Mixed Models for Longitudinal Data: An Applied Introduction

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

hedeker@uchicago.edu

Hedeker, D. (2004). An introduction to growth modeling. In D. Kaplan (Ed.), Quantitative Methodology for the Social Sciences. Thousand Oaks CA: Sage.

Hedeker, D. & Gibbons, R.D. (2006). Longitudinal Data Analysis, chapters 4 & 5. Wiley.

This work was supported by National Institute of Mental Health Contract N44MH32056.

2-level model for longitudinal data

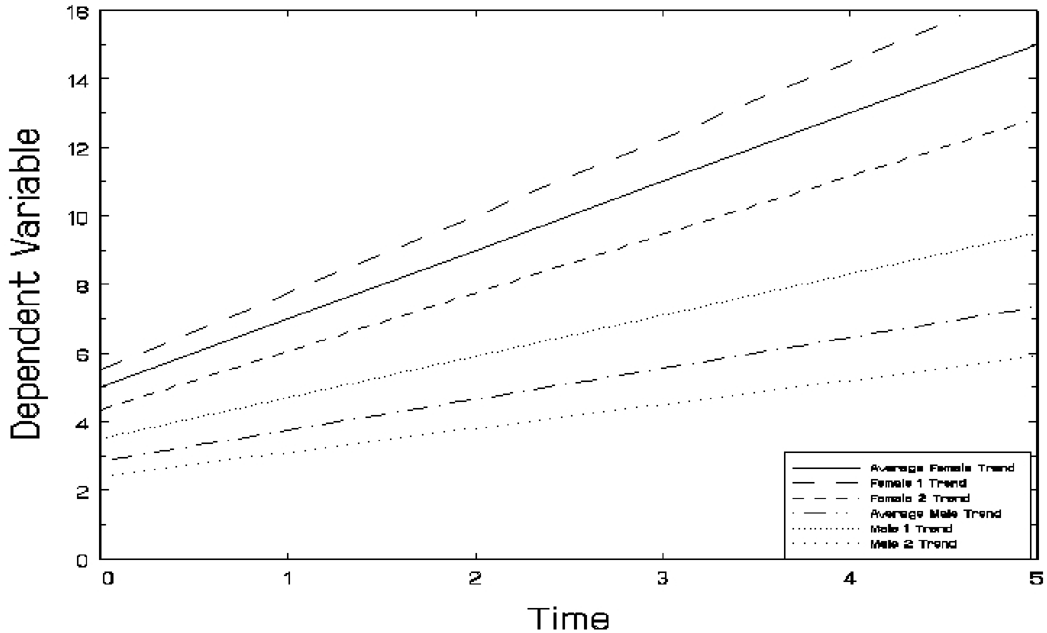
$$\underset{n_i \times 1}{\boldsymbol{y}_i} = \underset{n_i \times p}{\boldsymbol{X}_i} \underset{p \times 1}{\boldsymbol{\beta}} + \underset{n_i \times r}{\boldsymbol{Z}_i} \underset{r \times 1}{\boldsymbol{\upsilon}_i} + \underset{n_i \times 1}{\boldsymbol{\varepsilon}_i}$$

$i = 1 \ldots N$ individuals
$j = 1 \ldots n_i$ observations for individual i

$$\begin{aligned}
\boldsymbol{y}_i &= n_i \times 1 \text{ response vector for individual } i \\
\boldsymbol{X}_i &= n_i \times p \text{ design matrix for the fixed effects} \\
\boldsymbol{\beta} &= p \times 1 \text{ vector of unknown fixed parameters} \\
\boldsymbol{Z}_i &= n_i \times r \text{ design matrix for the random effects} \\
\boldsymbol{\upsilon}_i &= r \times 1 \text{ vector of unknown random effects} \sim \mathcal{N}(0, \boldsymbol{\Sigma}_\upsilon) \\
\boldsymbol{\varepsilon}_i &= n_i \times 1 \text{ residual vector} \sim \mathcal{N}(0, \sigma^2 \boldsymbol{I}_{n_i})
\end{aligned}$$

Random Intercepts and Trend Model

subjects deviate in terms of both intercept & slope



$$y \;=\; Time + Grp + (G \times T) + Subj + (S \times T) + Error$$

$$y_{ij} \;=\; \beta_0 + \beta_1 T_{ij} + \beta_2 G_i + \beta_3 (G_i \times T_{ij}) + \upsilon_{0i} + \upsilon_{1i} T_{ij} + \varepsilon_{ij}$$

$$\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{bmatrix} \sim \mathcal{N}\left\{ \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_{\upsilon_0} & \sigma_{\upsilon_0 \upsilon_1} \\ \sigma_{\upsilon_0 \upsilon_1} & \sigma^2_{\upsilon_1} \end{bmatrix} \right\} \qquad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$$

Within-Unit / Between-Unit representation

Within-subjects model - *level 1* $\quad (j = 1, \ldots, n_i)$

$$y_{ij} = b_{0i} + b_{1i}X_{1_{ij}} + \ldots + b_{p1i}X_{p1_{ij}} + \varepsilon_{ij}$$

Between-subjects model - *level 2* $\quad (i = 1, \ldots, N)$

$$\begin{aligned} b_{0i} &= \beta_0 \ + \ \boldsymbol{\beta}'_{0(2)}\boldsymbol{x}_i \ + \ \upsilon_{0i} \\ b_{1i} &= \beta_1 \ + \ \boldsymbol{\beta}'_{1(2)}\boldsymbol{x}_i \ + \ \upsilon_{1i} \\ . &= \ldots \\ b_{p1i} &= \beta_{p1} \ + \ \boldsymbol{\beta}_{p1(2)}\boldsymbol{x}_i \end{aligned}$$

$\Rightarrow$ "slopes as outcomes" model

$$\boldsymbol{\beta}' = \left[\begin{array}{c|c|c|c} \beta_0 & \beta_1 \ldots \beta_{p1} & \boldsymbol{\beta}'_{0(2)} & \boldsymbol{\beta}'_{1(2)} \ldots \boldsymbol{\beta}'_{p1(2)} \\ \text{intercept} & \text{level-1} & \text{level-2} & \text{cross-level} \end{array} \right]$$

Matrix form of model for individual i

$$\underset{n_i \times 1}{\underset{\boldsymbol{y}_i}{\begin{bmatrix} y_{i1} \\ y_{i2} \\ \ldots \\ y_{in_i} \end{bmatrix}}} = \underset{n_i \times p}{\underset{\boldsymbol{X}_i}{\begin{bmatrix} 1 & Time_{i1} & Group_i & Grp_i \times T_{i1} \\ 1 & Time_{i2} & Group_i & Grp_i \times T_{i2} \\ \ldots & \ldots & \ldots & \ldots \\ 1 & Time_{in_i} & Group_i & Grp_i \times T_{in_i} \end{bmatrix}}} \underset{p \times 1}{\underset{\boldsymbol{\beta}}{\begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix}}}$$

$$+ \underset{n_i \times r}{\underset{\boldsymbol{Z}_i}{\begin{bmatrix} 1 & Time_{i1} \\ 1 & Time_{i2} \\ \ldots & \ldots \\ 1 & Time_{in_i} \end{bmatrix}}} \underset{r \times 1}{\underset{\boldsymbol{\upsilon}_i}{\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{bmatrix}}} + \underset{n_i \times 1}{\underset{\boldsymbol{\varepsilon}_i}{\begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \ldots \\ \varepsilon_{in_i} \end{bmatrix}}}$$

Time might be years or months, and could differ for each subject

The conditional variance-covariance matrix is now of the form:

- $\Sigma_{\boldsymbol{y}_i} = \boldsymbol{Z}_i \boldsymbol{\Sigma}_\upsilon \boldsymbol{Z}_i' + \sigma^2 \boldsymbol{I}_{n_i}$

For example, with $r = 2$, $n = 3$, and $\boldsymbol{Z}_i' = \begin{bmatrix} 1 & 1 & 1 \\ 0 & 1 & 2 \end{bmatrix}$

the conditional variance-covariance $\Sigma_{\boldsymbol{y}_i} = \sigma^2 \boldsymbol{I}_{n_i} +$

$$\begin{bmatrix} \sigma^2_{\upsilon_0} & \sigma^2_{\upsilon_0} + \sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_0} + 2\sigma_{\upsilon_0\upsilon_1} \\ \sigma^2_{\upsilon_0} + \sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_0} + 2\sigma_{\upsilon_0\upsilon_1} + \sigma^2_{\upsilon_1} & \sigma^2_{\upsilon_0} + 3\sigma_{\upsilon_0\upsilon_1} + 2\sigma^2_{\upsilon_1} \\ \sigma^2_{\upsilon_0} + 2\sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_0} + 3\sigma_{\upsilon_0\upsilon_1} + 2\sigma^2_{\upsilon_1} & \sigma^2_{\upsilon_0} + 4\sigma_{\upsilon_0\upsilon_1} + 4\sigma^2_{\upsilon_1} \end{bmatrix}$$

- variances and covariances change across time

More general models allow autocorrelated errors, $\boldsymbol{\varepsilon}_i \sim \mathcal{N}(0, \sigma^2 \boldsymbol{\Omega}_i)$, where $\boldsymbol{\Omega}$ might represent AR or MA process

Example: Drug Plasma Levels and Clinical Response

Riesby and associates (Riesby *et al.*, 1977) examined the relationship between Imipramine (IMI) and Desipramine (DMI) plasma levels and clinical response in 66 depressed inpatients (37 endogenous and 29 non-endogenous)

	Drug-Washout					
	day0	day7	day14	day21	day28	day35
	wk 0	wk 1	wk 2	wk 3	wk 4	wk 5
Hamilton Depression	HD_1	HD_2	HD_3	HD_4	HD_5	HD_6
Diagnosis	Dx					
IMI			IMI_3	IMI_4	IMI_5	IMI_6
DMI			DMI_3	DMI_4	DMI_5	DMI_6
n	61	63	65	65	63	58

outcome variable - Hamilton Depression Scores (HD)

independent variables - Dx, IMI and DMI

- Dx - endogenous (=1) or non-endogenous (=0)
- IMI (imipramine) drug-plasma levels (μg/l)
  - antidepressant given 225 mg/day, weeks 3-6
- DMI (desipramine) drug-plasma levels (μg/l)
  - metabolite of imipramine

Descriptive Statistics

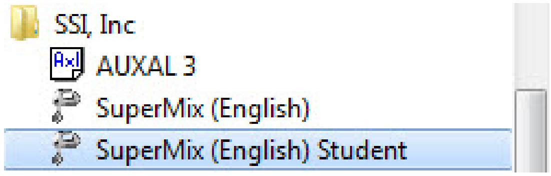
Observed HDRS Means, n, and sd

	Washout					
	wk 0	wk 1	wk 2	wk 3	wk 4	wk 5
Endog	24.0	23.0	19.3	17.3	14.5	12.6
n	33	34	37	36	34	31
Non-Endog	22.8	20.5	17.0	15.3	12.6	11.2
n	28	29	28	29	29	27
pooled sd	4.5	4.7	5.5	6.4	7.0	7.2

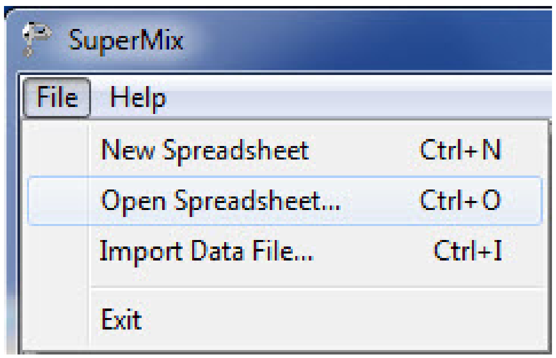
Correlations: **n = 46** and *46* $\leq n \leq$ *66*

	wk 0	wk 1	wk 2	wk 3	wk 4	wk 5
week 0	1.0	*.49*	*.41*	*.33*	*.23*	*.18*
week 1	**.49**	1.0	*.49*	*.41*	*.31*	*.22*
week 2	**.42**	**.49**	1.0	*.74*	*.67*	*.46*
week 3	**.44**	**.51**	**.73**	1.0	*.82*	*.57*
week 4	**.30**	**.35**	**.68**	**.78**	1.0	*.65*
week 5	**.22**	**.23**	**.53**	**.62**	**.72**	1.0

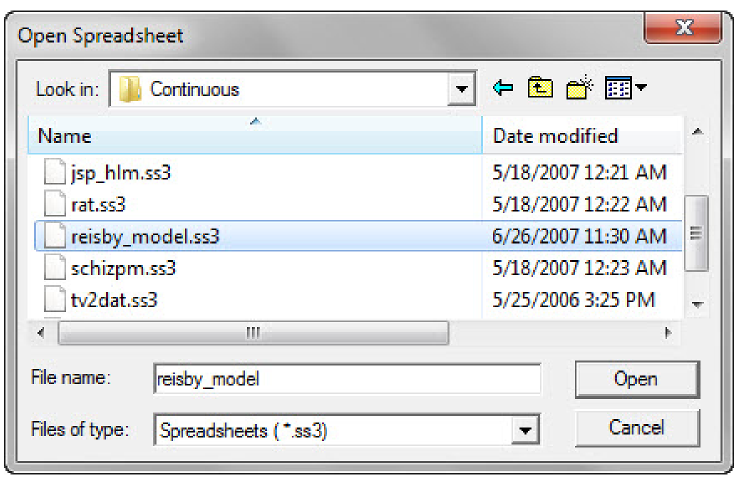
- Under SSI, Inc > “SuperMix (English)” or ‘SuperMix (English) Student”



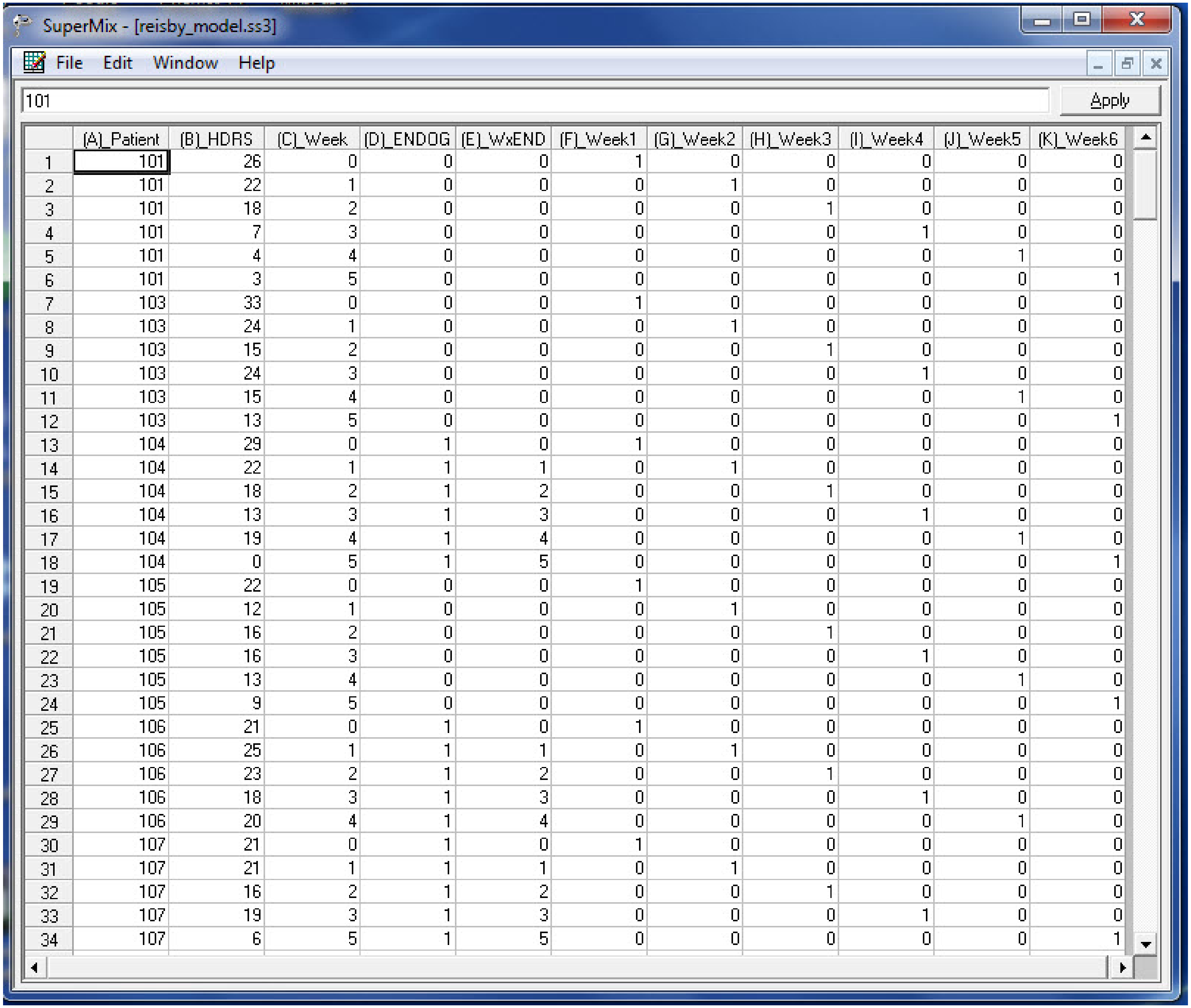
- Under “File” click on “Open Spreadsheet”



- Open C:\SuperMixEn Examples\Workshop\Continuous\reisby_model.ss3 (or C:\SuperMixEn Student Examples\Workshop\Continuous\reisby_model.ss3)

