Introduction to Mixed Models for Longitudinal Continuous Data

Don Hedeker
University of Illinois at Chicago

hedeker@uic.edu
www.uic.edu/∼hedeker/ml.html

Chapters 4 and 5 in Hedeker & Gibbons (2006), Longitudinal Data Analysis, Wiley.

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

Advantages of Longitudinal Studies

- Economizes on subjects; subjects serve as own control
- Between-subject variation excluded from error
- Can provide more efficient estimators than cross-sectional designs with same number and pattern of observations
- Can separate aging effects (changes over time within individuals) from cohort effects (differences between subjects at baseline)
  $\Rightarrow$ cross-sectional design can't do this
- Can provide information about individual change

Analysis Considerations

- Response variable
  - continuous (normal or non-normal)
  - categorical (dichotomous, ordinal, nominal, counts)
- Number of subjects N, & number of obs per subject n_i
  - $n_i = 2$ for all: change score analysis or ANCOVA
  - $n_i = n$ for all: balanced design - ANOVA or MANOVA
  - n_i varies: more general methods
- Number & type of covariates - $E(\boldsymbol{y}_i)$
  - one sample, multiple samples
  - regression (continuous or categorical covariates)
  - time-varying covariates
- Type of variance-covariance structure - $V(\boldsymbol{y}_i)$
  - homogeneous or heterogeneous variances/covariances

General Approaches

- Derived variable: not really longitudinal, per se, reduce the repeated observations into a summary variable
  - average across time, change score, linear trend across time, last observation
- Longitudinal Analysis
  - ANOVA/MANOVA for repeated measures
  - Mixed-effects regression models
  - Covariance pattern models
  - Generalized Estimating Equations (GEE) models
  - Structural Equations Models
  - Transition Models

Advantages of Mixed-effects Regression Models (MRM)

1. MRM explicitly models individual change across time
2. MRM more flexible in terms of repeated measures
   (a) need not have same number of obs per subject
   (b) time can be continuous, rather than a fixed set of points
3. Flexible specification of the covariance structure among repeated measures $\Rightarrow$ methods for testing specific determinants of this structure
4. MRM can be extended to higher-level models $\Rightarrow$ repeated observations within individuals within clusters
5. Generalizations for non-normal data

2-level model for longitudinal data

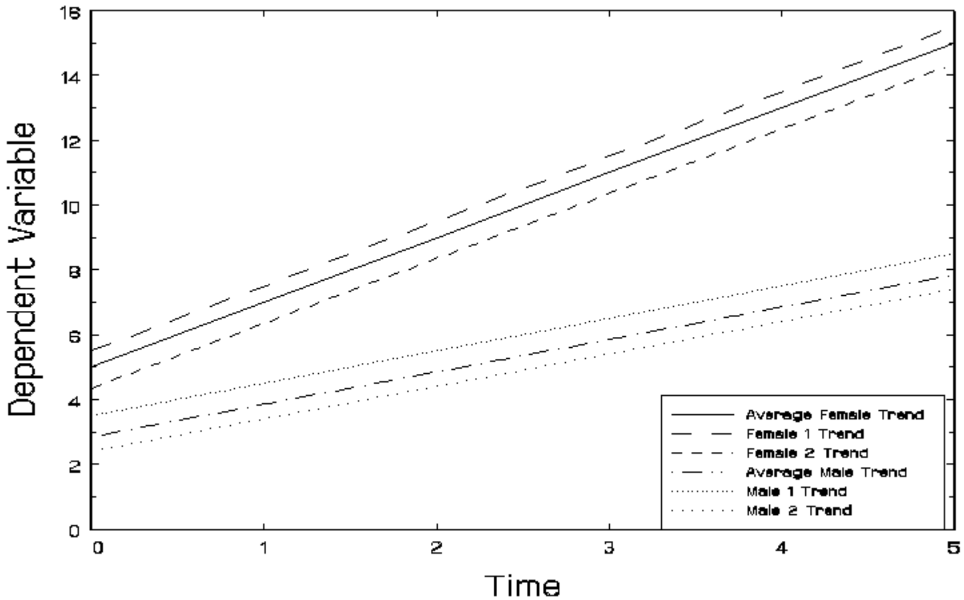
$$\underset{n_i \times 1}{\boldsymbol{y}_i} = \underset{n_i \times p}{\boldsymbol{X}_i} \; \underset{p \times 1}{\boldsymbol{\beta}} + \underset{n_i \times r}{\boldsymbol{Z}_i} \; \underset{r \times 1}{\boldsymbol{\upsilon}_i} + \underset{n_i \times 1}{\boldsymbol{\varepsilon}_i}$$

