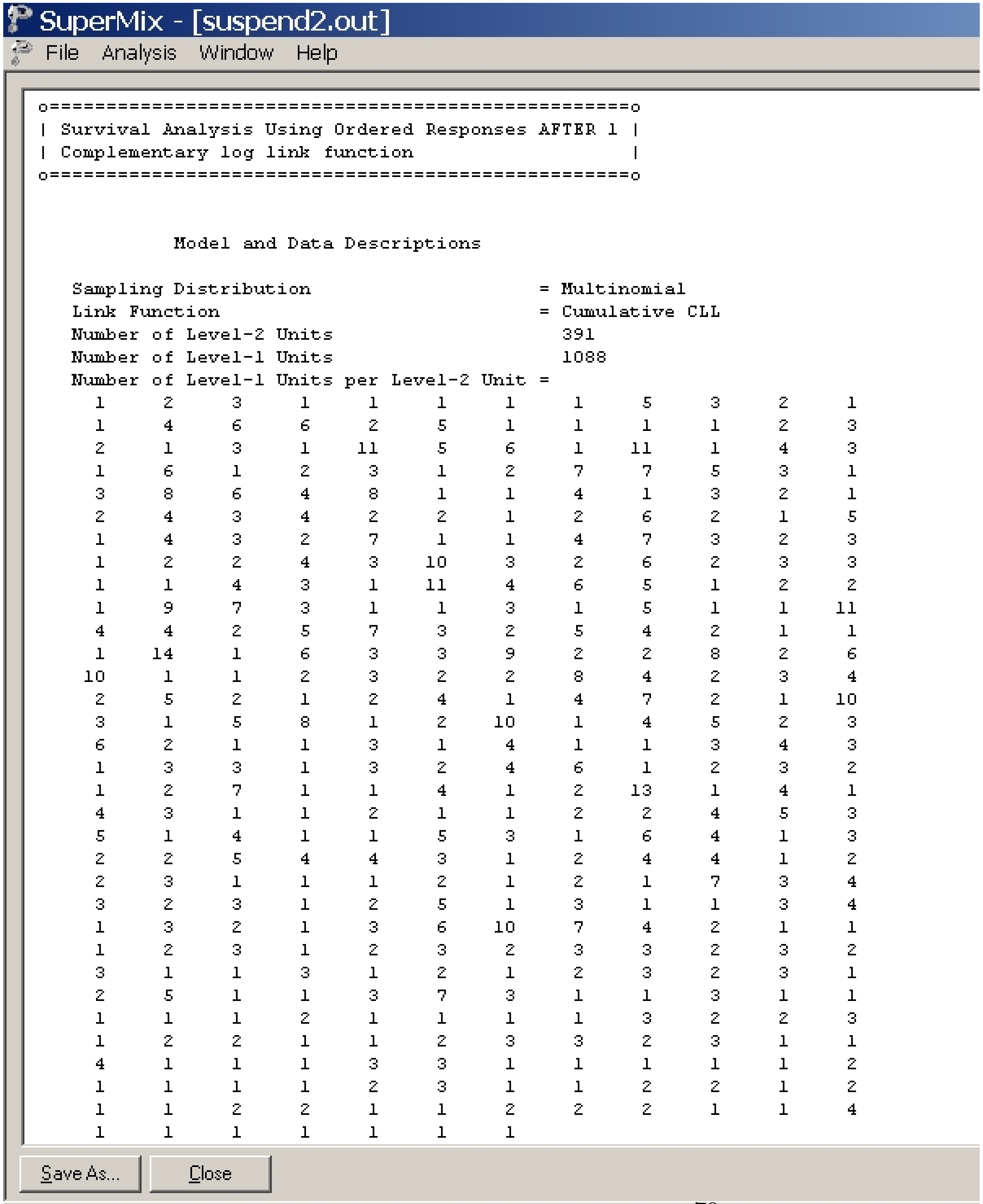
- Being suspended at baseline seems unrelated to therapist effectiveness