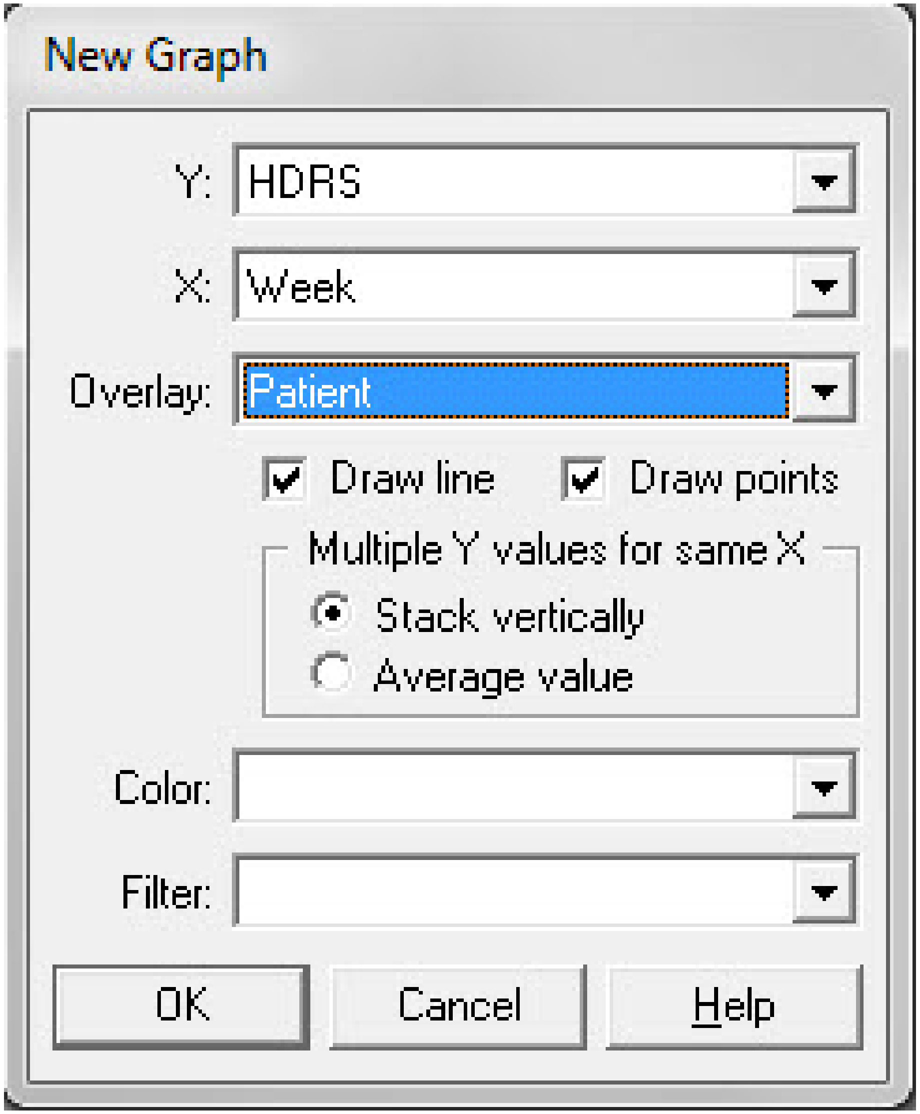


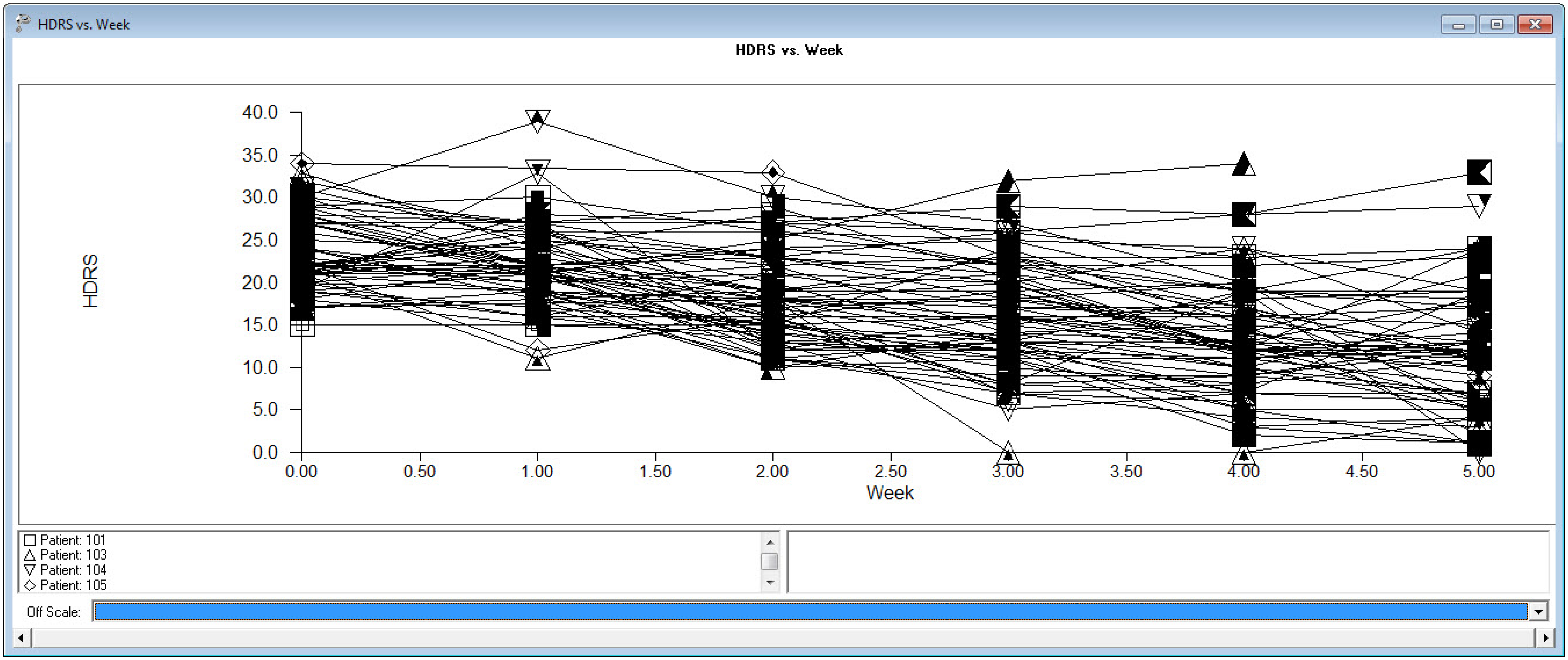
c:\SuperMixEn Examples\Workshop\Continuous\reisby_model.ss3



	(A)_Patient	(B)_HDRS	(C)_Week	(D)_ENDOG	(E)_WxEND	(F)_Week1	(G)_Week2	(H)_Week3	(I)_Week4	(J)_Week5	(K)_Week6
1	101	26	0	0	0	1	0	0	0	0	0
2	101	22	1	0	0	0	1	0	0	0	0
3	101	18	2	0	0	0	0	1	0	0	0
4	101	7	3	0	0	0	0	0	1	0	0
5	101	4	4	0	0	0	0	0	0	1	0
6	101	3	5	0	0	0	0	0	0	0	1
7	103	33	0	0	0	1	0	0	0	0	0
8	103	24	1	0	0	0	1	0	0	0	0
9	103	15	2	0	0	0	0	1	0	0	0
10	103	24	3	0	0	0	0	0	1	0	0
11	103	15	4	0	0	0	0	0	0	1	0
12	103	13	5	0	0	0	0	0	0	0	1
13	104	29	0	1	0	1	0	0	0	0	0
14	104	22	1	1	1	0	1	0	0	0	0
15	104	18	2	1	2	0	0	1	0	0	0
16	104	13	3	1	3	0	0	0	1	0	0
17	104	19	4	1	4	0	0	0	0	1	0
18	104	0	5	1	5	0	0	0	0	0	1
19	105	22	0	0	0	1	0	0	0	0	0
20	105	12	1	0	0	0	1	0	0	0	0
21	105	16	2	0	0	0	0	1	0	0	0
22	105	16	3	0	0	0	0	0	1	0	0
23	105	13	4	0	0	0	0	0	0	1	0
24	105	9	5	0	0	0	0	0	0	0	1
25	106	21	0	1	0	1	0	0	0	0	0
26	106	25	1	1	1	0	1	0	0	0	0
27	106	23	2	1	2	0	0	1	0	0	0
28	106	18	3	1	3	0	0	0	1	0	0
29	106	20	4	1	4	0	0	0	0	1	0
30	107	21	0	1	0	1	0	0	0	0	0
31	107	21	1	1	1	0	1	0	0	0	0
32	107	16	2	1	2	0	0	1	0	0	0
33	107	19	3	1	3	0	0	0	1	0	0
34	107	6	5	1	5	0	0	0	0	0	1

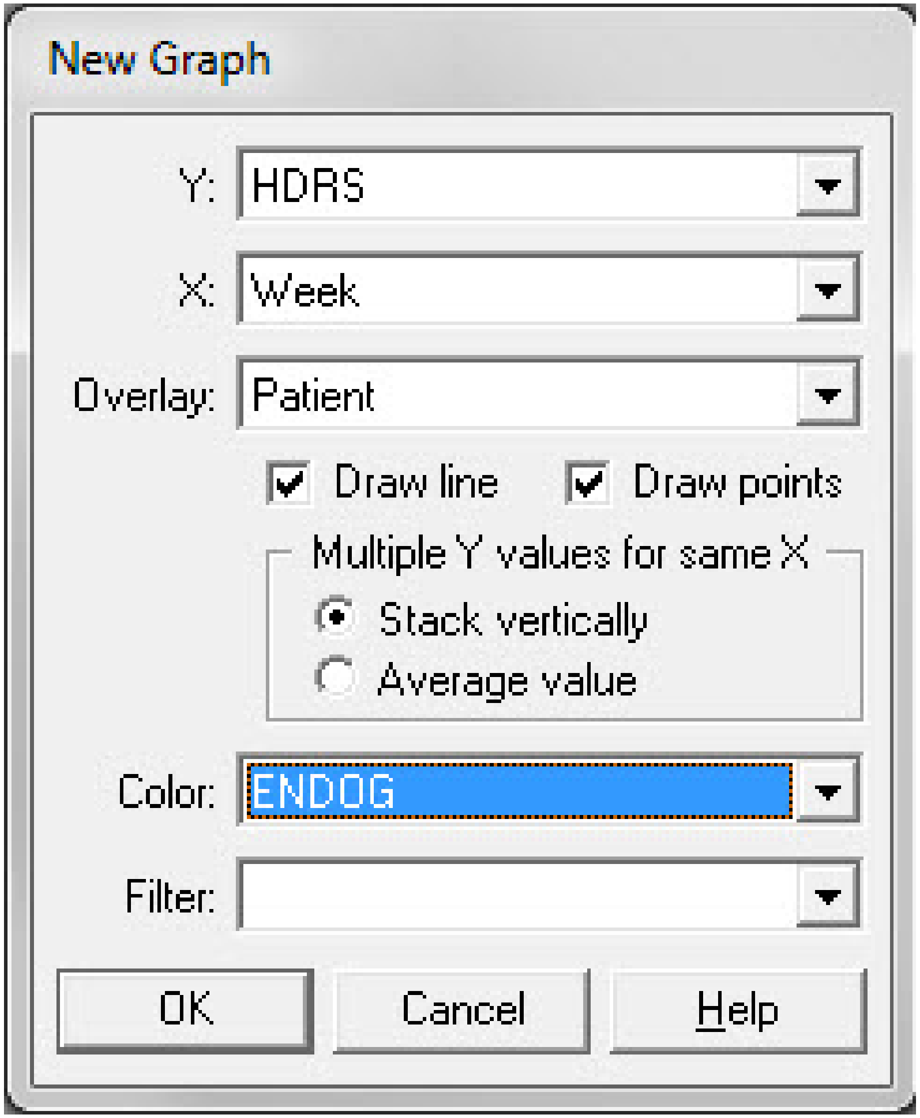
Select “File” > “Data-based Graphs” > “Exploratory”

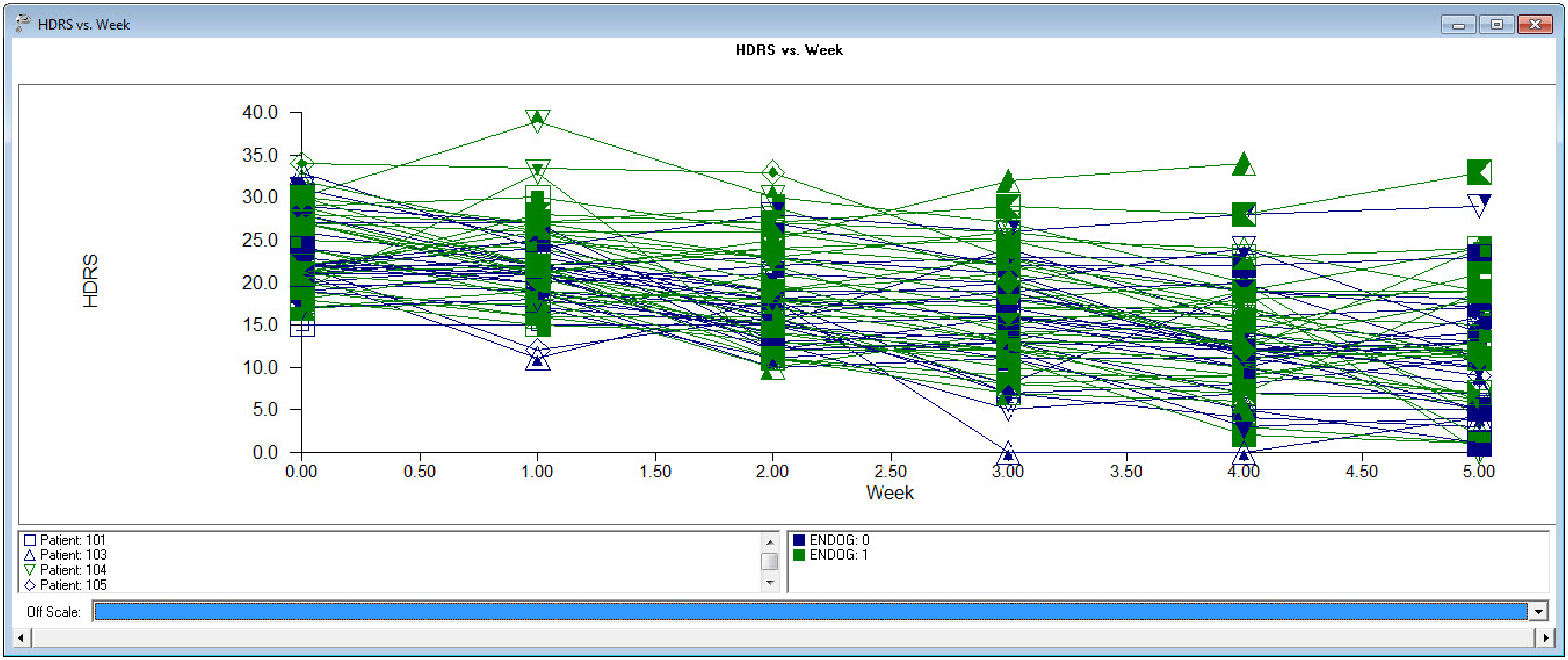




- increasing variance across time
- general linear decline over time

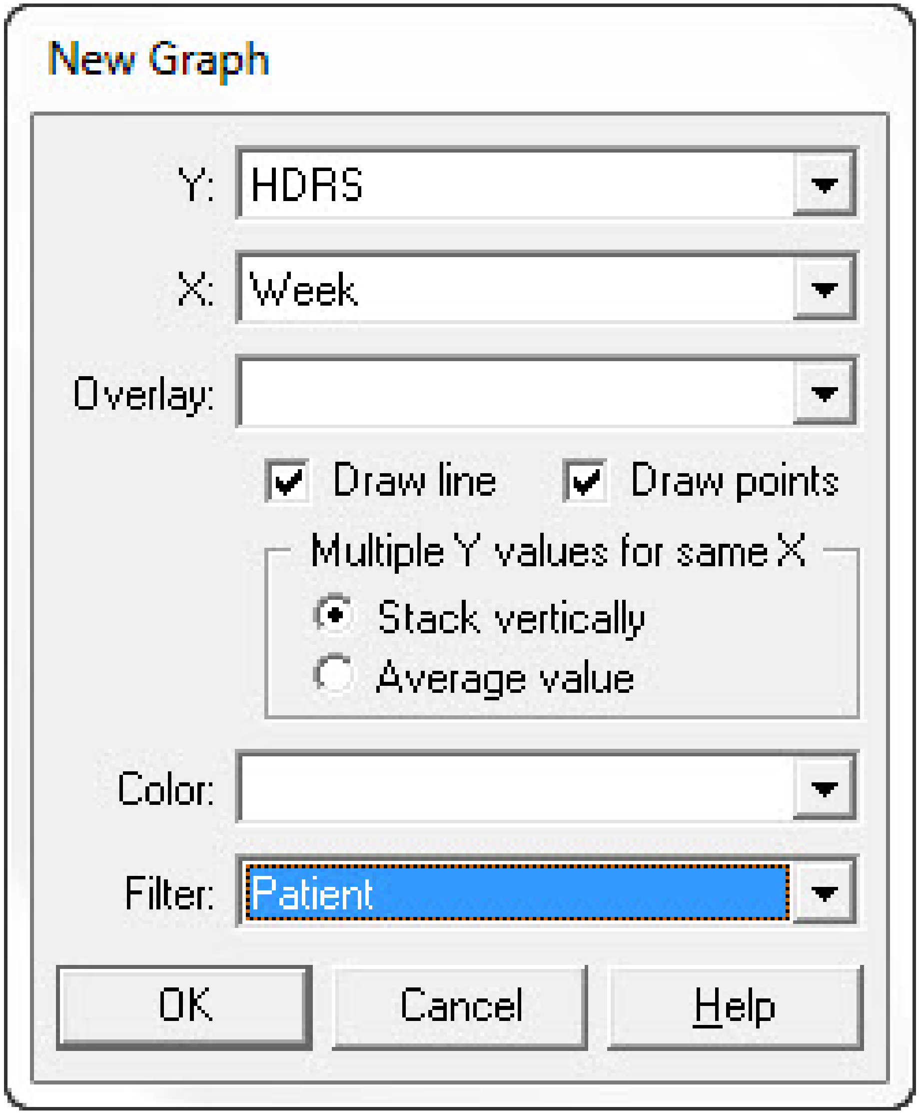
Select “File” > “Data-based Graphs” > “Exploratory”



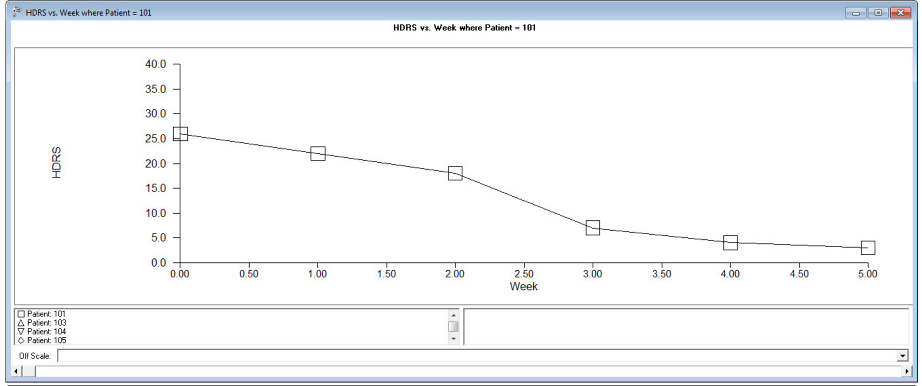


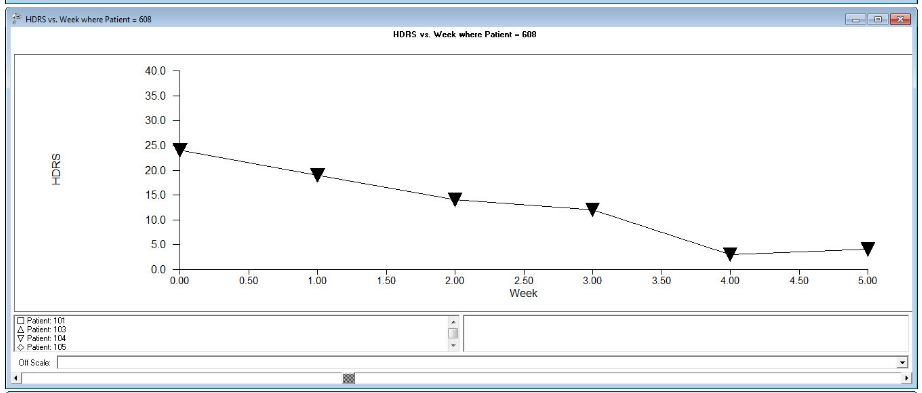
- Plot of Endogenous and Non-Endogenous patients

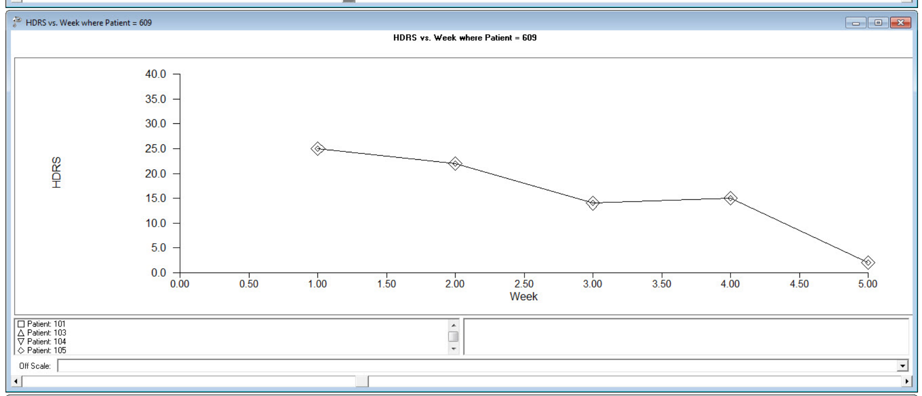
Select "File" > "Data-based Graphs" > "Exploratory"