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

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

Random-intercepts Model

each subject is parallel to their group trend



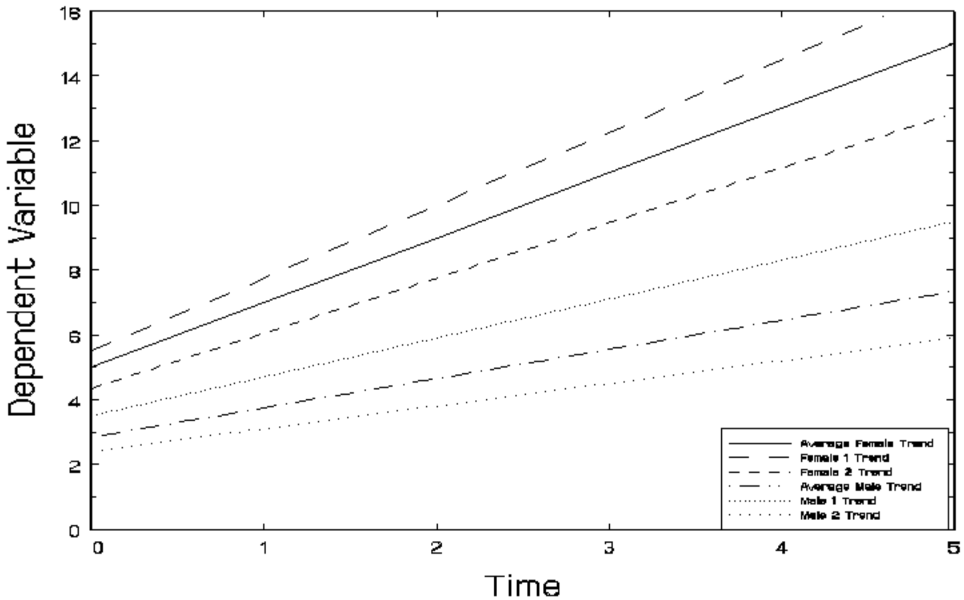
$$y = Time + Grp + (Grp \times Time) + Subj + Error$$

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

$$\upsilon_{0i} \sim \mathcal{N}(0, \sigma_\upsilon^2) \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$$