- some therapists might be getting more (or less) kids with baseline suspension

- seems reasonable to exclude baseline, and focus on time to first suspension after baseline

Excluding baseline visit





SuperMix - [suspend2.out]

File Analysis Window Help

```
o==================================================o
| Survival Analysis Using Ordered Responses AFTER 1 |
| Complementary log link function                   |
o==================================================o


           Model and Data Descriptions

   Sampling Distribution                  = Multinomial
   Link Function                          = Cumulative CLL
   Number of Level-2 Units                  391
   Number of Level-1 Units                  1088
   Number of Level-1 Units per Level-2 Unit =
     1     2     3     1     1     1     1     1     5     3     2     1
     1     4     6     6     2     5     1     1     1     1     2     3
     2     1     3     1    11     5     6     1    11     1     4     3
     1     6     1     2     3     1     2     7     7     5     3     1
     3     8     6     4     8     1     1     4     1     3     2     1
     2     4     3     4     2     2     1     2     6     2     1     5
     1     4     3     2     7     1     1     4     7     3     2     3
     1     2     2     4     3    10     3     2     6     2     3     3
     1     1     4     3     1    11     4     6     5     1     2     2
     1     9     7     3     1     1     3     1     5     1     1    11
     4     4     2     5     7     3     2     5     4     2     1     1
     1    14     1     6     3     3     9     2     2     8     2     6
    10     1     1     2     3     2     2     8     4     2     3     4
     2     5     2     1     2     4     1     4     7     2     1    10
     3     1     5     8     1     2    10     1     4     5     2     3
     6     2     1     1     3     1     4     1     1     3     4     3
     1     3     3     1     3     2     4     6     1     2     3     2
     1     2     7     1     1     4     1     2    13     1     4     1
     4     3     1     1     2     1     1     2     2     4     5     3
     5     1     4     1     1     5     3     1     6     4     1     3
     2     2     5     4     4     3     1     2     4     4     1     2
     2     3     1     1     1     2     1     2     1     7     3     4
     3     2     3     1     2     5     1     3     1     1     3     4
     1     3     2     1     3     6    10     7     4     2     1     1
     1     2     3     1     2     3     2     3     3     2     3     2
     3     1     1     3     1     2     1     2     3     2     3     1
     2     5     1     1     3     7     3     1     1     3     1     1
     1     1     1     2     1     1     1     1     3     2     2     3
     1     2     2     1     1     2     3     3     2     3     1     1
     4     1     1     1     3     3     1     1     1     1     1     2
     1     1     1     1     2     3     1     1     2     2     1     2
     1     1     2     2     1     1     2     2     2     1     1     4
     1     1     1     1     1     1     1
```

Save As... Close

SuperMix - [suspend2.out]

File Analysis Window Help

```
 o=============================================o
 | Optimization Method: Non-Adaptive Quadrature |
 o=============================================o

Number of quadrature points =              25
Number of free parameters =                 7
Number of iterations used =                11

-2lnL (deviance statistic) =       2194.40487
Akaike Information Criterion       2208.40487
Schwarz Criterion                  2243.34954
```

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
Threshold1	-1.2948	0.0858	-15.0906	0.0000
Threshold2	-0.8298	0.0790	-10.5021	0.0000
Threshold3	-0.5279	0.0765	-6.8980	0.0000
SexF	-0.2707	0.1270	-2.1315	0.0330
FinnAsst	0.2489	0.1206	2.0644	0.0390
SexFin	-0.1470	0.2163	-0.6794	0.4969

Alternative Parameterization, setting Threshold1= 0

Estimated regression weights

Parameter	Estimate	Standard Error	z Value	P Value
intcept	-1.2948	0.0858	-15.0906	0.0000
Threshold2	0.4650	0.0431	10.7957	0.0000
Threshold3	0.7669	0.0529	14.5033	0.0000

Estimated level 2 variances and covariances

Parameter	Estimate	Standard Error	z Value	P Value
intercept/intercept	0.0010	0.0076	0.1354	0.8923