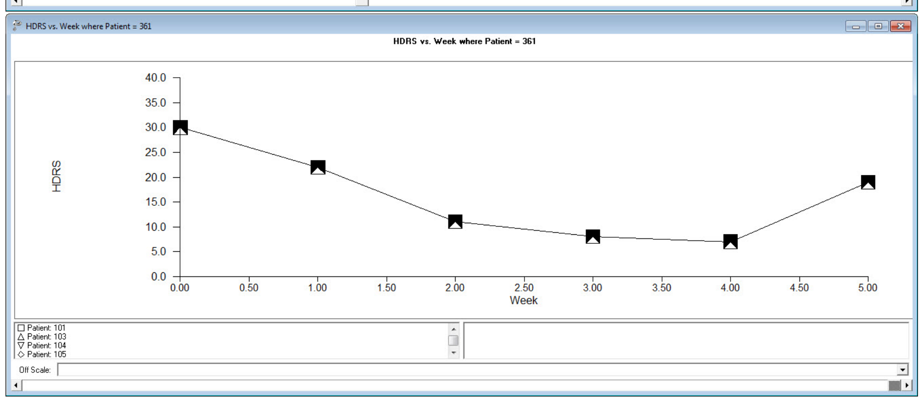


⇒ Produces plots for each subject

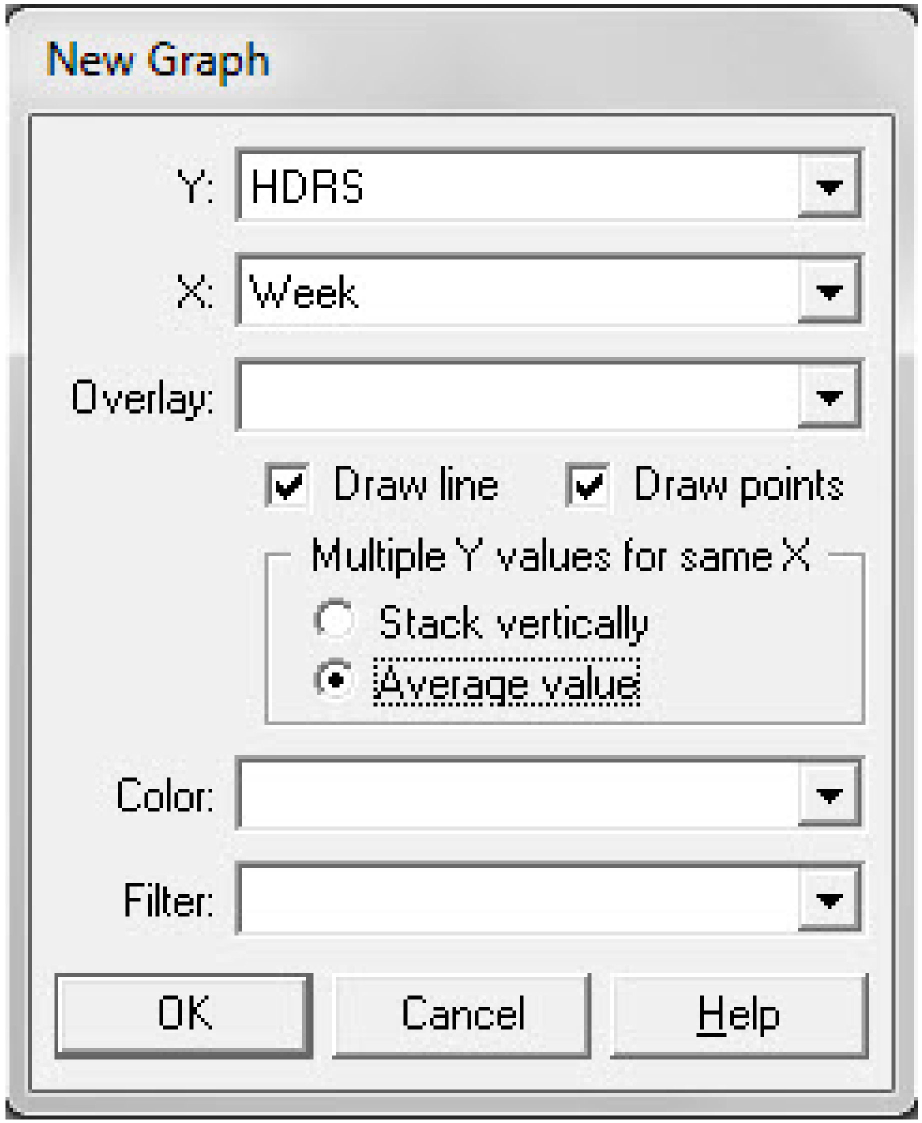

HDRS vs. Week where Patient = 101
HDRS
Week
Patient: 101
Patient: 103
Patient: 104
Patient: 105
Off Scale:

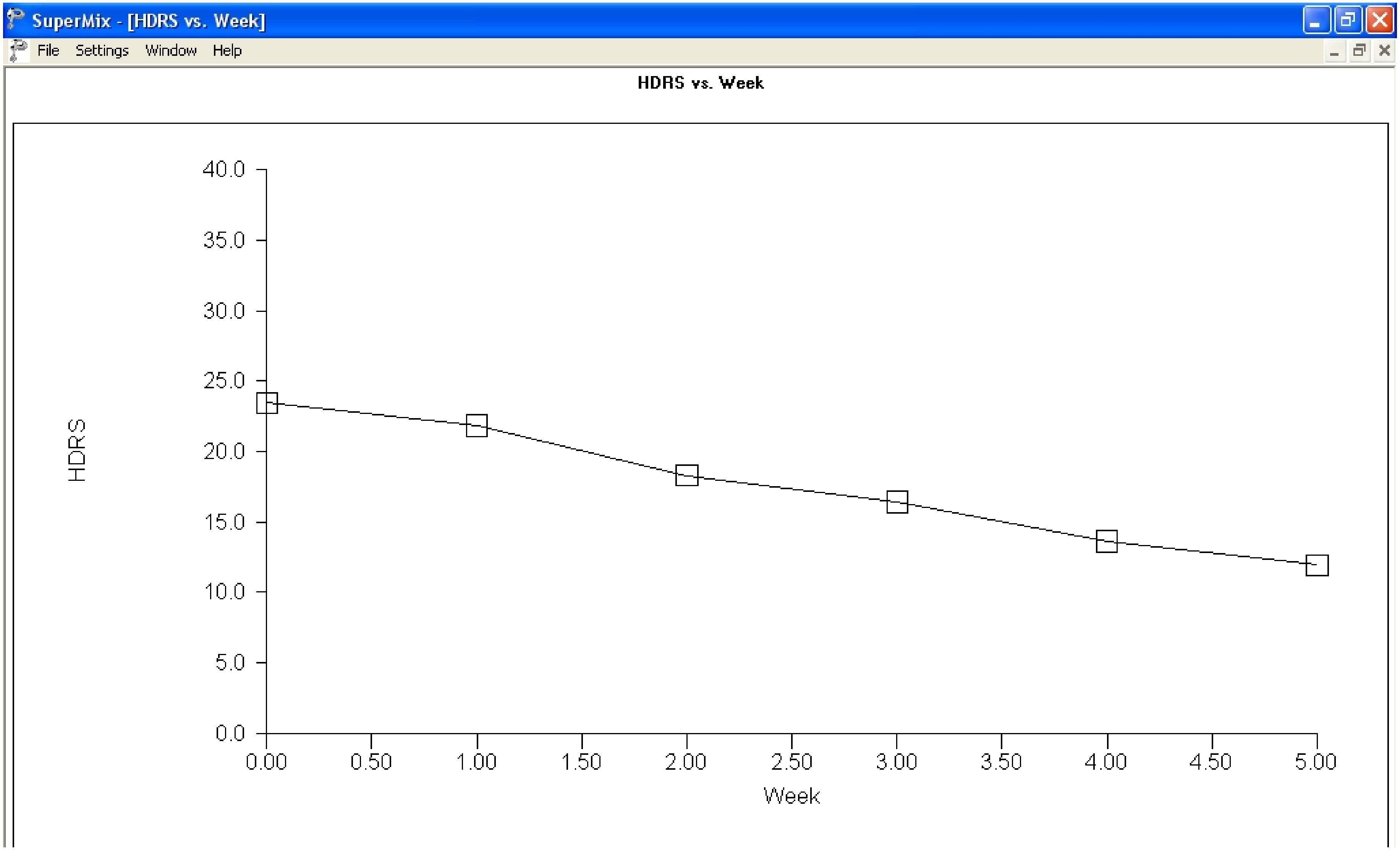

HDRS vs. Week where Patient = 608
HDRS
Week
Patient: 101
Patient: 103
Patient: 104
Patient: 105
Off Scale:


HDRS vs. Week where Patient = 609
HDRS
Week
Patient: 101
Patient: 103
Patient: 104
Patient: 105
Off Scale:


HDRS vs. Week where Patient = 361
HDRS
Week
Patient: 101
Patient: 103
Patient: 104
Patient: 105
Off Scale:

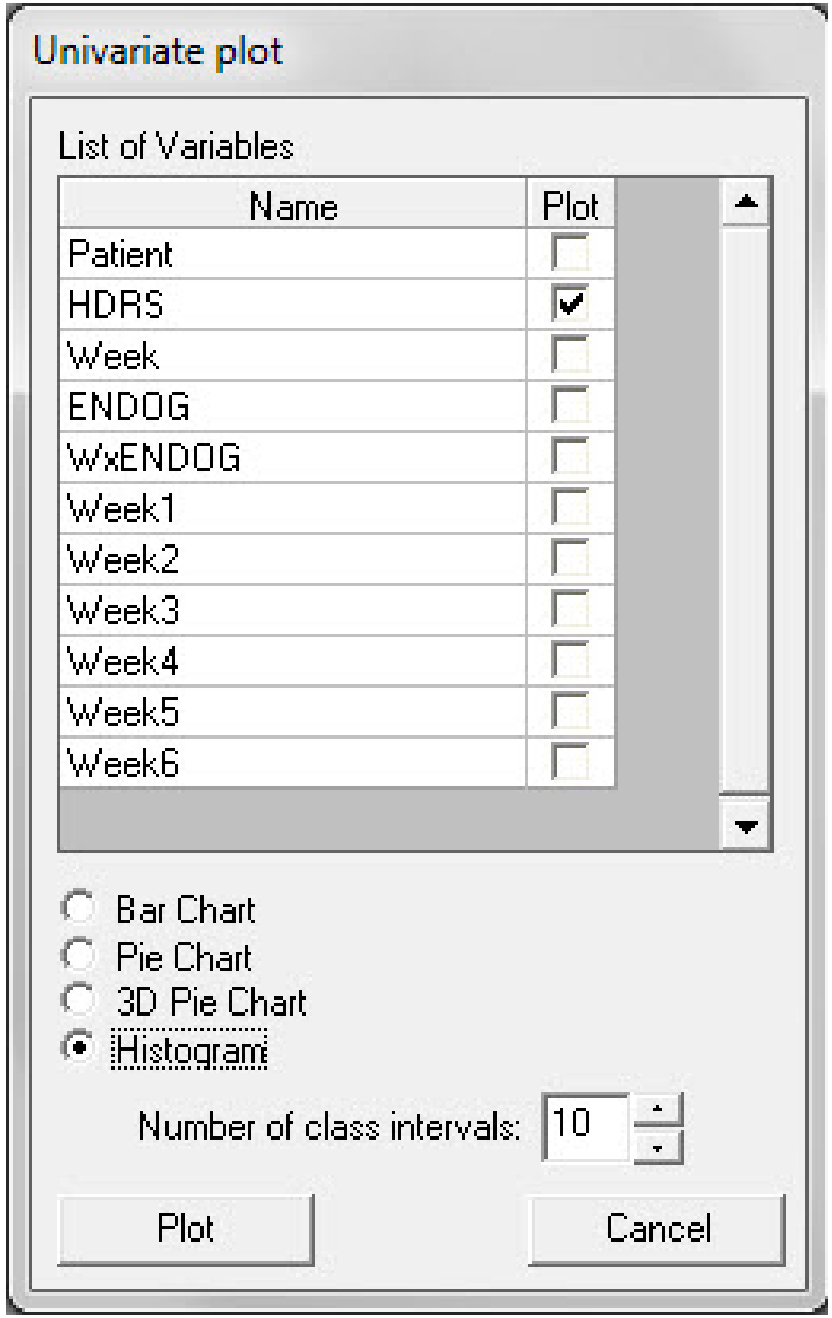
Select "File" > "Data-based Graphs" > "Exploratory"

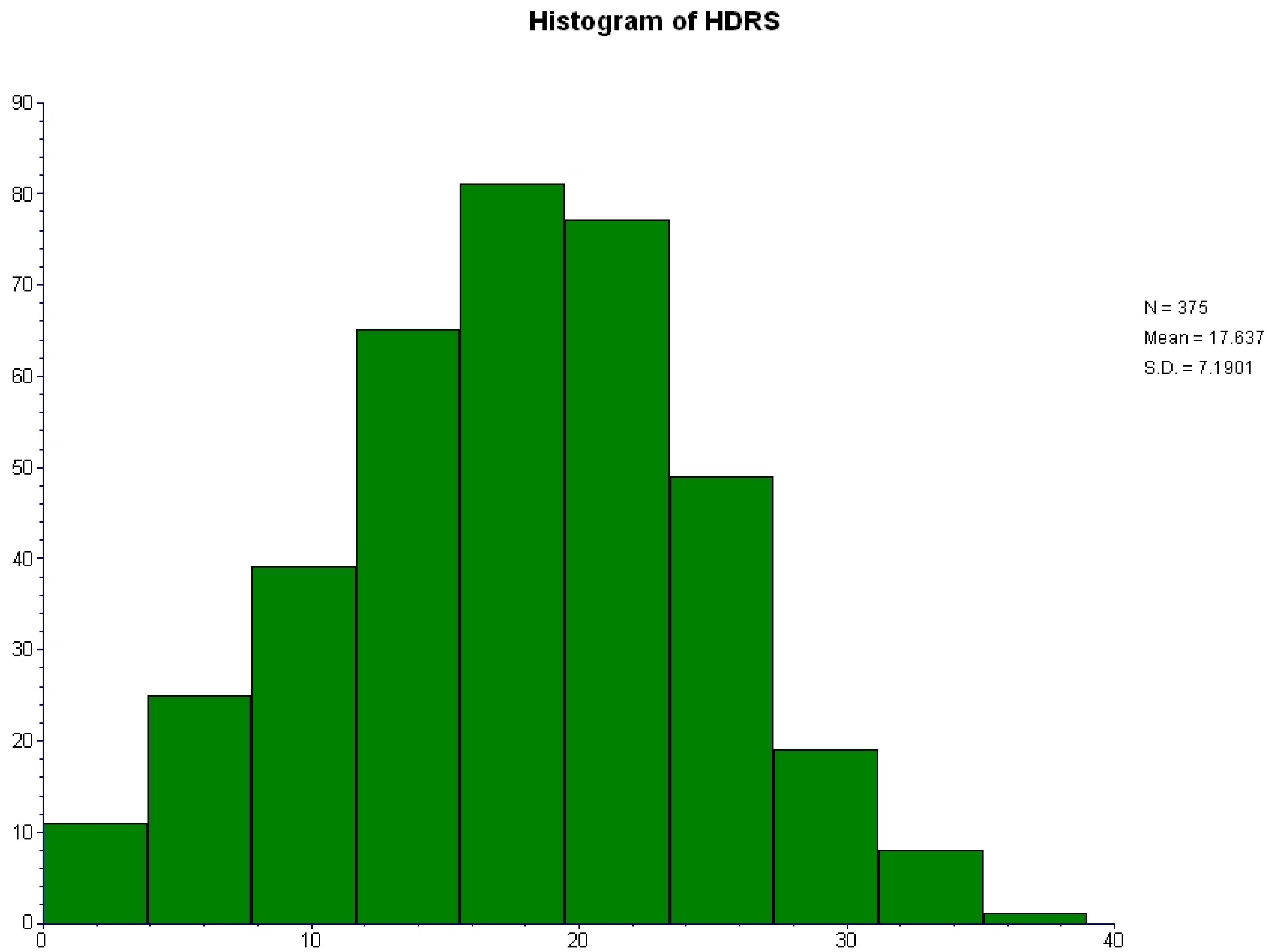




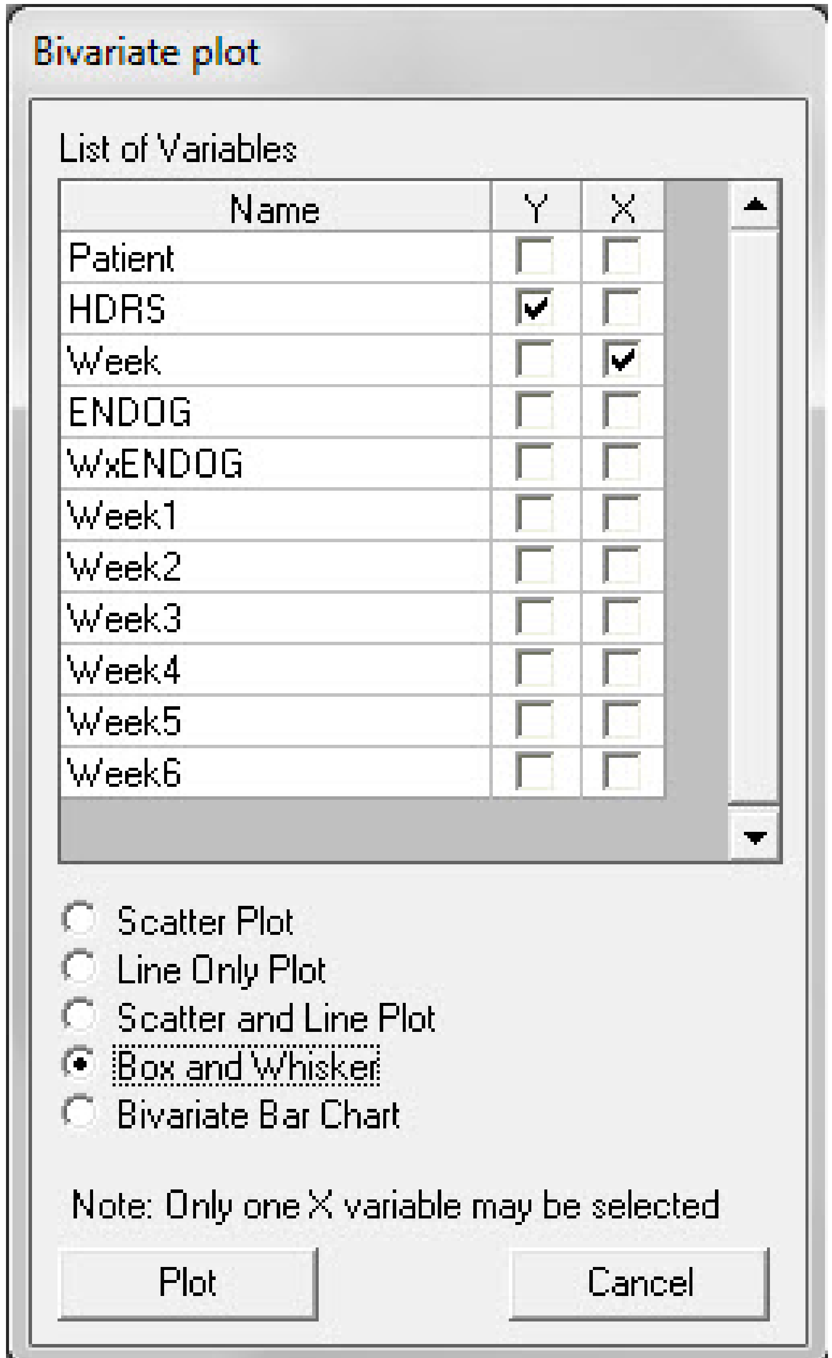
- Mean response across time

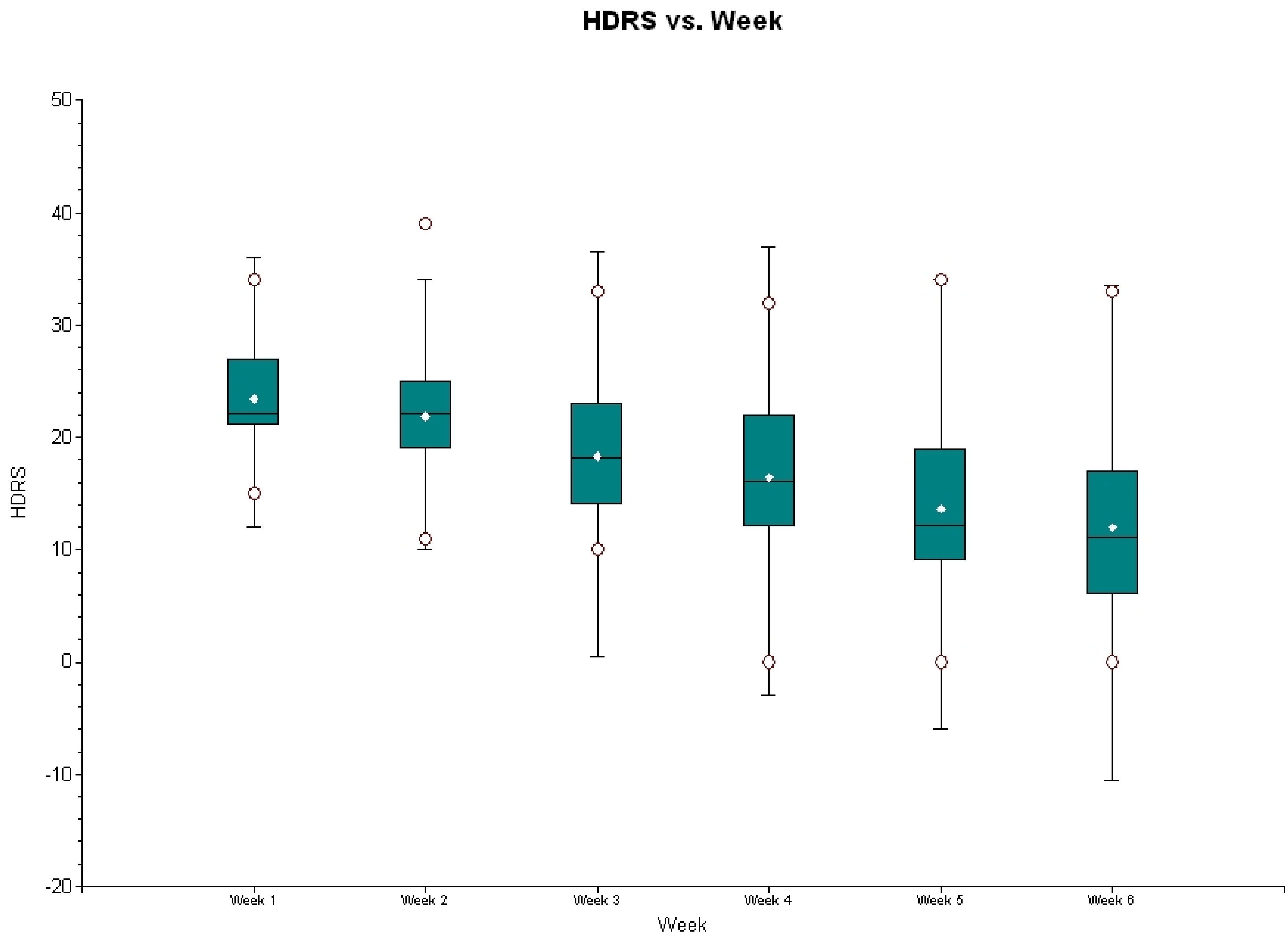
Select "File" > "Data-based Graphs" > "Univariate"