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

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

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

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

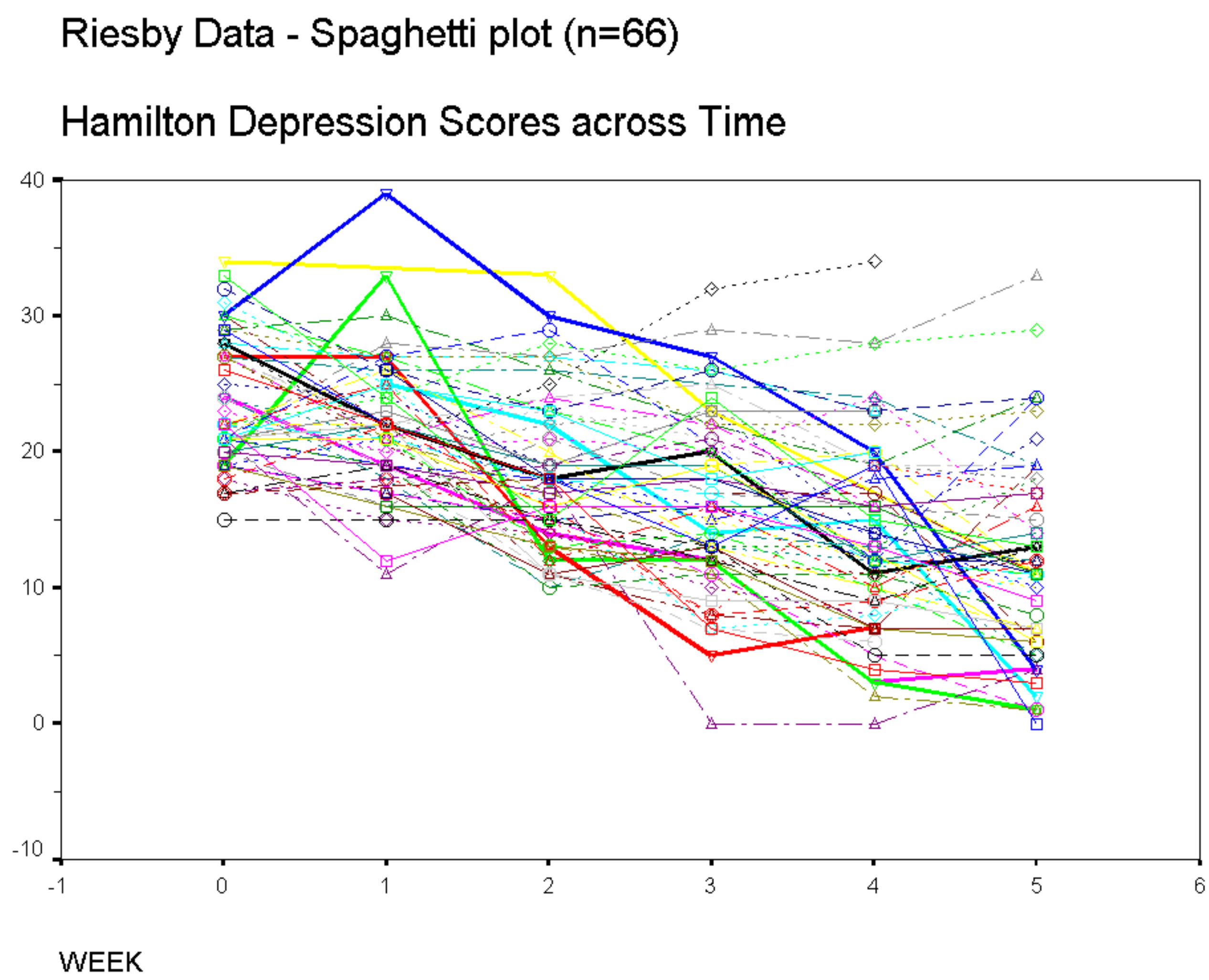
Descriptive Statistics

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: $\mathbf{n = 46}$ and $\mathit{46} \leq n \leq \mathit{66}$

	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



- increasing variance across time
- general linear decline over time

Examination of HD across all weeks

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

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

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

Within-subjects and between-subjects components

Within-subjects model

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

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

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

Between-subjects models

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

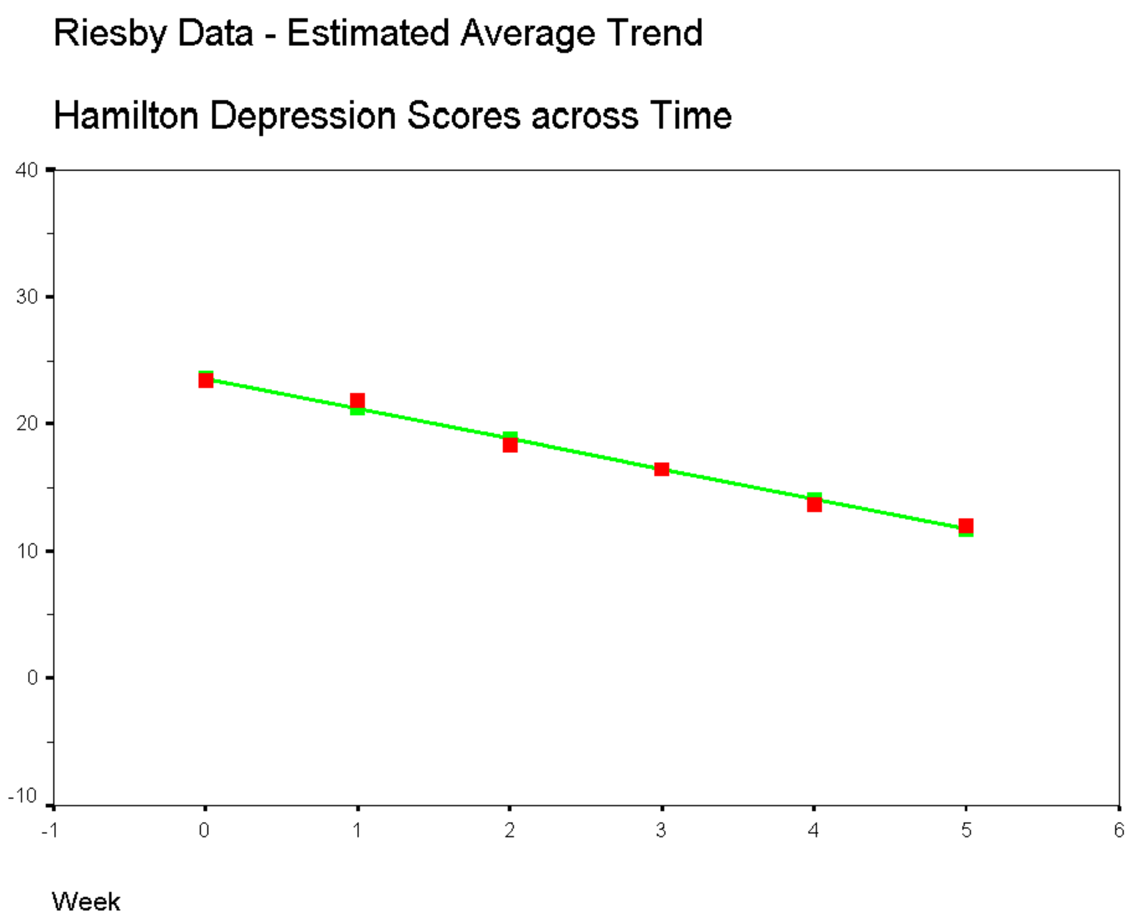
$$\begin{aligned} \beta_0 &= \text{average week 0 } HD \text{ level} \\ \beta_1 &= \text{average } HD \text{ weekly improvement} \\ \upsilon_{0i} &= \text{individual deviation from average intercept} \\ \upsilon_{1i} &= \text{individual deviation from average improvement} \end{aligned}$$

parameter	ML estimate	se	z	$p <$
β_0	23.58	0.55	43.22	.0001
β_1	-2.38	0.21	-11.39	.0001
$\sigma^2_{\upsilon_0}$	12.63	3.47		
$\sigma_{\upsilon_0\upsilon_1}$	-1.42	1.03		
$\sigma^2_{\upsilon_1}$	2.08	0.50		
σ^2	12.22	1.11		
$\log L = -1109.52$				