Save As... Close

Degree of clustering attributable to therapists

```
Calculation of the intracluster correlation
------------------------------------------------------------------------
residual variance        = pi*pi / 6 (assumed)
cluster variance         = 0.0010
intracluster correlation = 0.0010 / ( 0.0010 + (pi*pi/6)) = 0.001
```

⇒ very small degree of clustering within therapists

SAS for reading in NEW Empirical Bayes estimates

```
DATA two;
INFILE 'c:\SuperMixEn Examples\Primer\Survival\Suspend2.ba2';
INPUT id r1 TherInt TherPrec intercpt $;
PROC SORT; BY TherInt;
PROC PRINT; VAR id TherInt TherPrec;
RUN;
```

```
 Obs   id   TherInt TherPrec
   1  122  -0.17915 0.056097
   2  211  -0.17415 0.056336
   3  354  -0.14976 0.051612
   4  103  -0.14740 0.051710
   .    .         .        .
   .    .         .        .
 388  481   0.18269 0.061248
 389  482   0.21592 0.063285
 390  238   0.21776 0.059572
 391  610   0.26182 0.058515
```

And the NEW winner is ...

Therapst	YouthID	Suspend	Event	SexF	FinnAsst	SexFin
122	243	3	0	1	0	0
122	391	4	0	1	0	0
122	531	4	0	0	0	0
122	576	4	0	0	0	0
122	577	3	0	0	0	0
122	704	3	0	1	0	0
122	705	4	0	1	0	0

And the NEW loser is ...

Therapst	YouthID	Suspend	Event	SexF	FinnAsst	SexFin
610	1291	4	1	1	0	0
610	1371	2	1	0	0	0
610	1728	4	0	1	0	0
610	1740	2	1	0	1	0
610	2082	2	1	0	1	0
610	2188	2	1	0	0	0

Model without Sex by Financial Assistance

comparing models with and without interaction, via likelihood-ratio test, $\chi^2_1 = 2194.86989 - 2194.40487 = .565$

variable	estimate	std error	z-value	p-value
SexF	-0.3223	0.1027	-3.1391	0.0017
FinAsst	0.2026	0.0999	2.0266	0.0427

$\exp(-.3223) = .725 \quad \Rightarrow$ Females hazard of school suspension is significantly reduced (a reduction of about 27% relative to males)

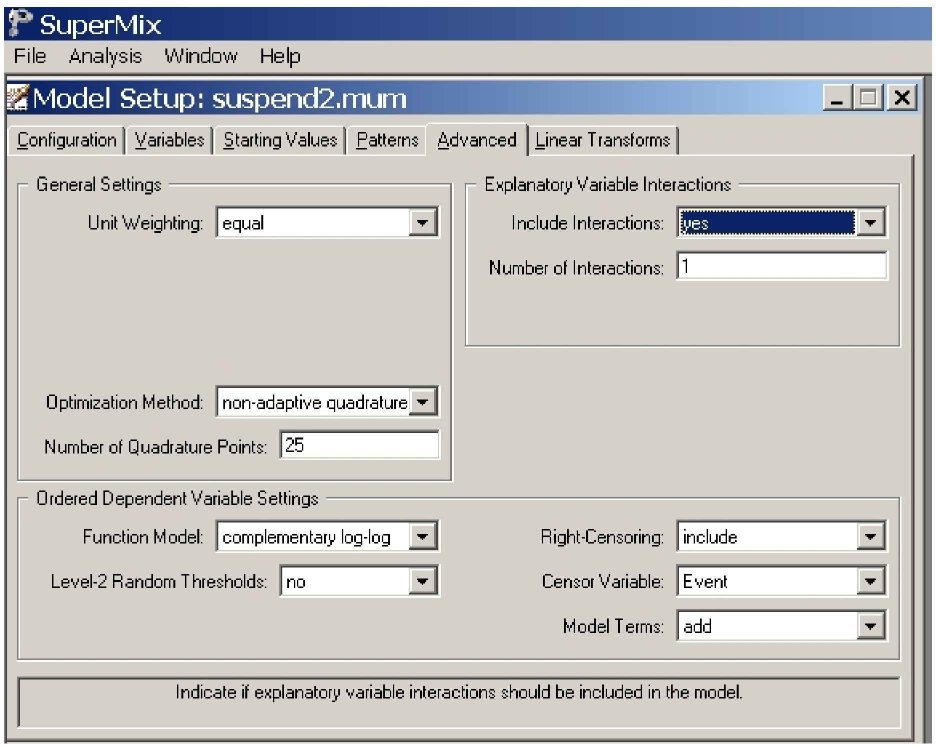
$\exp(.2026) = 1.225 \quad \Rightarrow$ Financial assistance kids have significantly increased hazard (an increase of about 23%)