Histogram of HDRS
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
N = 375
Mean = 17.637
S.D. = 7.1901

Select “File” > “Data-based Graphs” > “Bivariate”




HDRS vs. Week
50
40
30
20
10
0
-10
-20
HDRS
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week

Examination of HD across all weeks

$$\underset{n_i \times 1}{\underset{\boldsymbol{y}_i}{\begin{bmatrix} HD_{i1} \\ HD_{i2} \\ \ldots \\ HD_{in_i} \end{bmatrix}}} = \underset{n_i \times p}{\underset{\boldsymbol{X}_i}{\begin{bmatrix} 1 & WEEK_{i1} \\ 1 & WEEK_{i2} \\ \ldots & \ldots \\ 1 & WEEK_{in_i} \end{bmatrix}}} \underset{p \times 1}{\underset{\boldsymbol{\beta}}{\begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}}}$$

$$+ \underset{n_i \times r}{\underset{\boldsymbol{Z}_i}{\begin{bmatrix} 1 & WEEK_{i1} \\ 1 & WEEK_{i2} \\ \ldots & \ldots \\ 1 & WEEK_{in_i} \end{bmatrix}}} \underset{r \times 1}{\underset{\boldsymbol{\upsilon}_i}{\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{bmatrix}}} + \underset{n_i \times 1}{\underset{\boldsymbol{\varepsilon}_i}{\begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \ldots \\ \varepsilon_{in_i} \end{bmatrix}}}$$

where $\max(n_i) = 6$, and $\quad \boldsymbol{X}_i' = \boldsymbol{Z}_i' = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 & 4 & 5 \end{bmatrix}$

Within-subjects and between-subjects components

Within-subjects model

$$\begin{aligned} HD_{ij} &= b_{0i} + b_{1i} Time_{ij} + E_{ij} \\ y_{ij} &= b_{0i} + b_{1i} x_{ij} + \varepsilon_{ij} \end{aligned}$$

$$\begin{aligned} i &= 1 \ldots 66 \text{ patients} \\ j &= 1 \ldots n_i \text{ observations (max = 6) for patient } i \end{aligned}$$

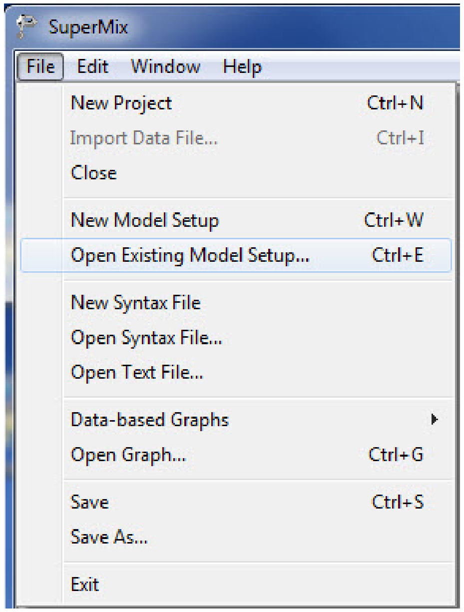
b_{0i} = week 0 HD level for patient i
b_{1i} = weekly change in HD for patient i

Between-subjects models

$$\begin{aligned} b_{0i} &= \beta_0 + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \upsilon_{1i} \end{aligned}$$

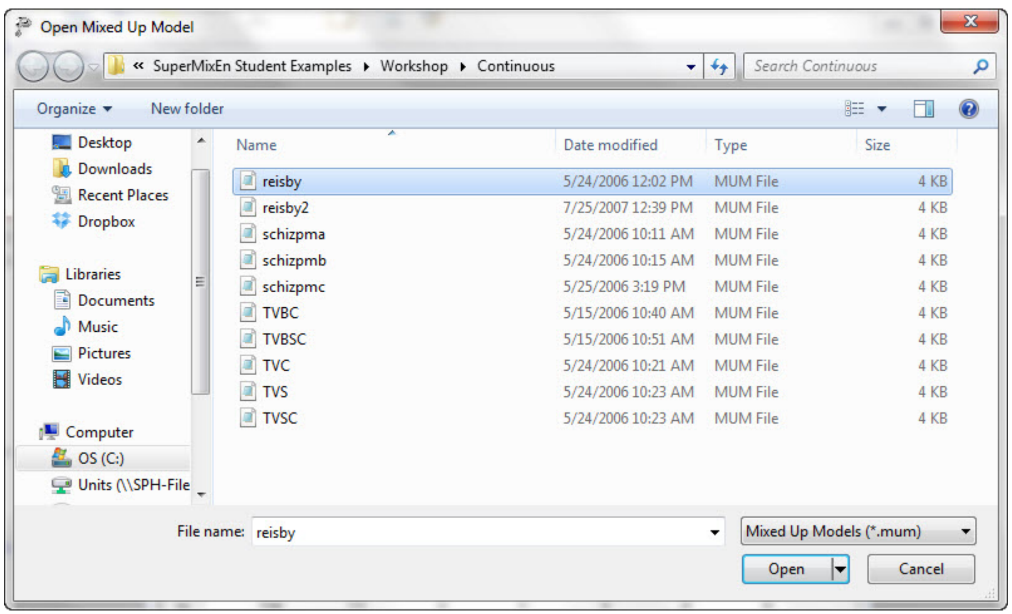
β_0 = average week 0 HD level
β_1 = average HD weekly improvement
υ_{0i} = individual deviation from average intercept
υ_{1i} = individual deviation from average improvement

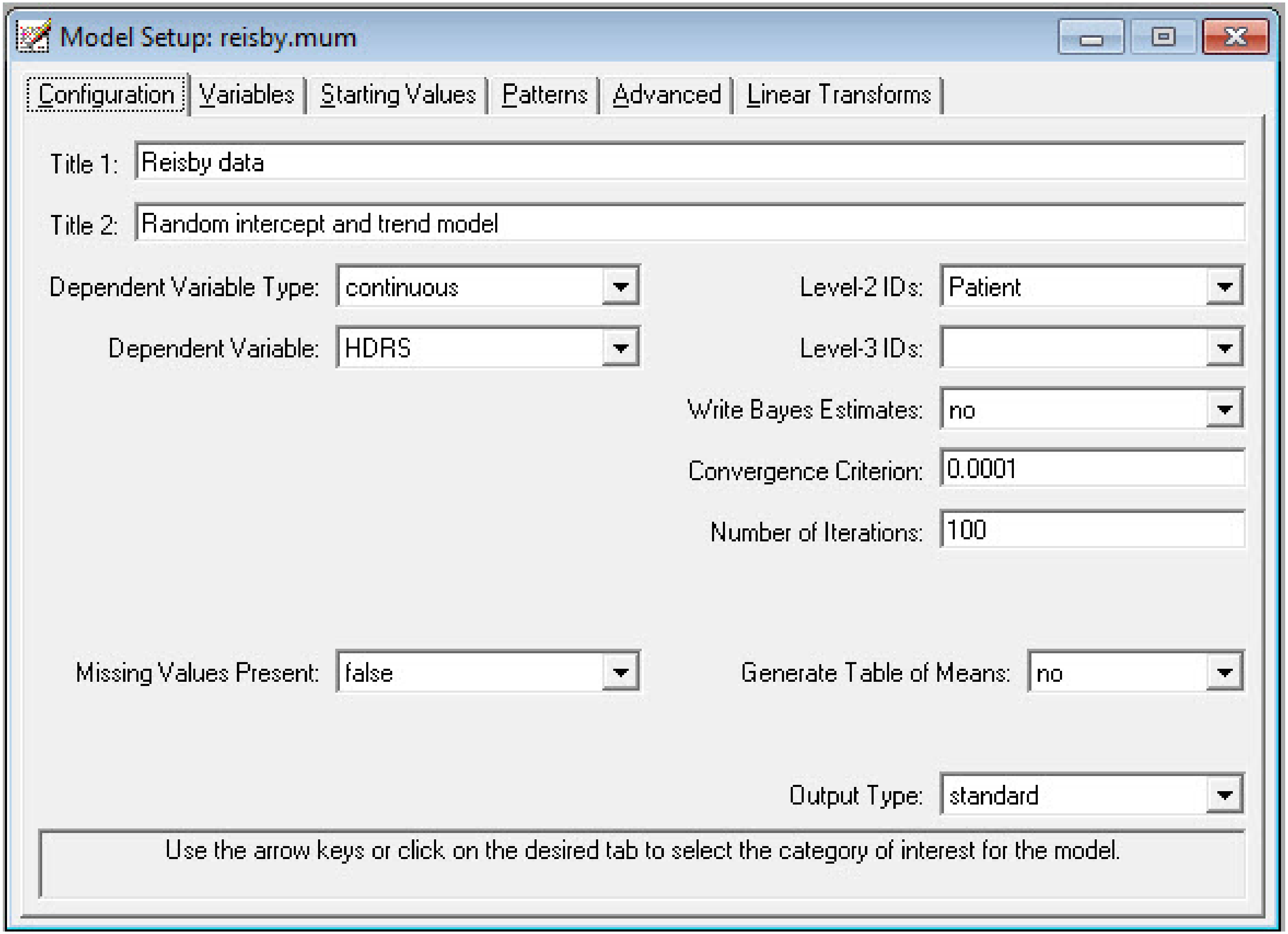
Under "File" click on "Open Existing Model Setup"

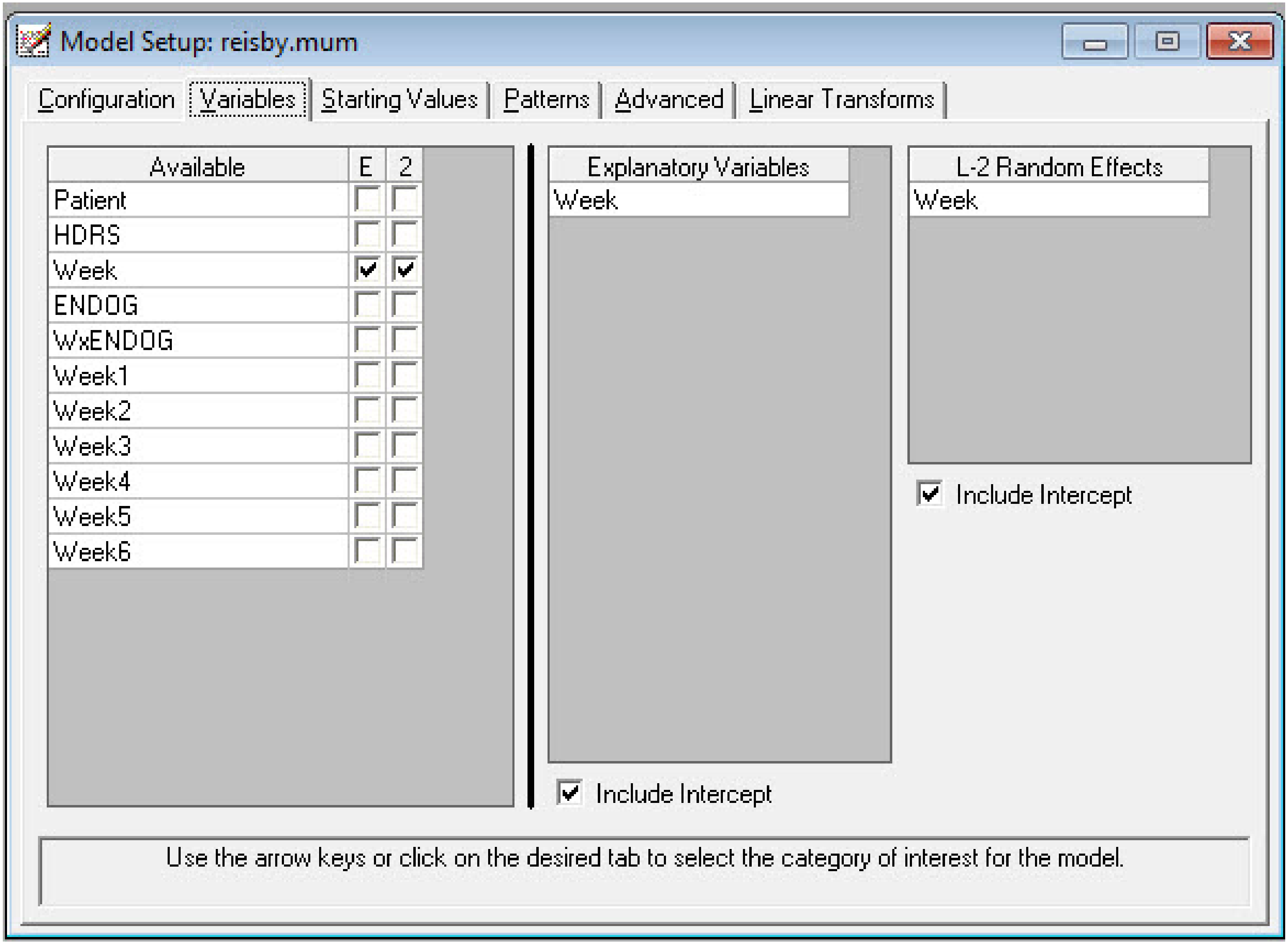


Open C:\SuperMixEn Examples\Workshop\Continuous\reisby.mum

(or C:\SuperMixEn Student Examples\Workshop\Continuous\reisby.mum)




Model Setup: reisby.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1:
Reisby data
Title 2:
Random intercept and trend model
Dependent Variable Type:
continuous
Dependent Variable:
HDRS
Level-2 IDs:
Patient
Level-3 IDs:
Write Bayes Estimates:
no
Convergence Criterion:
0.0001
Number of Iterations:
100
Missing Values Present:
false
Generate Table of Means:
no
Output Type:
standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.


Model Setup: reisby.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
Patient
HDRS
Week
ENDOG
WxENDOG
Week1
Week2
Week3
Week4
Week5
Week6
Explanatory Variables
Week
Include Intercept
L-2 Random Effects
Week
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.

```
SuperMix - [reisby.out]
File  Analysis  Window  Help

        o-----------------------------------------------------------o
        |                                                           |
        |   SuperMix Module for Continuous Outcomes                 |
        |                                                           |
        |     Copyright  2005-2008                                  |
        |     Scientific Software International, Inc.               |
        |     7383 N. Lincoln Avenue,Suite 100                      |
        |     Lincolnwood, IL 60712, U.S.A                          |
        |     Phone:    (847)675-0720                               |
        |     Fax:      (847)675-2140                               |
        |     Website: www.ssicentral.com                           |
        |     Support: techsupport@ssicentral.com                   |
        |                                                           |
        |   Date of analysis: January 17, 2013                      |
        |   Time of analysis: 15H07:32                              |
        |                                                           |
        o-----------------------------------------------------------o

Model specifications are as follows:


Model=Continuous;
Options Output=standard Converge=0.0001 Maxiter=100 Bayes=No;
Link=identity;
Distribution=nor;
Varnames=  Patient HDRS Week ENDOG WxENDOG Week1 Week2 Week3 Week4 Week5 Week6 intercept;
Title1=Reisby data;
Title2=Random intercept and trend model;
DataFile=C:\SuperMixEn Examples\Workshop\Continuous\reisby.dat;
Level2ID= Patient;
Dependent= HDRS;
Predictors= intercept Week;
L1Random= intercept;
L2Random= intercept Week;
FixPatType=Free;
Cov2PatType=Correlated;
AutoCor=None;

Numbers of observations
-----------------------

Level 2 observations =       66
Level 1 observations =      375

N2      :       1       2       3       4       5       6       7       8
N1      :       6       6       6       6       5       5       6       5

N2      :       9      10      11      12      13      14      15      16
N1      :       5       5       6       5       6       6       6       6

N2      :      17      18      19      20      21      22      23      24
N1      :       6       6       6       6       6       5       6       6
```

reisby.out

```
o==================================o
| Reisby data                      |
| Random intercept and trend model |
o==================================o

Maximum likelihood estimates
----------------------------


Fixed regressor(s)
------------------

 Variable                  Estimate     Std.Err.      Z-value      p-value
 --------                  --------     --------      -------      -------
 intercept                 23.57695      0.54555     43.21714      0.00000
 Week                      -2.37707      0.20865    -11.39280      0.00000

Log Likelihood                  =    -1109.5188
-2 Log Likelihood (Deviance)    =     2219.0375
Akaike's Information Criterion =     2231.0375
Schwarz's Bayesian Criterion    =     2244.1754
Number of free parameters       =             6



Variance/covariance components
------------------------------


 Level 2                                Estimate     Std.Err.      Z-value   p-value
 -------                                --------     --------      -------   -------
 intercept       /intercept             12.62930      3.46653      3.64322   0.00027
 Week            /intercept             -1.42093      1.02595     -1.38500   0.16605
 Week            /Week                   2.07899      0.50417      4.12363   0.00004

 Level 1                                Estimate     Std.Err.      Z-value   p-value
 -------                                --------     --------      -------   -------
 intercept       /intercept             12.21663      1.10696     11.03615   0.00000
```

Save As... Close

reisby.out

```
Level 2 Correlation Matrix
--------------------------

                    intercept           Week

  intercept            1.0000
  Week                -0.2773          1.0000
```

Save As... Close

Empirical Bayes Estimates of Random Effects

Select "Analysis" > "View Level-2 Bayes Results"