$\chi^2_2 = 66.1, p < .0001$ for $H_0 : \sigma_{\upsilon_0\upsilon_1} = \sigma^2_{\upsilon_1} = 0$

$\sigma_{\upsilon_0\upsilon_1}$ as corr between intercept and slope = -0.28

- Wald tests are dubious for variance parameters, likelihood-ratio tests are preferred (though divide p-value by 2)
- Wald z-statistics sometimes expressed as χ^2_1 (by squaring z-value)



Observed and estimated means $(= \boldsymbol{X}\hat{\boldsymbol{\beta}})$

	wk 0	wk 1	wk 2	wk 3	wk 4	wk 5
n	61	63	65	65	63	58
obs	23.44	21.84	18.31	16.42	13.62	11.95
est	23.58	21.21	18.82	16.45	14.07	11.69

Obs. (pairwise) and est. variance-covariance matrix

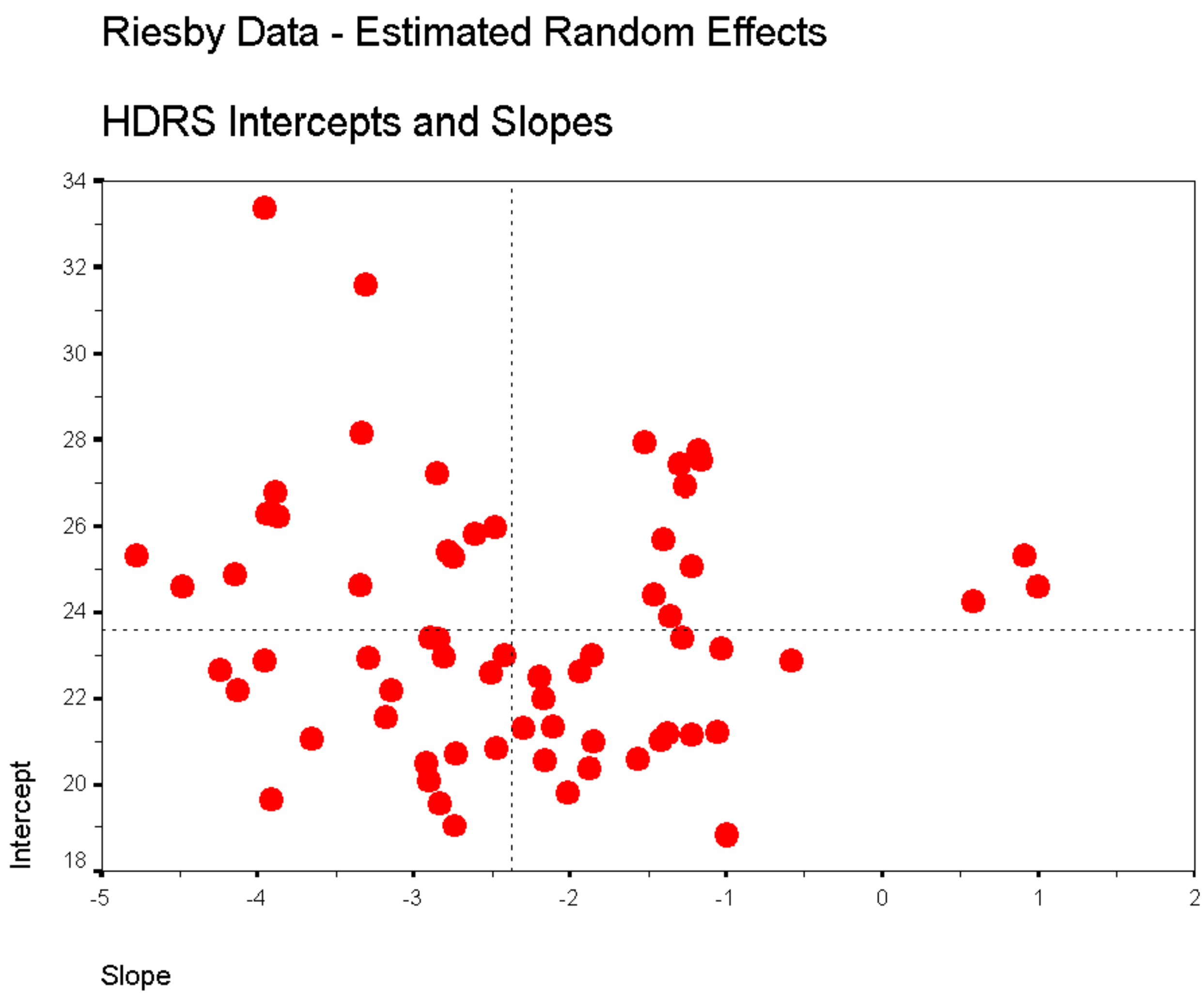
$$\Sigma_{\boldsymbol{y}} = \begin{bmatrix} 20.55 & & & & & \\ 10.50 & 22.07 & & & & \\ 10.20 & 12.74 & 30.09 & & & \\ 9.69 & 12.43 & 25.96 & 41.15 & & \\ 7.17 & 10.10 & 25.56 & 36.54 & 48.59 & \\ 6.02 & 7.39 & 18.25 & 26.31 & 32.93 & 52.12 \end{bmatrix}$$