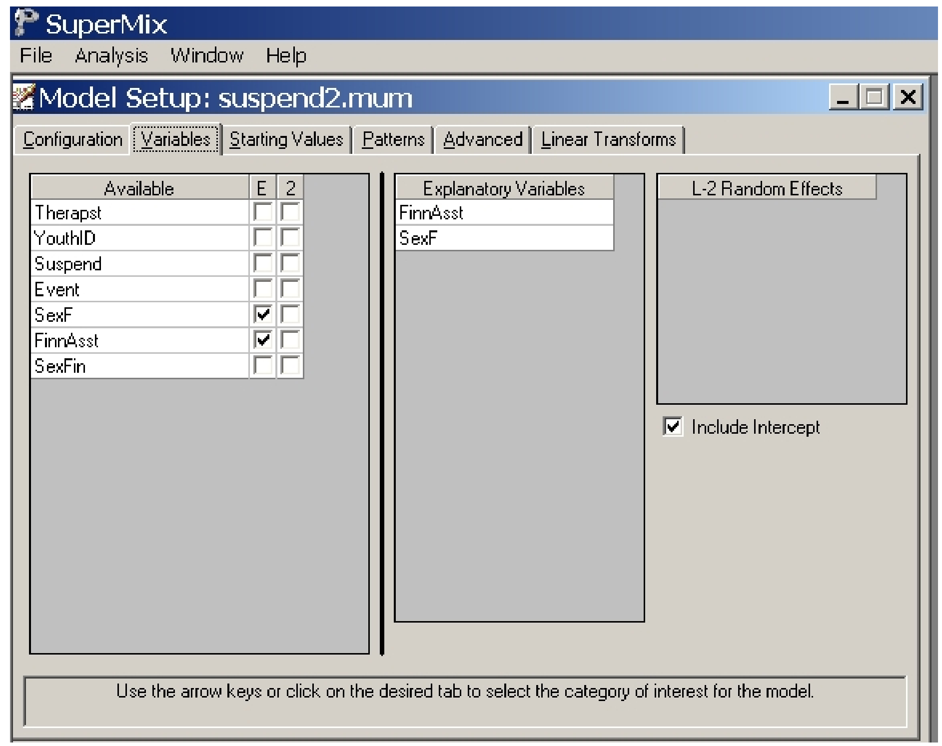
note: these estimates are conditional estimates, accounting for the (near-zero) therapist effects

Tests of proportional hazards assumption

In ordinal, fit models with and without "Explanatory Variable Interactions" on Advanced card

term	likelihood-ratio χ^2	df	$p <$
financial assistance	3.45	2	ns
sex	2.03	2	ns





Summary

- Time-to-event analysis for clustered (or repeated) discrete- and grouped-time data
  - dichotomous or ordinal mixed regression models
- Extenstions to competing risk survival models (Gibbons et al, 2003, *Biostatistics*)
  - person-time indicators (0=no event or censoring, 1=event A, 2=event B)
  - nominal (mixed) regression model
- Can also be used for continuous-time analysis (grouping time-to-event outcomes in, say, 10 quantiles of time periods)
  - lack of software for continuous-time (mixed) analysis
  - Liu & Huang, (Stat Med, 2008) provide simulation results supporting this approach