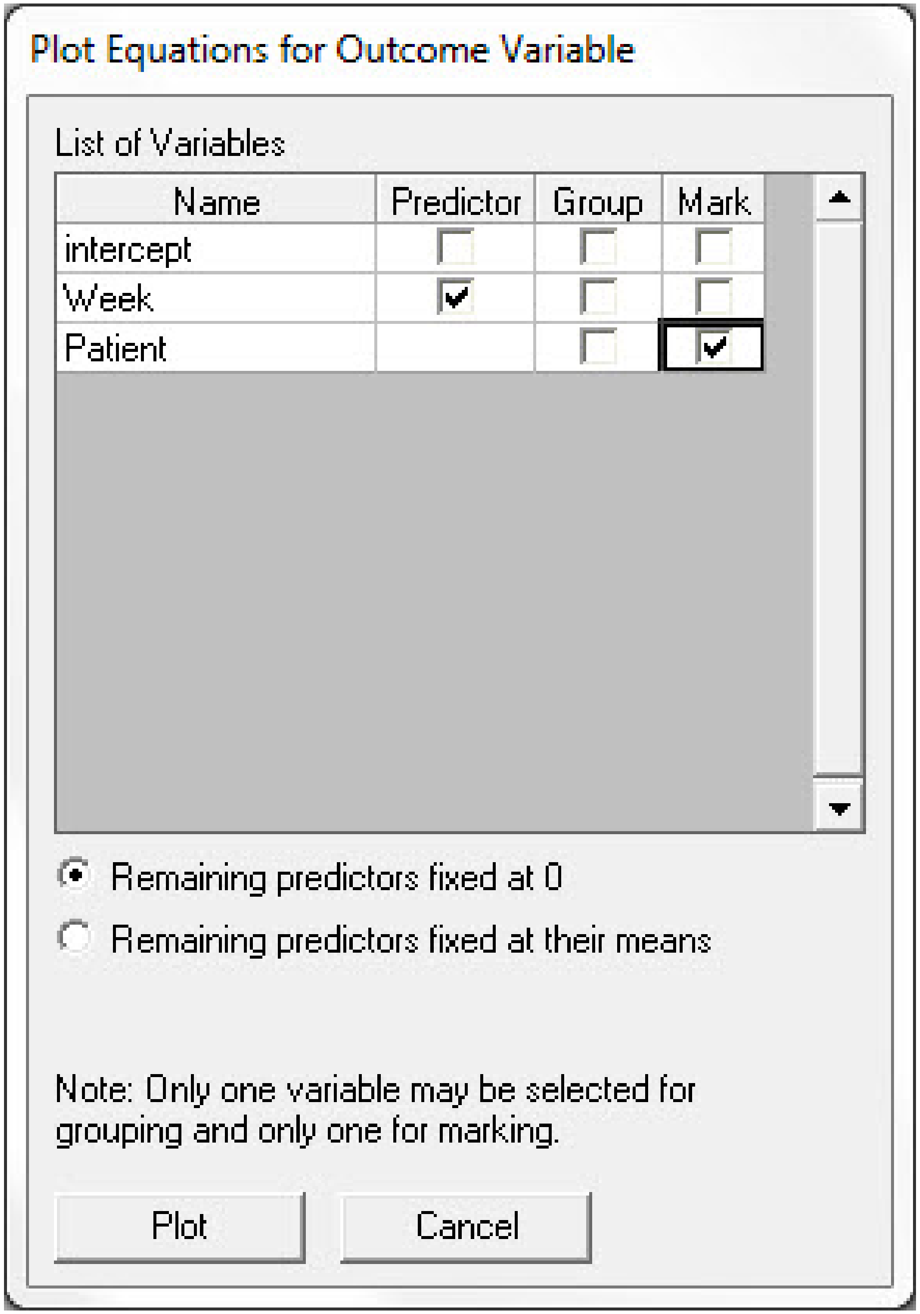
reisby.ba2

101.00	1	1.0298	4.0414	intercept
101.00	2	-2.1038	0.46416	Week
103.00	1	3.6395	4.0414	intercept
103.00	2	-0.47444	0.46416	Week
104.00	1	2.6392	4.0414	intercept
104.00	2	-1.4893	0.46416	Week
105.00	1	-3.0169	4.0414	intercept
105.00	2	0.21997	0.46416	Week
106.00	1	0.32487	4.2271	intercept
106.00	2	1.0191	0.70300	Week
107.00	1	-0.61438	4.0425	intercept
107.00	2	-0.42857	0.53892	Week
108.00	1	-2.0122	4.0414	intercept
108.00	2	-0.80324	0.46416	Week
113.00	1	-0.71648	4.2271	intercept
113.00	2	1.7935	0.70300	Week
114.00	1	-3.0895	6.0393	intercept
114.00	2	-0.54364	0.59520	Week
115.00	1	-2.5714	6.0393	intercept
115.00	2	0.52956	0.59520	Week
117.00	1	-3.4887	4.0414	intercept
117.00	2	-0.52286	0.46416	Week
118.00	1	1.8416	6.0393	intercept
118.00	2	-0.40508	0.59520	Week
120.00	1	-2.4079	4.0414	intercept
120.00	2	1.1558	0.46416	Week
121.00	1	-0.95956	4.0414	intercept
121.00	2	0.44268	0.46416	Week
123.00	1	-4.5497	4.0414	intercept
123.00	2	-0.36520	0.46416	Week
501.00	1	4.3613	4.0414	intercept
501.00	2	0.85619	0.46416	Week
502.00	1	-0.92278	4.0414	intercept
502.00	2	-1.8644	0.46416	Week

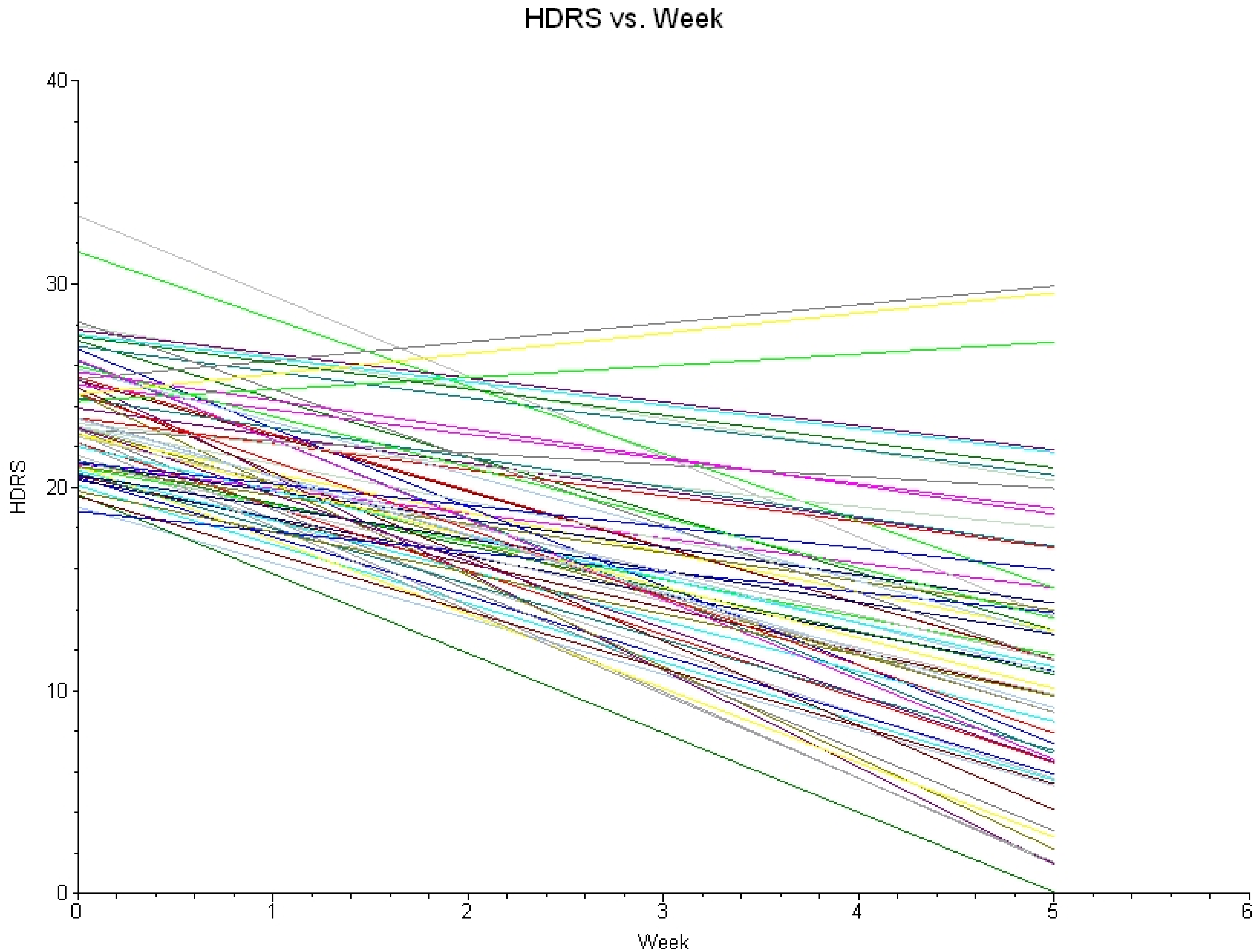
Save As... Close

ID, random effect number, estimate, variance, name

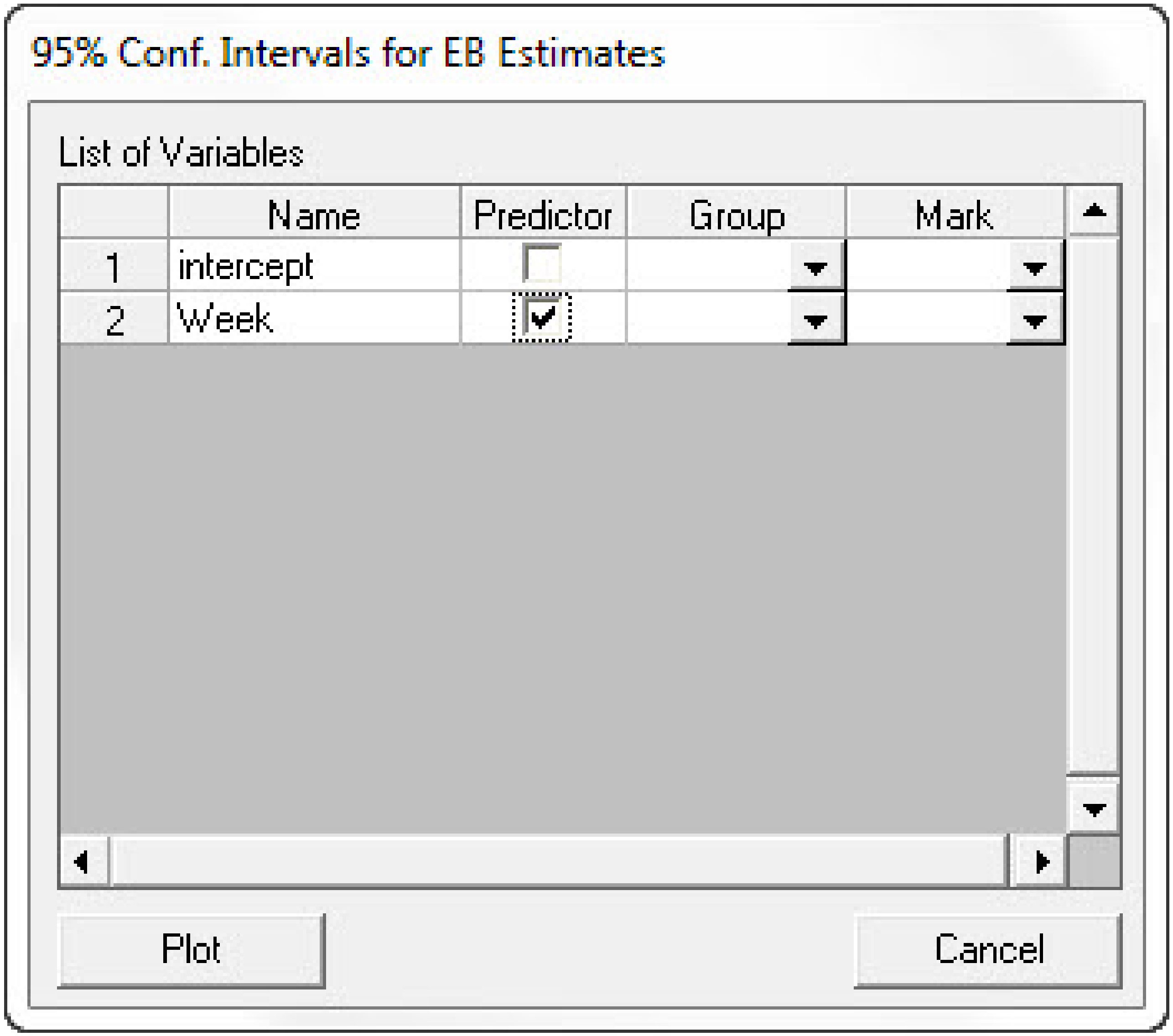
Select "File" > "Model-based Graphs" > "Equations'



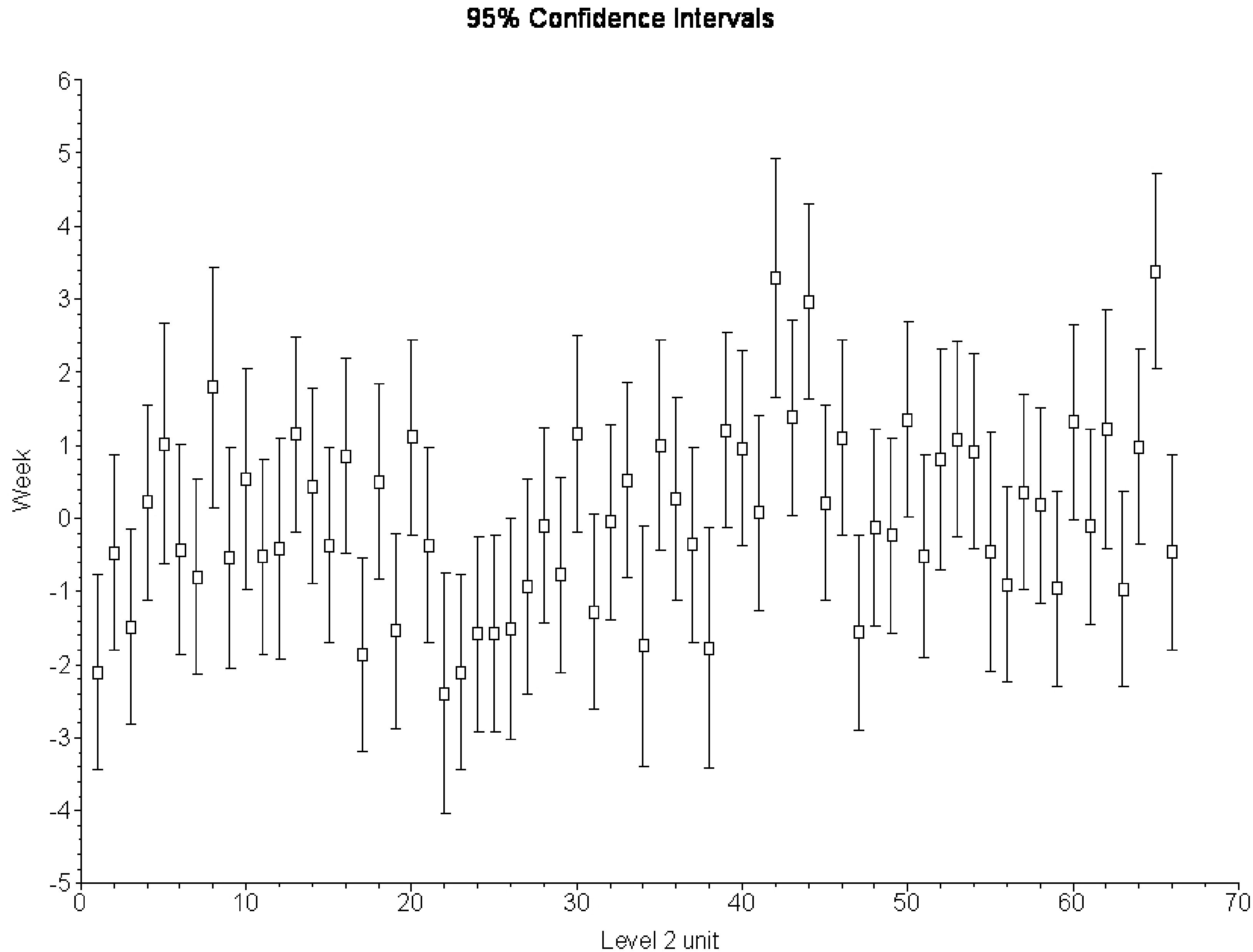
Empirical Bayes estimates of Subject Trends



Select “File” > “Model-based Graphs” > “Confidence Intervals’



Confidence Intervals for Subject Week Effects



Examination of HD across all weeks by diagnosis

$$\underset{n_i \times 1}{\underset{\boldsymbol{y}_i}{\begin{bmatrix} HD_{i1} \\ HD_{i2} \\ \dots \\ HD_{in_i} \end{bmatrix}}} = \underset{n_i \times p}{\underset{\boldsymbol{X}_i}{\begin{bmatrix} 1 & WEEK_{i1} & Dx_i & Dx_i * Wk_{i1} \\ 1 & WEEK_{i2} & Dx_i & Dx_i * Wk_{i2} \\ \dots & \dots & \dots & \dots \\ 1 & WEEK_{in_i} & Dx_i & Dx_i * Wk_{in_i} \end{bmatrix}}} \underset{p \times 1}{\underset{\boldsymbol{\beta}}{\begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix}}}$$

$$+ \underset{n_i \times r}{\underset{\boldsymbol{Z}_i}{\begin{bmatrix} 1 & WEEK_{i1} \\ 1 & WEEK_{i2} \\ \dots & \dots \\ 1 & WEEK_{in_i} \end{bmatrix}}} \underset{r \times 1}{\underset{\boldsymbol{\upsilon}_i}{\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{bmatrix}}} + \underset{n_i \times 1}{\underset{\boldsymbol{\varepsilon}_i}{\begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \dots \\ \varepsilon_{in_i} \end{bmatrix}}}$$

where $\max(n_i) = 6$, $\quad \boldsymbol{Z}_i' = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 & 4 & 5 \end{bmatrix}$, $\quad Dx_i = \begin{cases} 0 & \text{for NE} \\ 1 & \text{for E} \end{cases}$

Within-subjects and between-subjects components

Within-subjects model

$$HD_{ij} = b_{0i} + b_{1i}Time_{ij} + E_{ij}$$

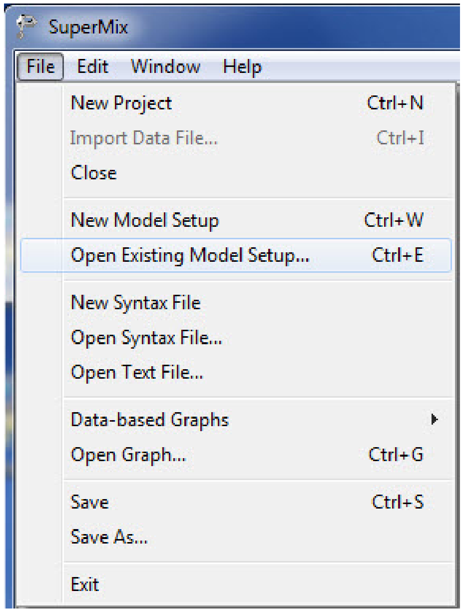
$$\begin{aligned} b_{0i} &= \text{week 0 HD level for patient } i \\ b_{1i} &= \text{weekly change in HD for patient } i \end{aligned}$$

Between-subjects models

$$\begin{aligned} b_{0i} &= \beta_0 + \beta_2 Dx_i + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \beta_3 Dx_i + \upsilon_{1i} \end{aligned}$$

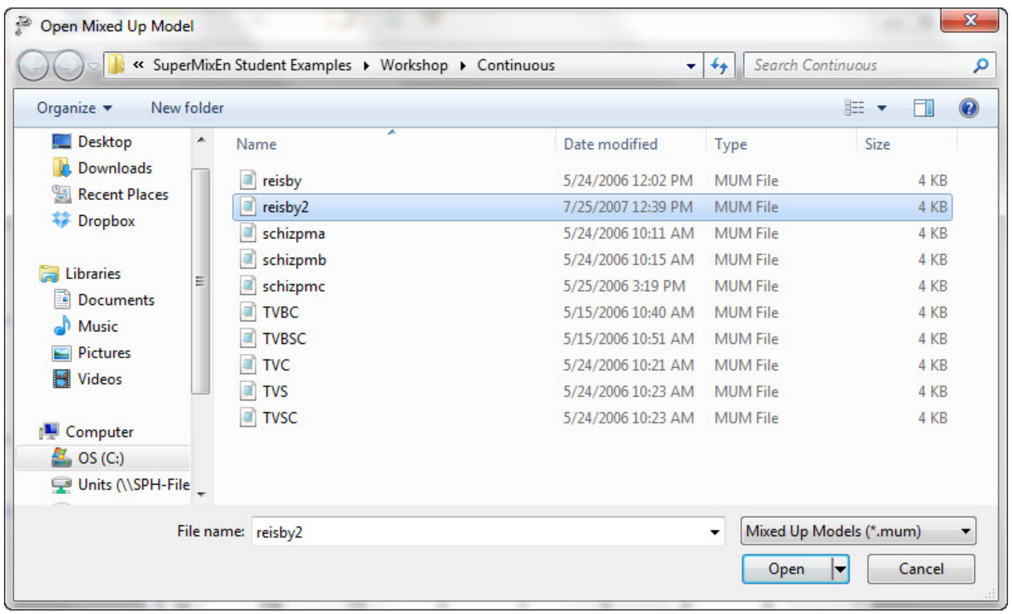
$$\begin{aligned} \beta_0 &= \text{average week 0 } HD \text{ level for NE patients } (Dx_i = 0) \\ \beta_1 &= \text{average } HD \text{ weekly improvement for NE patients } (Dx_i = 0) \\ \beta_2 &= \text{average week 0 } HD \text{ difference for E patients} \\ \beta_3 &= \text{average } HD \text{ weekly improvement difference for endogenous patients} \\ \upsilon_{0i} &= \text{individual deviation from average intercept} \\ \upsilon_{1i} &= \text{individual deviation from average improvement} \end{aligned}$$