$$\begin{aligned} \hat{\Sigma}_{\boldsymbol{y}} &= \boldsymbol{Z}\hat{\boldsymbol{\Sigma}}_{\upsilon}\boldsymbol{Z}' + \hat{\sigma}^2\boldsymbol{I} \\ &= \begin{bmatrix} 24.85 & & & & & \\ 11.21 & 24.08 & & & & \\ 9.79 & 12.52 & 27.48 & & & \\ 8.37 & 13.18 & 18.00 & 35.03 & & \\ 6.95 & 13.84 & 20.73 & 27.63 & 46.74 & \\ 5.53 & 14.50 & 23.47 & 32.44 & 41.41 & 62.60 \end{bmatrix} \end{aligned}$$

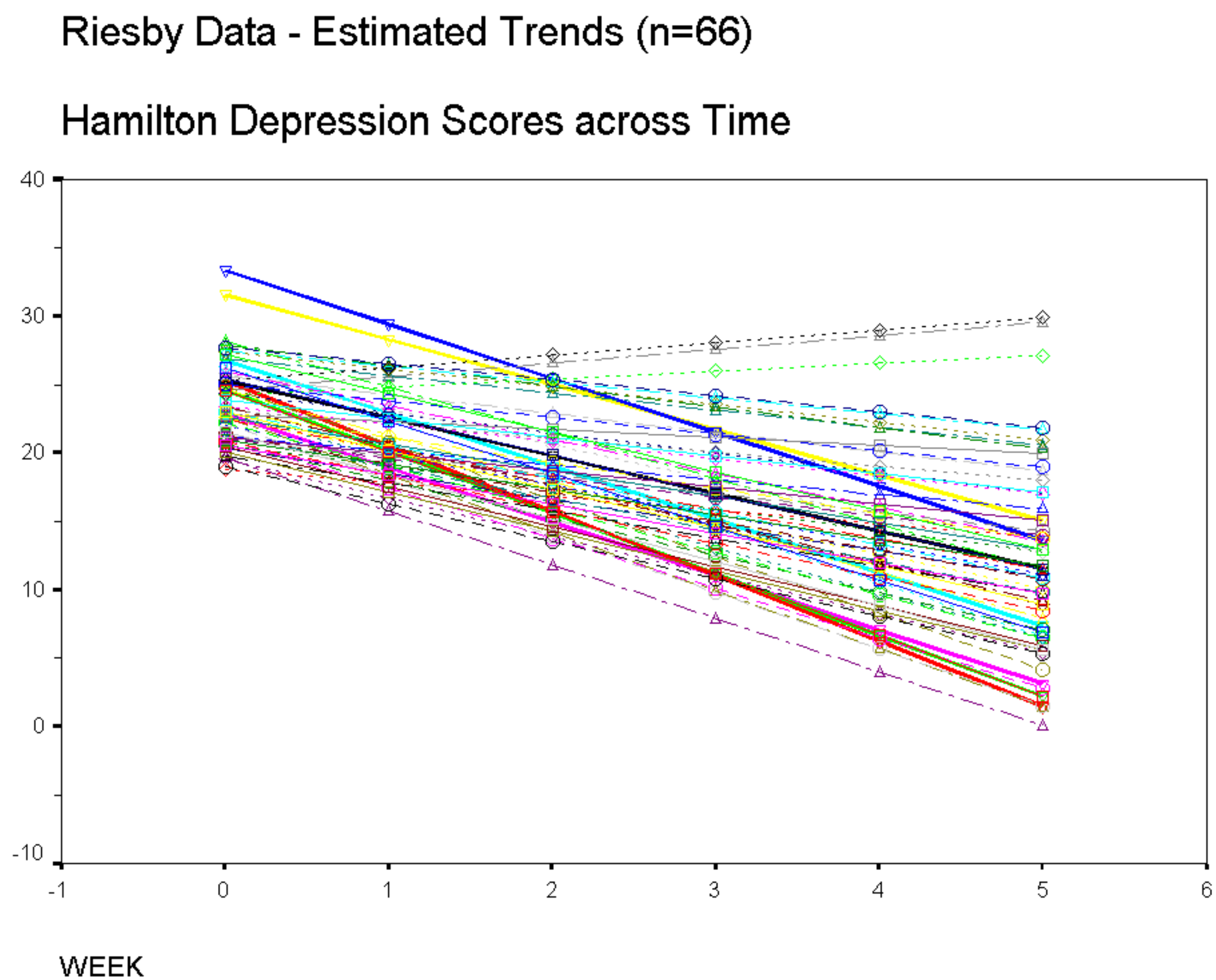
$$\boldsymbol{Z}' = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 & 4 & 5 \end{bmatrix} \qquad \hat{\boldsymbol{\Sigma}}_{\upsilon} = \begin{bmatrix} 12.63 & -1.42 \\ -1.42 & 2.08 \end{bmatrix}$$