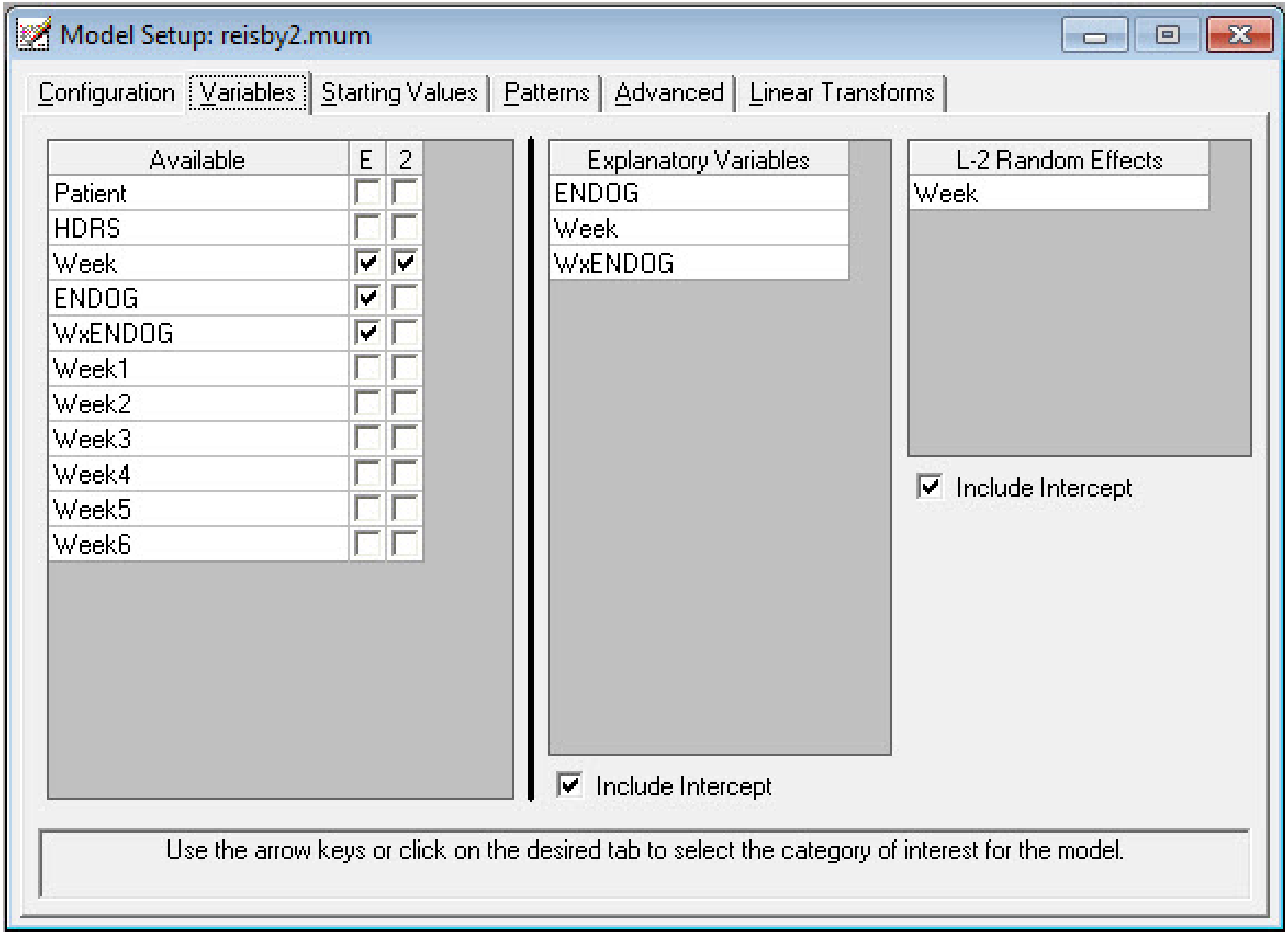
Under "File" click on "Open Existing Model Setup"



Open C:\SuperMixEn Examples\Workshop\Continuous\reisby2.mum

(or C:\SuperMixEn Student Examples\Workshop\Continuous\reisby2.mum)




Model Setup: reisby2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
Patient
HDRS
Week
ENDOG
WxENDOG
Week1
Week2
Week3
Week4
Week5
Week6
Explanatory Variables
ENDOG
Week
WxENDOG
Include Intercept
L-2 Random Effects
Week
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.

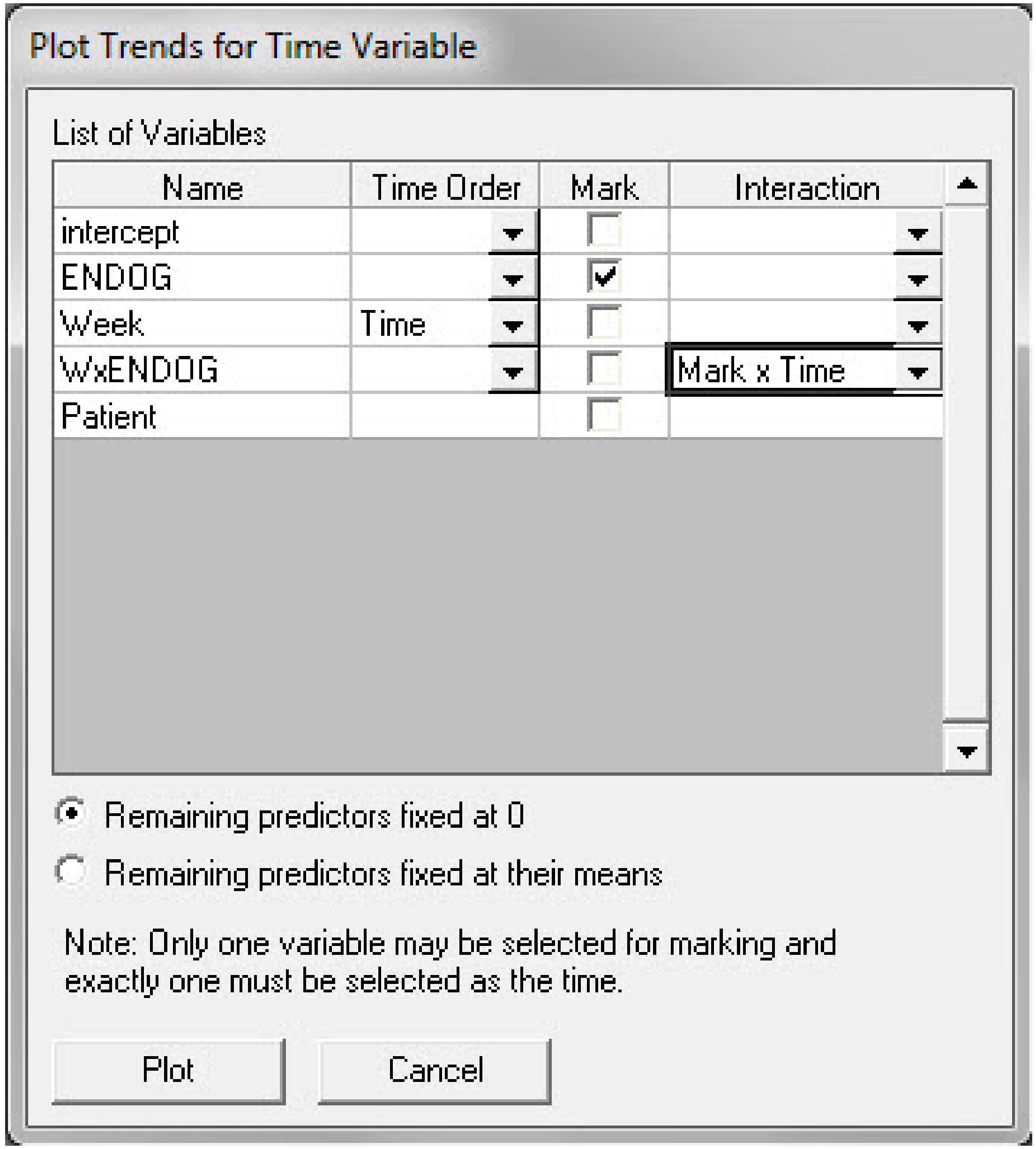
reisby2.out

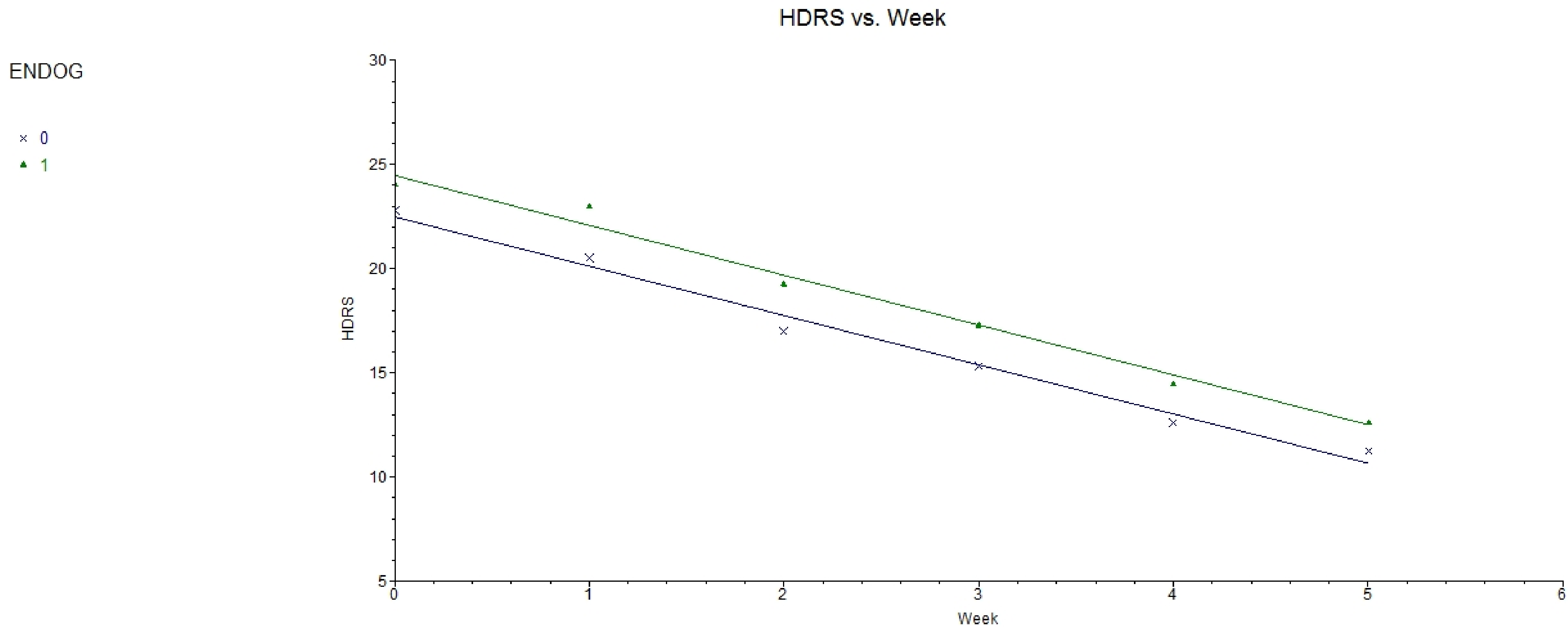
```
Maximum likelihood estimates
----------------------------


Fixed regressor(s)
------------------

 Variable                 Estimate      Std.Err.      Z-value       p-value
 --------                 --------      --------      -------       -------
 intercept                22.47626       0.79435      28.29524       0.00000
 ENDOG                     1.98802       1.06905       1.85961       0.06294
 Week                     -2.36569       0.31181      -7.58693       0.00000
 WxENDOG                  -0.02706       0.41947      -0.06450       0.94857

Log Likelihood                 =    -1107.4646
-2 Log Likelihood (Deviance)   =     2214.9292
Akaike's Information Criterion =     2230.9292
Schwarz's Bayesian Criterion   =     2248.4465
Number of free parameters      =             8



Variance/covariance components
------------------------------


 Level 2                                 Estimate      Std.Err.       Z-value   p-value
 -------                                 --------      --------       -------   -------
 intercept       /intercept              11.64121       3.29646       3.53142   0.00041
 Week            /intercept              -1.40161       1.00338      -1.39689   0.16245
 Week            /Week                    2.07707       0.50380       4.12283   0.00004

 Level 1                                 Estimate      Std.Err.       Z-value   p-value
 -------                                 --------      --------       -------   -------
 intercept       /intercept              12.21847       1.10707      11.03673   0.00000
```

Save As... Close

$\Rightarrow \ \chi^2_2 = 4.11, p$ ns, *compared to model with* $\beta_2 = \beta_3 = 0$

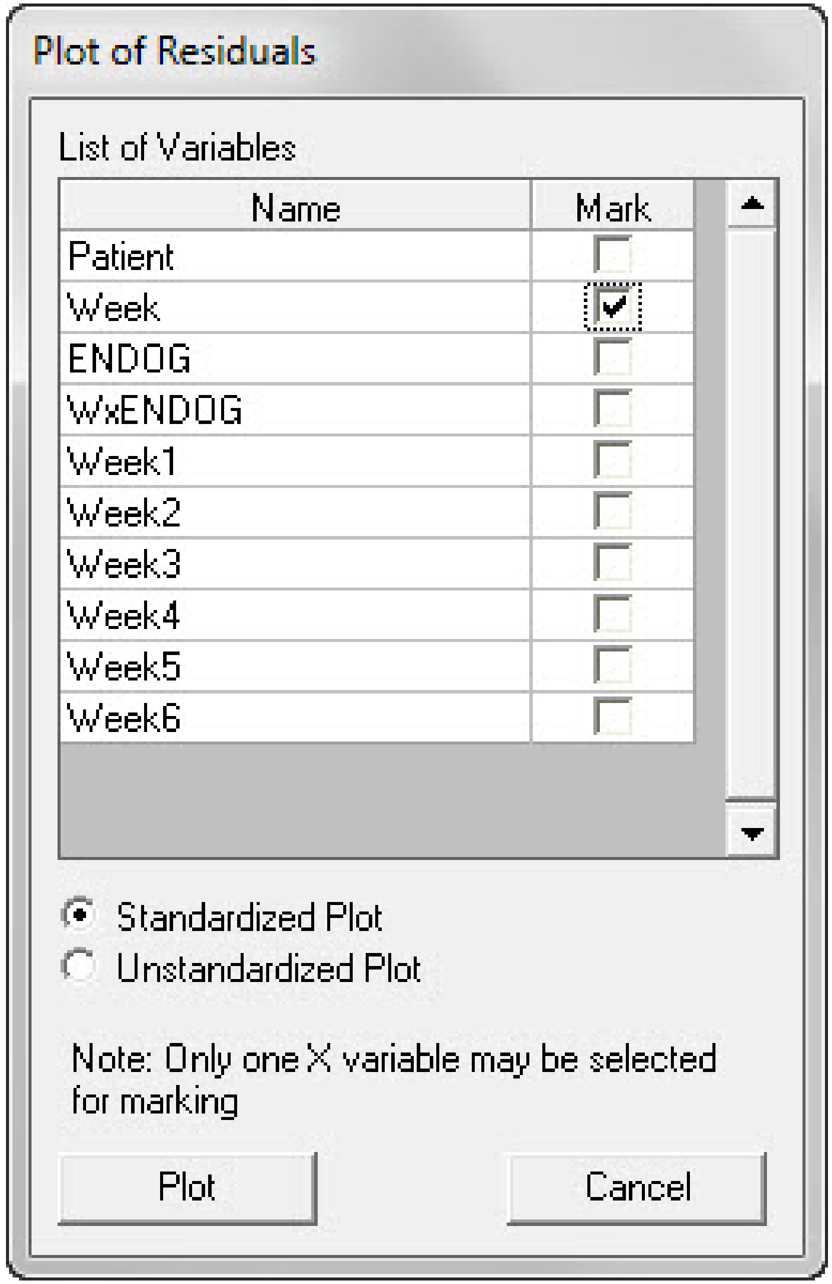
Select "File" > "Model-based Graphs" > "Trends"
(sorry, but "Trends" is not include in the student edition)

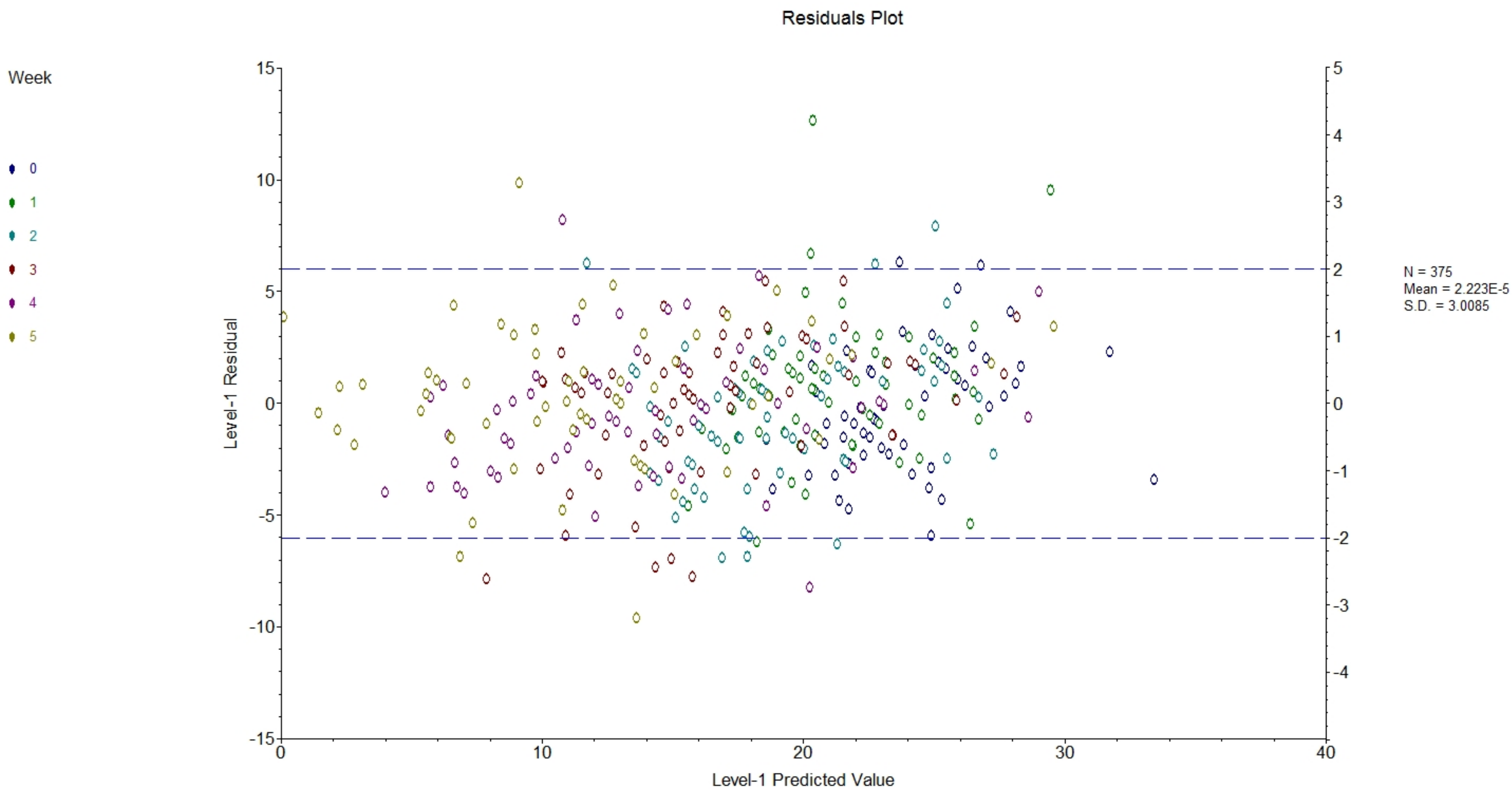




⇒ Endogenous group by time interaction is non-significant; groups are about 2 points different at all timepoints

Select “File” > “Model-based Graphs” > “Residuals”




Residuals Plot
Week
0
1
2
3
4
5
Level-1 Residual
Level-1 Predicted Value
N = 375
Mean = 2.223E-5
S.D. = 3.0085
15
10
5
0
-5
-10
-15
0
10
20
30
40
5
4
3
2
1
0
-1
-2
-3
-4

Linear Transforms

Fixed part of model:

$$\hat{HD}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 Endog + \hat{\beta}_2 Week + \hat{\beta}_3 (Endog \times Week)$$

in terms of the Endogenous group effect

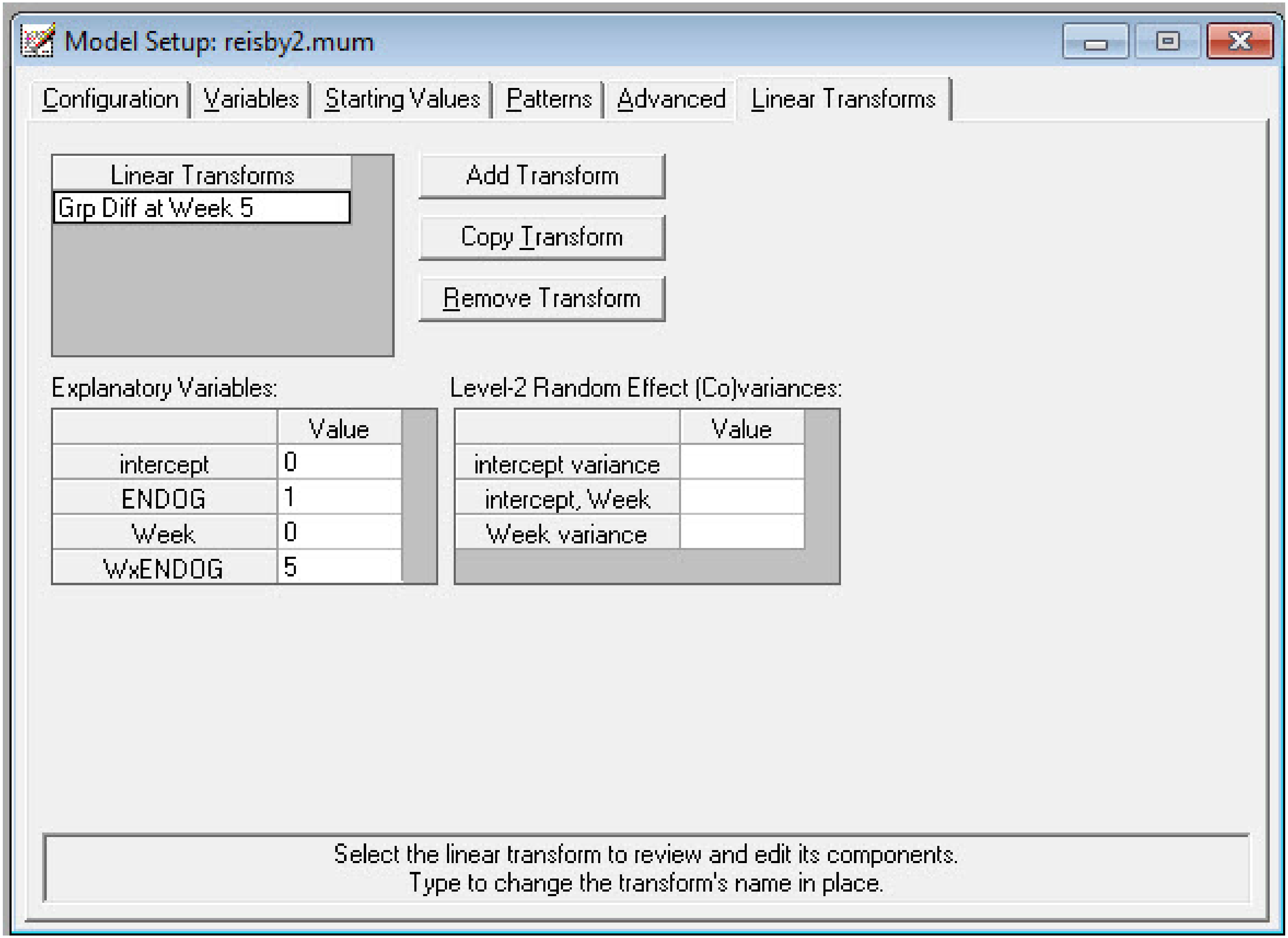
$$(\hat{\beta}_1 + \hat{\beta}_3 Week) Endog$$

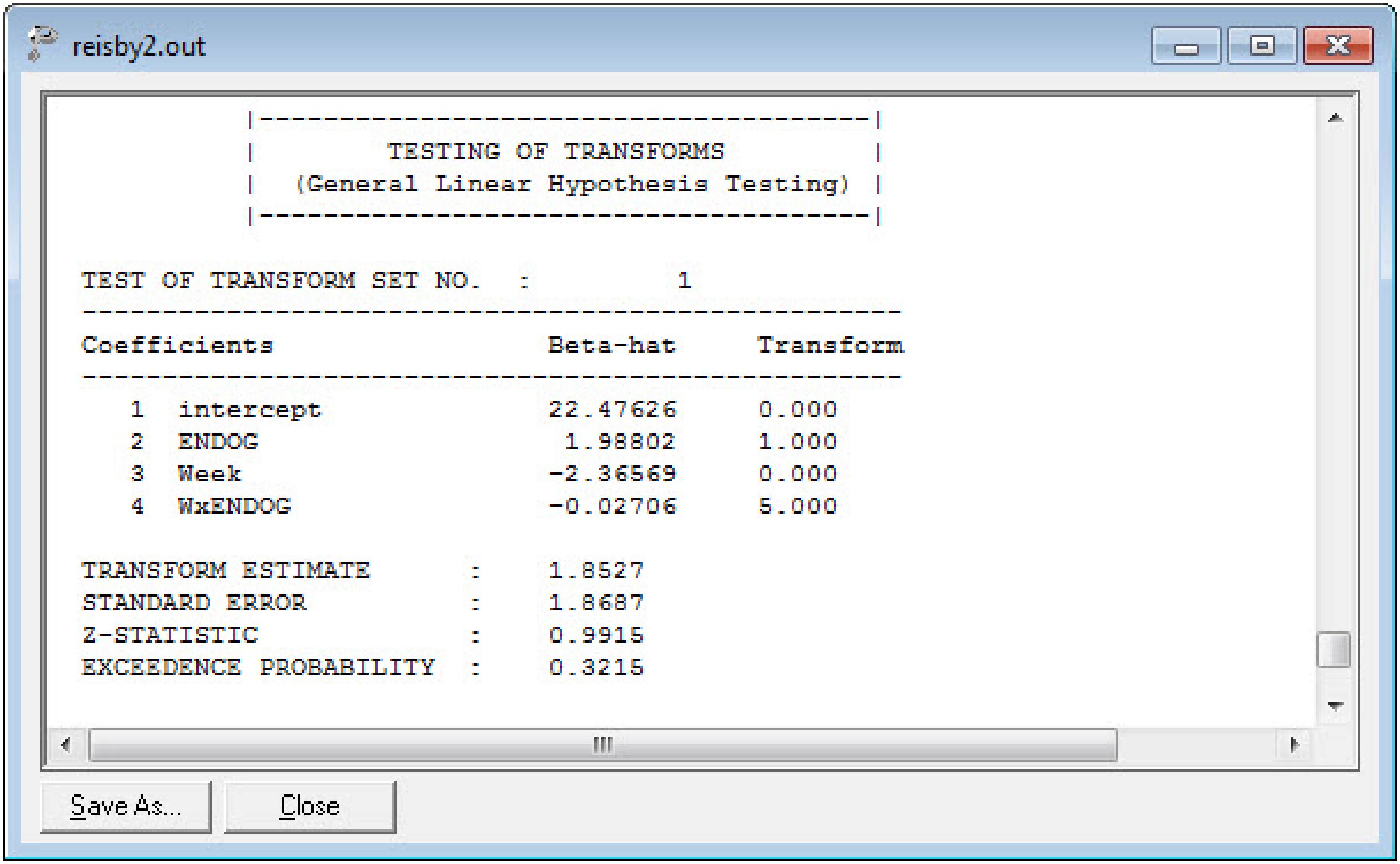
For example, the estimated group effect at the end of the study is

$$\hat{\beta}_1 + 5\hat{\beta}_3$$

$H_0 : \beta_1 + 5\beta_3 = 0$; null that groups are equivalent at the study's end

$$z = \frac{\hat{\beta}_1 + 5\hat{\beta}_3}{SE(\hat{\beta}_1 + 5\hat{\beta}_3)}$$


Model Setup: reisby2.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Linear Transforms
Grp Diff at Week 5
Add Transform
Copy Transform
Remove Transform
Explanatory Variables:
Value
intercept
0
ENDOG
1
Week
0
WxENDOG
5
Level-2 Random Effect (Co)variances:
Value
intercept variance
intercept, Week
Week variance
Select the linear transform to review and edit its components.
Type to change the transform's name in place.


reisby2.out
|-------------------------------------|
| TESTING OF TRANSFORMS |
(General Linear Hypothesis Testing)
TEST OF TRANSFORM SET NO. : 1
Coefficients Beta-hat Transform
1 intercept 22.47626 0.000
2 ENDOG 1.98802 1.000
3 Week -2.36569 0.000
4 WxENDOG -0.02706 5.000
TRANSFORM ESTIMATE : 1.8527
STANDARD ERROR : 1.8687
Z-STATISTIC : 0.9915
EXCEEDENCE PROBABILITY : 0.3215
Save As...
Close

HD across 4 weeks by plasma drug-levels

$$\underset{n_i \times 1}{\underset{\boldsymbol{y}_i}{\begin{bmatrix} HD_{i1} \\ HD_{i2} \\ \dots \\ HD_{in_i} \end{bmatrix}}} = \underset{n_i \times p}{\underset{\boldsymbol{X}_i}{\begin{bmatrix} 1 & WEEK_{i1} & lnIMI_{i1} & lnDMI_{i1} \\ 1 & WEEK_{i2} & lnIMI_{i2} & lnDMI_{i2} \\ \dots & \dots & \dots & \dots \\ 1 & WEEK_{in_i} & lnIMI_{in_i} & lnDMI_{in_i} \end{bmatrix}}} \underset{p \times 1}{\underset{\boldsymbol{\beta}}{\begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix}}}$$

$$+ \underset{n_i \times r}{\underset{\boldsymbol{Z}_i}{\begin{bmatrix} 1 & WEEK_{i1} \\ 1 & WEEK_{i2} \\ \dots & \dots \\ 1 & WEEK_{in_i} \end{bmatrix}}} \underset{r \times 1}{\underset{\boldsymbol{\upsilon}_i}{\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{bmatrix}}} + \underset{n_i \times 1}{\underset{\boldsymbol{\varepsilon}_i}{\begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \dots \\ \varepsilon_{in_i} \end{bmatrix}}}$$

where $\max(n_i) = 4$, and $\boldsymbol{Z}_i' = \begin{bmatrix} 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 \end{bmatrix}$

Within-subjects and between-subjects components

Within-subjects model

$$HD_{ij} = b_{0i} + b_{1i}T_{ij} + b_{2i}\ln IMI_{ij} + b_{3i}\ln DMI_{ij} + E_{ij}$$

$$\begin{aligned}
b_{0i} &= \text{week 2 HD level for patient } i \text{ with both } \ln IMI \text{ and } \ln DMI = 0 \\
b_{1i} &= \text{weekly change in HD for patient } i \\
b_{2i} &= \text{change in HD due to } \ln IMI \\
b_{3i} &= \text{change in HD due to } \ln DMI
\end{aligned}$$

Between-subjects models

$$\begin{aligned}
b_{0i} &= \beta_0 + \upsilon_{0i} \\
b_{1i} &= \beta_1 + \upsilon_{1i} \\
b_{2i} &= \beta_2 \\
b_{3i} &= \beta_3
\end{aligned}$$

$$
\begin{aligned}
\beta_0 &= \text{average week 2 } HD \text{ level for subjects with ln drug values of 0} \\
\beta_1 &= \text{average } HD \text{ weekly improvement} \\
\beta_2 &= \text{average } HD \text{ difference for unit change in } \ln IMI \\
\beta_3 &= \text{average } HD \text{ difference for unit change in } \ln DMI \\
\upsilon_{0i} &= \text{individual intercept deviation from model} \\
\upsilon_{1i} &= \text{individual slope deviation from model}
\end{aligned}
$$

Here, week 2 is the actual study week ($i.e.$, one week after the drug washout period), which is coded as 0 in this analysis of the last four study timepoints

parameter	ML estimate	se	z	$p <$
int β_0	21.37	3.89	5.49	.0001
slope β_1	-2.03	0.28	-7.15	.0001
$\ln IMI$ β_2	0.60	0.85	0.71	.48
$\ln DMI$ β_3	-1.20	0.63	-1.90	.06
$\sigma^2_{\upsilon_0}$	24.83	5.75		
$\sigma_{\upsilon_0 \upsilon_1}$	-0.72	1.72		
$\sigma^2_{\upsilon_1}$	2.73	0.93		
σ^2	10.46	1.35		

$\log L = -751.23$

$\sigma_{\upsilon_0 \upsilon_1}$ as corr between intercept and slope = -0.09

parameter	estimate	se	$p <$
HD total score			
intercept β_0	10.97	4.44	.013
slope β_1	-1.99	0.28	.0001
Baseline HD β_2	0.54	0.14	.0001
ln IMI β_3	0.54	0.78	.49
ln DMI β_4	-1.63	0.59	.006
$\sigma^2_{\upsilon_0}$	17.82	4.55	
$\sigma_{\upsilon_0 \upsilon_1}$	0.08	1.53	
$\sigma^2_{\upsilon_1}$	2.74	0.94	
σ^2	10.50	1.36	
HD change from baseline			
intercept β_0	1.52	3.74	ns
slope β_1	-1.97	0.28	.0001
ln IMI β_3	0.63	0.82	ns
ln DMI β_4	-1.97	0.60	.001
$\sigma^2_{\upsilon_0}$	20.50	5.01	
$\sigma_{\upsilon_0 \upsilon_1}$	0.84	1.58	
$\sigma^2_{\upsilon_1}$	2.78	0.94	
σ^2	10.53	1.36	

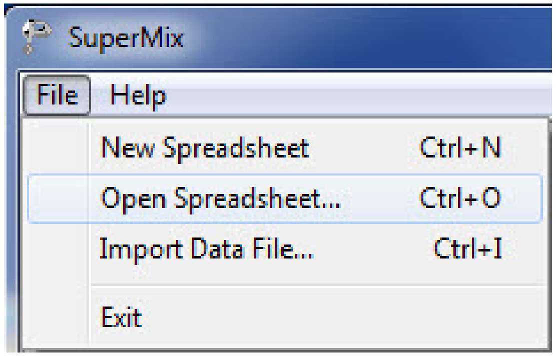
Correlation between HD scores and plasma levels (ln units)

	HD total score			
	week 2	week 3	week 4	week 5
IMI	-0.034	-0.034	-0.003	-0.189
DMI	-0.178	-0.075	-0.250*	-0.293*

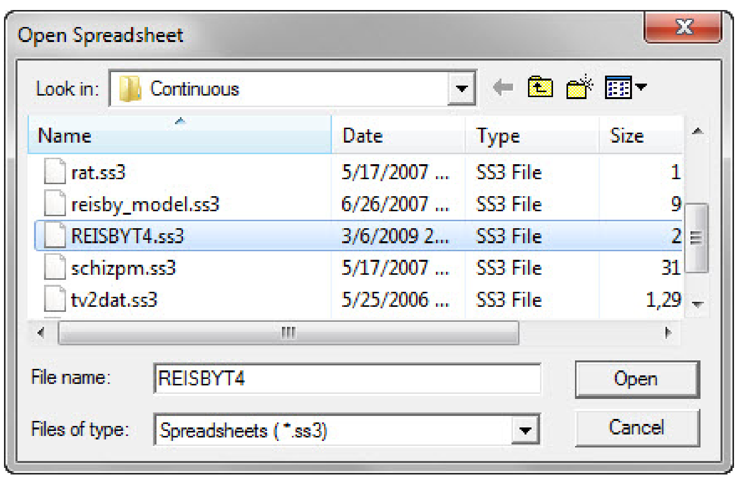
	HD change from baseline			
	week 2	week 3	week 4	week 5
IMI	-0.025	-0.100	-0.034	-0.250
DMI	-0.350*	-0.274*	-0.348*	-0.401*

*$p < 0.05$

- Under "File" click on "Open Spreadsheet"



- Open C:\SuperMixEn Examples\Workshop\Continuous\REISBYT4.ss3 (or C:\SuperMixEn Student Examples\Workshop\Continuous\REISBYT4.ss3)

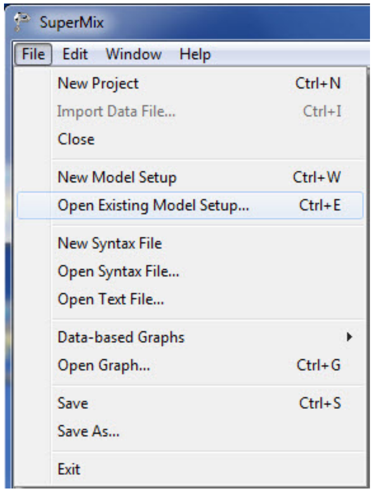


REISBYT4.ss3

101 Apply

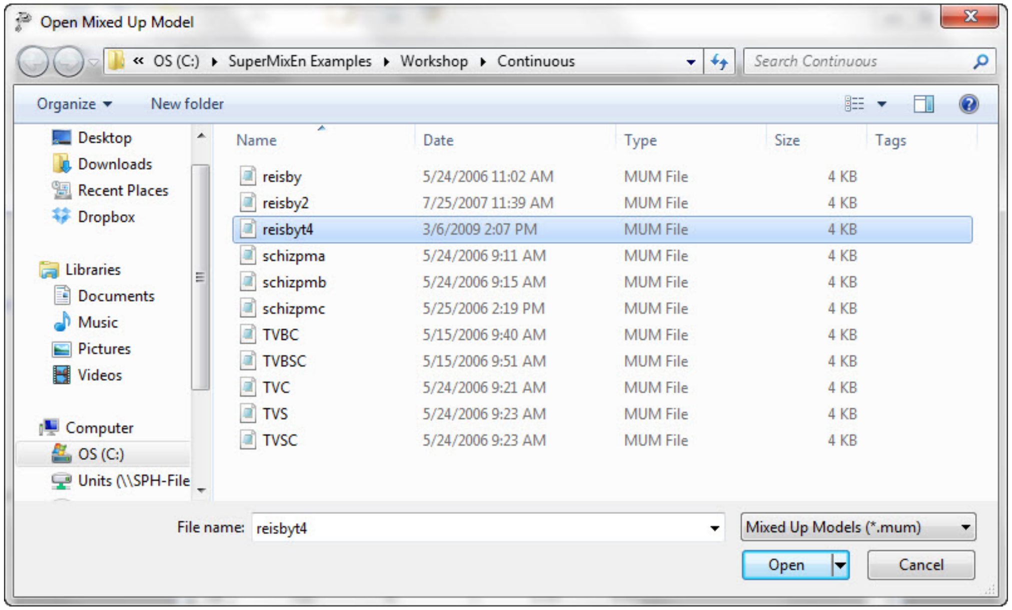
	(A)_ID	(B)_HAMDelt	(C)_Week	(D)_LnIMI	(E)_LnDMI
1	101	-8	0	4.04	4.20
2	101	-19	1	3.93	4.81
3	101	-22	2	4.33	4.96
4	101	-23	3	4.37	4.96
5	103	-18	0	2.77	5.24
6	103	-9	1	3.47	5.21
7	103	-18	2	3.53	5.34
8	103	-20	3	3.58	5.36
9	104	-11	0	5.34	4.75
10	104	-16	1	5.75	5.06
11	104	-10	2	5.56	5.08
12	104	-29	3	5.45	4.63
13	105	-6	0	3.09	4.36
14	105	-6	1	3.33	4.44
15	105	-9	2	2.94	4.17
16	105	-13	3	3.30	4.56
17	106	2	0	4.29	0.00
18	106	-3	1	4.78	2.89
19	106	-1	2	4.54	3.14

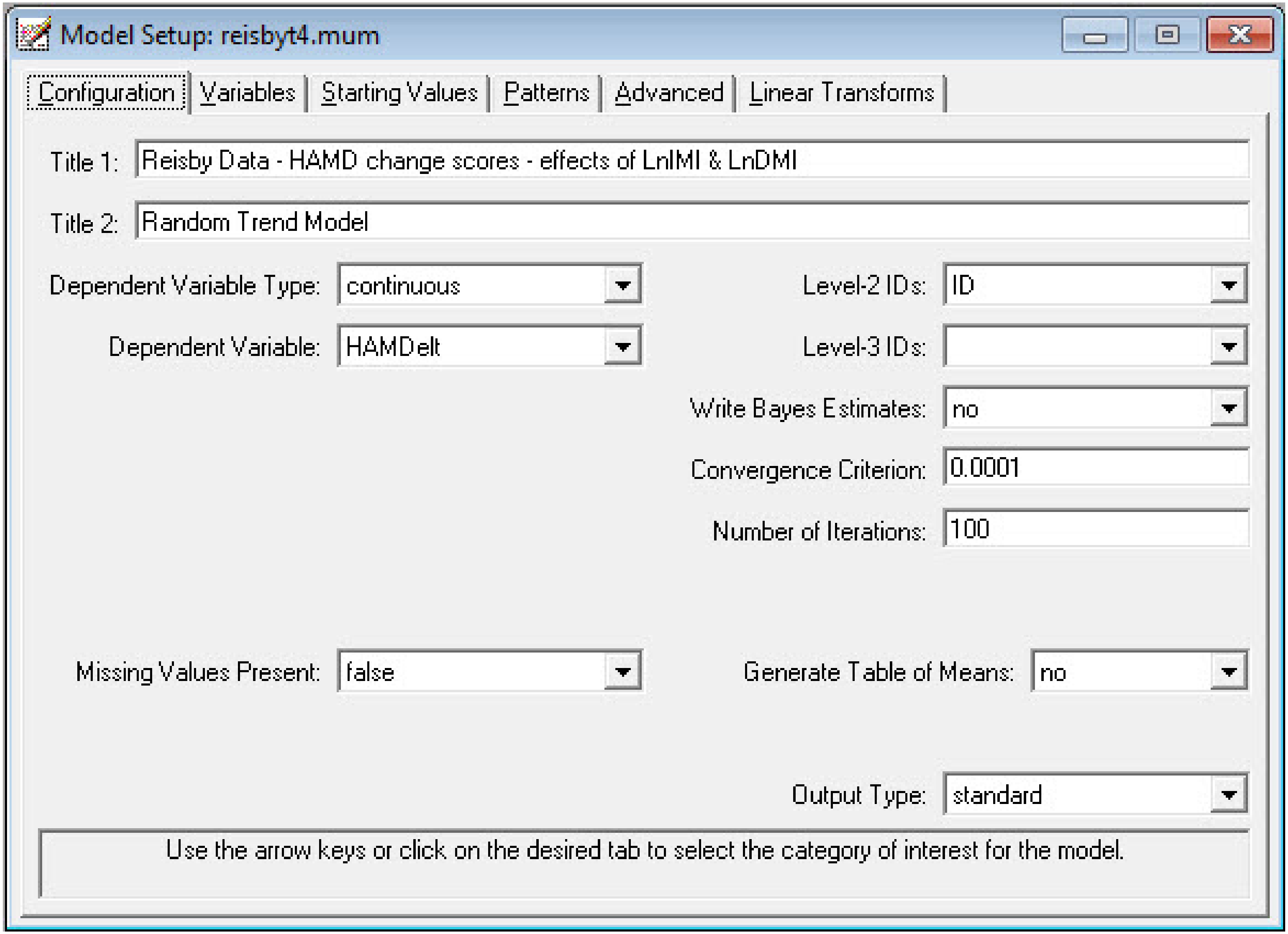
Under "File" click on "Open Existing Model Setup"