note: from random-int model: $\hat{\sigma}_{\upsilon}^2 = 16.16$ and $\hat{\sigma}^2 = 19.04$

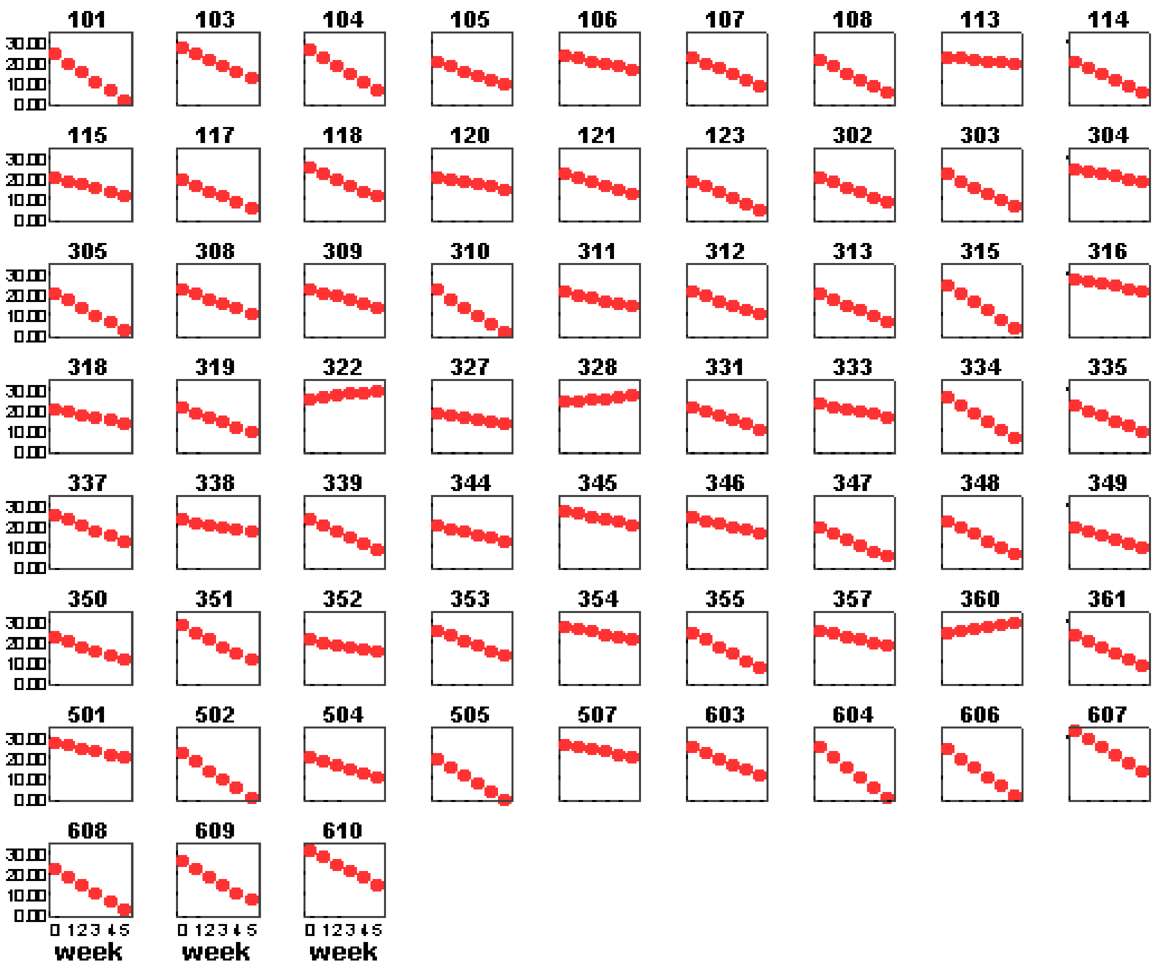
Empirical Bayes estimates of Subject Trends



Empirical Bayes estimates of Subject Trends



Empirical Bayes estimates of Subject Trends



Software for Mixed Models

SAS

- Singer, J. D. (1998). Using SAS PROC MIXED To Fit Multilevel Models, Hierarchical Models, and Individual Growth Models. *Journal of Educational and Behavioral Statistics, 23*, 323-355.
- Singer, J. D. (2002). Fitting individual growth models using SAS PROC MIXED. In D. S. Moskowitz & S. L. Hershberger (Eds.), Modeling intraindividual variability with repeated measures data: Methods and applications (pp. 135-170). Mahwah, NJ: Lawrence Erlbaum Associates.

SPSS

- Peugh, J. L. and Enders, C. K. (2005). Using the SPSS Mixed Procedure to Fit Cross-Sectional and Longitudinal Multilevel Models. *Educational and Psychological Measurement, 65*, 717-741.
- Painter, J. Notes on using SPSS Mixed Models. http://www.unc.edu/~painter/SPSSMixed/SPSSMixedModels.PDF

SAS MIXED code - RIESBYM.SAS

```
TITLE1 'analysis of riesby data - hdrs scores across time';
DATA one; INFILE 'c:\mixdemo\riesby.dat';
INPUT id hamd intcpt week endog endweek ;

PROC FORMAT;
VALUE endog 0='nonendog' 1='endog';
VALUE week 0='week 0' 1='week 1' 2='week 2' 3='week 3' 4='week 4' 5='week 5';

PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL hamd = week /SOLUTION;
RANDOM INTERCEPT /SUB=id TYPE=UN G;
TITLE2 'random intercepts model:  compound symmetry structure';

PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL hamd = week /SOLUTION;
RANDOM INTERCEPT week /SUB=id TYPE=UN G GCORR;
TITLE2 'random trend model';
```

SAS MIXED code - RIESBYM2.SAS

```
TITLE1 'analysis of riesby data - empirical bayes estimates';
DATA one; INFILE 'c:\mixdemo\riesby.dat';
INPUT id hamd intcpt week endog endweek ;

PROC FORMAT;
VALUE endog 0='nonendog' 1='endog';
VALUE week 0='week 0' 1='week 1' 2='week 2' 3='week 3' 4='week 4' 5='week 5';

PROC MIXED METHOD=ML;
CLASS id;
MODEL hamd = week /SOLUTION;
RANDOM INTERCEPT week /SUB=id TYPE=UN G S;
ODS LISTING EXCLUDE SOLUTIONR; ODS OUTPUT SOLUTIONR=randest;
TITLE2 'random trend model';

/* print out the estimated random effects dataset */
PROC PRINT DATA=randest;
```

```
/* get a printout of the data in multivariate form */
PROC SORT DATA=one; BY id;

DATA t0;SET one; IF week=0; hamd_0 = hamd;
DATA t1;SET one; IF week=1; hamd_1 = hamd;
DATA t2;SET one; IF week=2; hamd_2 = hamd;
DATA t3;SET one; IF week=3; hamd_3 = hamd;
DATA t4;SET one; IF week=4; hamd_4 = hamd;
DATA t5;SET one; IF week=5; hamd_5 = hamd;

DATA comp (KEEP=id hamd_0-hamd_5); MERGE t0 t1 t2 t3 t4 t5; BY id;

PROC PRINT DATA=comp; VAR id hamd_0-hamd_5;
```

```
/* extract the intercepts and slopes for each person */
/* and compute the estimated hamd values across time */
PROC SORT DATA=randest; BY id;
DATA randest2 (KEEP=id intdev slopedev int slope hdest_0-hdest_5);

ARRAY y(2) intdev slopedev;
DO par = 1 TO 2;
   SET randest; BY id;
   y(par) = ESTIMATE;
   IF par = 2 THEN DO;
     int = 23.5769 + intdev;
     slope = -2.3771 + slopedev;
     hdest_0 = int;
     hdest_1 = int + slope;
     hdest_2 = int + 2*slope;
     hdest_3 = int + 3*slope;
     hdest_4 = int + 4*slope;
     hdest_5 = int + 5*slope;
   END;
   IF LAST.id THEN RETURN;
END;
```

```
PROC PRINT DATA=randest2; VAR id hdest_0-hdest_5;

PROC PLOT DATA=randest2;
   PLOT intdev * slopedev;
   PLOT int * slope;
   TITLE2 'plot of individual intercepts versus slopes';
RUN;
```