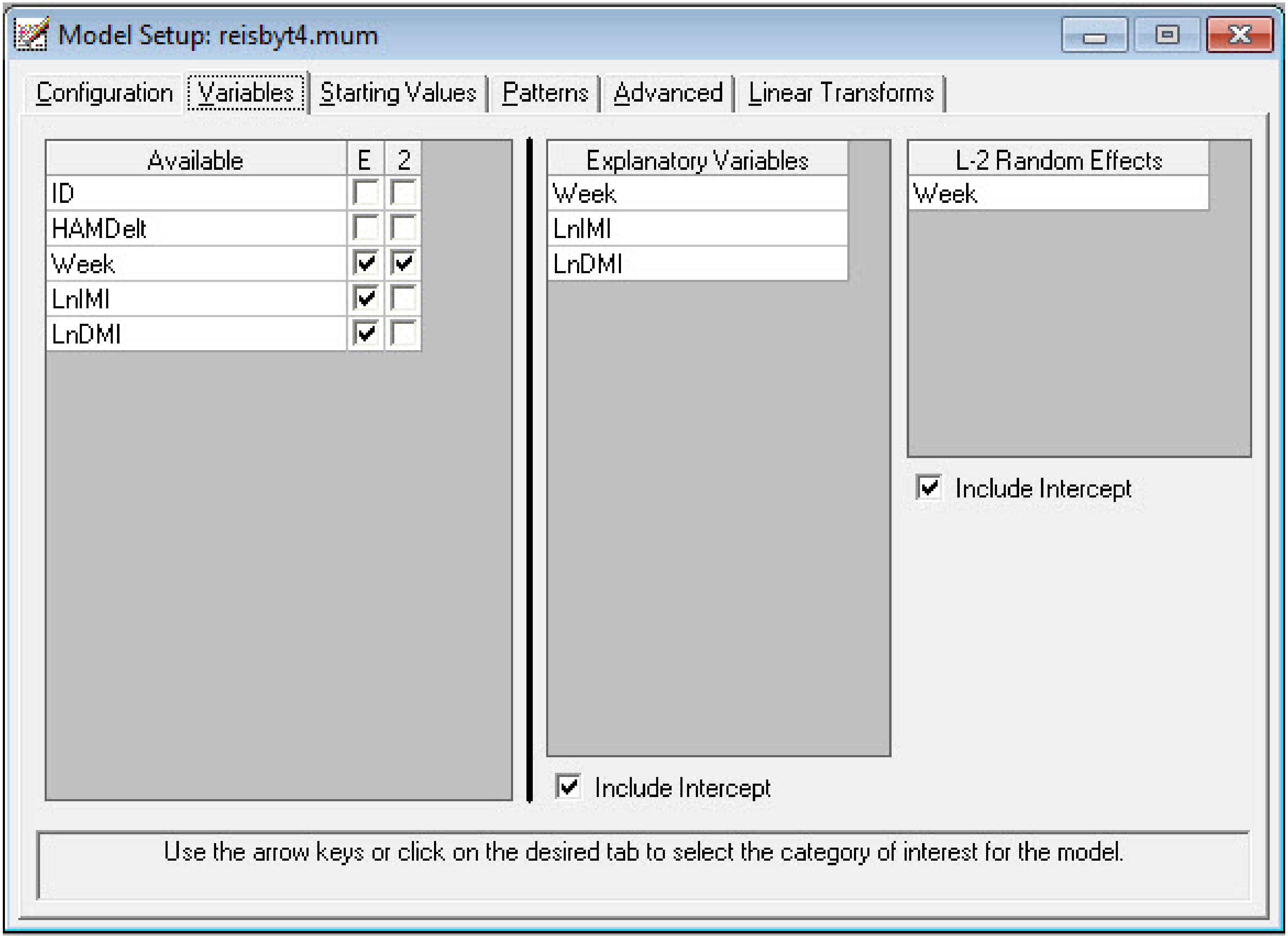


Open C:\SuperMixEn Examples\Workshop\Continuous\reisbyt4.mum

(or C:\SuperMixEn Student Examples\Workshop\Continuous\reisbyt4.mum)




Model Setup: reisbyt4.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Title 1:
Reisby Data - HAMD change scores - effects of LnIMI & LnDMI
Title 2:
Random Trend Model
Dependent Variable Type:
continuous
Level-2 IDs:
ID
Dependent Variable:
HAMDelt
Level-3 IDs:
Write Bayes Estimates:
no
Convergence Criterion:
0.0001
Number of Iterations:
100
Missing Values Present:
false
Generate Table of Means:
no
Output Type:
standard
Use the arrow keys or click on the desired tab to select the category of interest for the model.

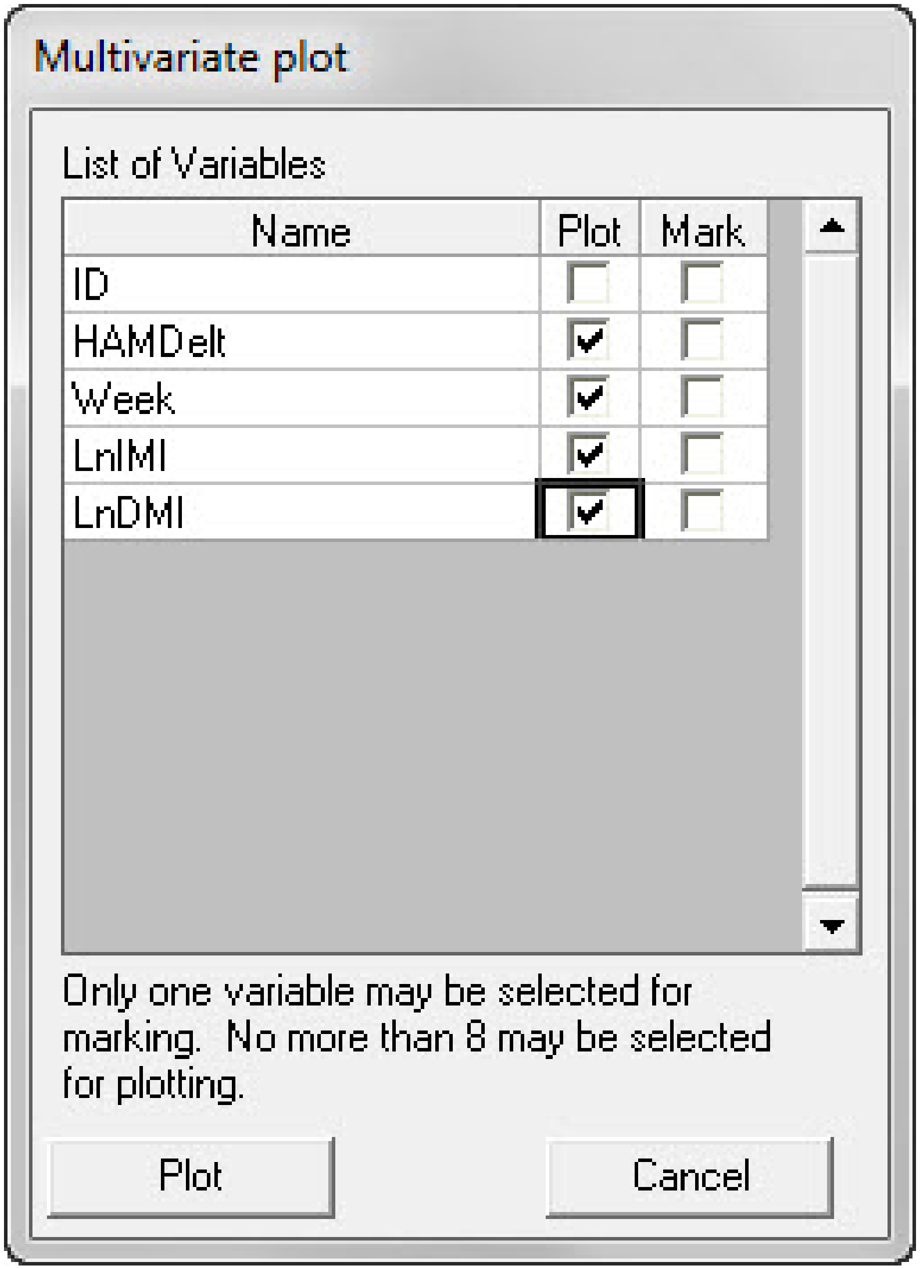

Model Setup: reisbyt4.mum
Configuration
Variables
Starting Values
Patterns
Advanced
Linear Transforms
Available
E
2
ID
HAMDelt
Week
LnIMI
LnDMI
Explanatory Variables
Week
LnIMI
LnDMI
Include Intercept
L-2 Random Effects
Week
Include Intercept
Use the arrow keys or click on the desired tab to select the category of interest for the model.

reisbyt4.out

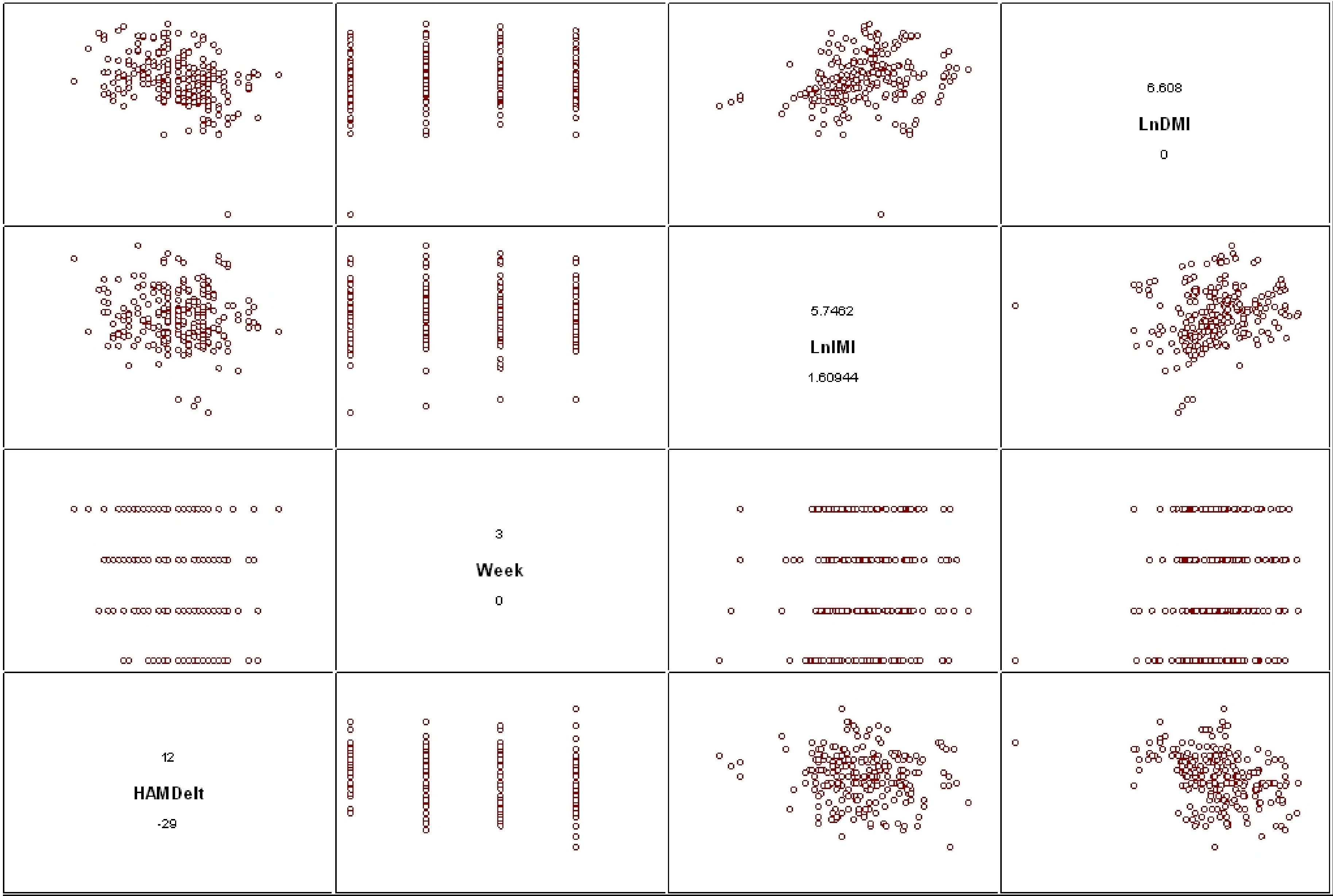
```
o==============================================================o
| Reisby Data - HAMD change scores - effects of LnIMI & LnDMI |
| Random Trend Model                                           |
o==============================================================o

Maximum likelihood estimates
----------------------------


Fixed regressor(s)
------------------

 Variable                  Estimate      Std.Err.      Z-value       p-value
 --------                  --------      --------      -------       -------
 intercept                  1.52133       3.74257       0.40649       0.68438
 Week                      -1.96686       0.28498      -6.90186       0.00000
 LnIMI                      0.63008       0.82112       0.76735       0.44288
 LnDMI                     -1.96663       0.60246      -3.26434       0.00110

Log Likelihood                   =     -749.4228
-2 Log Likelihood (Deviance)     =     1498.8457
Akaike's Information Criterion =     1514.8457
Schwarz's Bayesian Criterion     =     1532.3629
Number of free parameters        =             8



Variance/covariance components
------------------------------


 Level 2                                    Estimate      Std.Err.      Z-value    p-value
 -------                                    --------      --------      -------    -------
 intercept        /intercept                20.49970       5.01354      4.08887    0.00004
 Week             /intercept                 0.83717       1.57932      0.53008    0.59605
 Week             /Week                      2.78241       0.94285      2.95108    0.00317

 Level 1                                    Estimate      Std.Err.      Z-value    p-value
 -------                                    --------      --------      -------    -------
 intercept        /intercept                10.52780       1.36091      7.73585    0.00000
```

Save As... Close

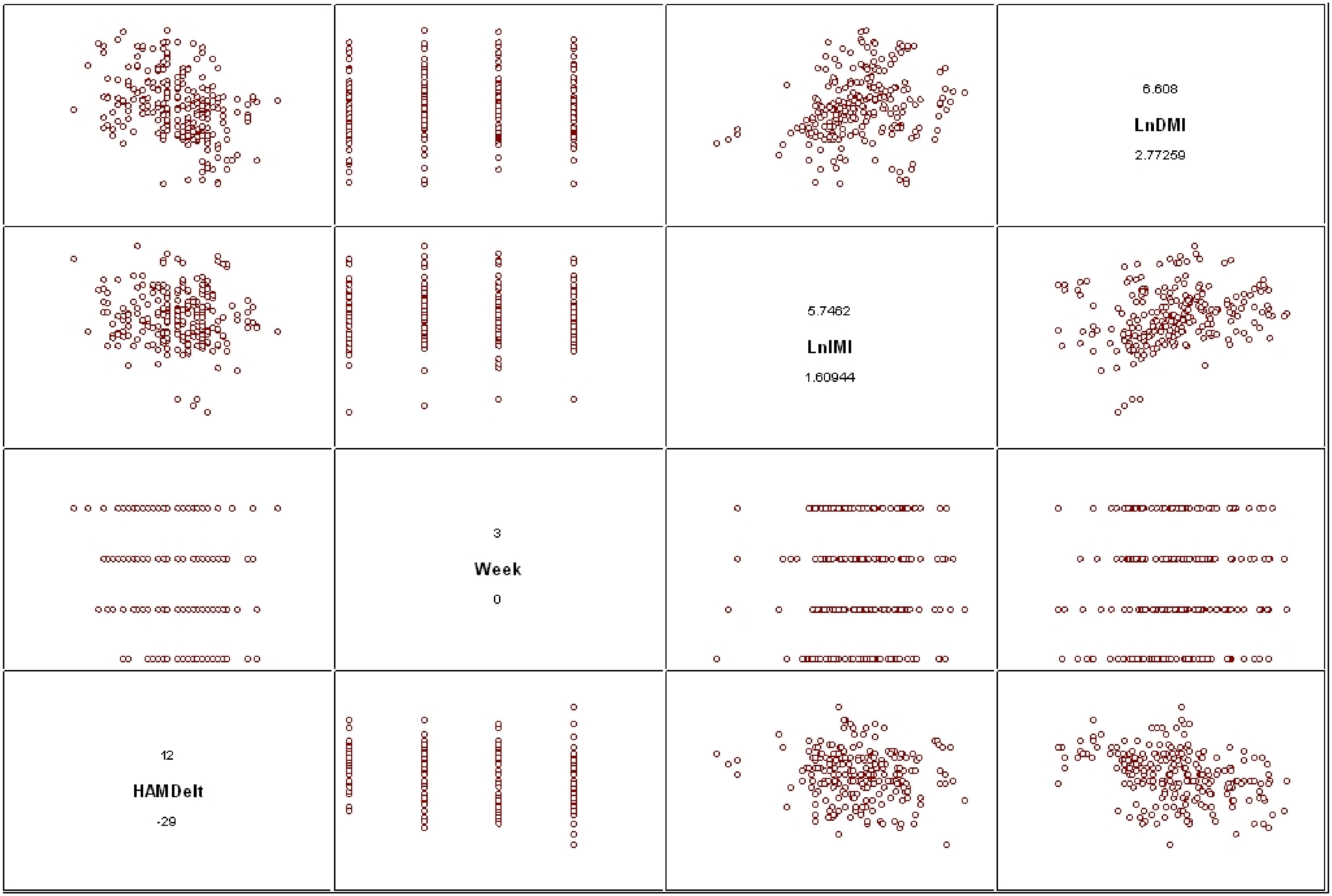
Select "File" > "Data-based Graphs" > "Multivariate"



Multivariate Plot of Data



Multivariate Plot of Data without DMI outlier



Analysis on HD change with and without DMI outlier

	with outlier			*without outlier*		
parameter	estimate	se	$p <$	estimate	se	$p <$
intercept β_0	1.52	3.74	ns	2.76	3.95	ns
slope β_1	-1.97	0.28	.0001	-1.96	0.28	.0001
ln IMI β_3	0.63	0.82	ns	0.72	0.83	ns
ln DMI β_4	-1.97	0.60	.001	-2.30	0.70	.0009
$\sigma^2_{v_0}$	20.50	5.01		20.53	5.04	
$\sigma_{v_0 v_1}$	0.84	1.58		0.72	1.59	
$\sigma^2_{v_1}$	2.78	0.94		2.77	0.94	
σ^2	10.53	1.36		10.56	1.37	

Summary

- Spreadsheet allows some data manipulation
  - add/delete columns or rows
  - transformations of variables (abs, exp, ln, sqrt, square)
  - summary statistics of variables (average, median, min, max, mode)
  - can create interaction terms and grand-mean centered variables
- Various kinds of data-based and model-based plots
- Up to 3-level models with full likelihood estimation (and empirical Bayes estimation of random effects)
- Linear transforms of parameter estimates
- Non-normal outcomes: binary, ordinal, nominal, and counts