SPSS MIXED code - RIESBYM.SPS - after opening RIESBY.SAV
(SPSS dataset with variables: id, hamd, week, endog, endweek)

```
* random intercept model .
MIXED
hamd WITH week
/FIXED = week
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT | SUBJECT(id) .

* random trend model .
MIXED
hamd WITH week
/FIXED = week
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
```

```
* getting predicted values from random trend model .
MIXED
hamd WITH week
/FIXED = week
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN)
/SAVE = PRED .


* plotting predicted values across time .
EXE.
IGRAPH /VIEWNAME='Scatterplot' /X1 = VAR(week) TYPE = CATEGORICAL
/Y = VAR(PRED_1) TYPE = SCALE /PANEL = VAR(id)
/SCATTER COINCIDENT = NONE.
```

```
GET
  FILE='C:\mixdemo\riesby.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
* random intercept model .
MIXED
  hamd  WITH week
  /FIXED = week
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
 /RANDOM INTERCEPT | SUBJECT(id)   .
```

Mixed Model Analysis

Notes

Output Created		24-SEP-2007 10:00:45
Comments		
Input	Data	C:\mixdemo\riesby.sav
	Active Dataset	DataSet1
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	396
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		MIXED hamd WITH week /FIXED = week /METHOD = ML /PRINT = SOLUTION TESTCOV /RANDOM INTERCEPT | SUBJECT(id) .
Resources	Elapsed Time	0:00:00.19
	Processor Time	0:00:00.05

```
[DataSet1] C:\mixdemo\riesby.sav
```

Model Dimension[a]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables
Fixed Effects	Intercept	1		1	
	week	1		1	
Random Effects	Intercept	1	Variance Components	1	id
Residual				1	
Total		3		4	

a. Dependent Variable: hamd.

Information Criteria[a]

-2 Log Likelihood	2285.189
Akaike's Information Criterion (AIC)	2293.189
Hurvich and Tsai's Criterion (AICC)	2293.297
Bozdogan's Criterion (CAIC)	2312.896
Schwarz's Bayesian Criterion (BIC)	2308.896

The information criteria are displayed in smaller-is-better forms.

a. Dependent Variable: hamd.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	121.332	1360.375	.000
week	1	310.988	309.802	.000

a. Dependent Variable: hamd.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	23.551773	.638549	121.332	36.883	.000	22.287631	24.815914
week	-2.375652	.134971	310.988	-17.601	.000	-2.641224	-2.110079

a. Dependent Variable: hamd.

Covariance Parameters

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Residual		19.037533	1.531582	12.430	.000	16.260390	22.288989
Intercept [subject = id]	Variance	16.155550	3.410247	4.737	.000	10.681767	24.434329

a. Dependent Variable: hamd.

```
* random trend model .
MIXED
  hamd  WITH week
  /FIXED = week
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
 /RANDOM INTERCEPT week  | SUBJECT(id) COVTYPE(UN) .
```

Mixed Model Analysis

Notes

Output Created		24-SEP-2007 10:00:46
Comments		
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	Active Dataset	DataSet1
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	396
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		MIXED hamd WITH week /FIXED = week /METHOD = ML /PRINT = SOLUTION TESTCOV /RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
Resources	Elapsed Time	0:00:00.05
	Processor Time	0:00:00.09

```
[DataSet1] C:\mixdemo\riesby.sav
```

Model Dimension[b]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables
Fixed Effects	Intercept	1		1	
	week	1		1	
Random Effects	Intercept + week[a]	2	Unstructured	3	id
Residual				1	
Total		4		6	

a. As of version 11.5, the syntax rules for the RANDOM subcommand have changed. Your command syntax may yield results that differ from those produced by prior versions. If you are using SPSS 11 syntax, please consult the current syntax reference guide for more information.

b. Dependent Variable: hamd.

Information Criteria[a]

-2 Log Likelihood	2219.038
Akaike's Information Criterion (AIC)	2231.038
Hurvich and Tsai's Criterion (AICC)	2231.266
Bozdogan's Criterion (CAIC)	2260.599
Schwarz's Bayesian Criterion (BIC)	2254.599

The information criteria are displayed in smaller-is-better forms.

a. Dependent Variable: hamd.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	63.764	1867.729	.000
week	1	63.105	129.797	.000

a. Dependent Variable: hamd.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	23.576946	.545545	63.764	43.217	.000	22.487017	24.666875
week	-2.377067	.208646	63.105	-11.393	.000	-2.793999	-1.960135

a. Dependent Variable: hamd.

Covariance Parameters

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Residual		12.216633	1.119005	10.917	.000	10.209022	14.619041
Intercept + week [subject = id]	UN (1,1)	12.629293	3.527438	3.580	.000	7.305220	21.833571
	UN (2,1)	-1.420930	1.037669	-1.369	.171	-3.454723	.612864
	UN (2,2)	2.078989	.516580	4.025	.000	1.277463	3.383421

a. Dependent Variable: hamd.

Examination of HD across all weeks by diagnosis

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

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

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

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

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

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

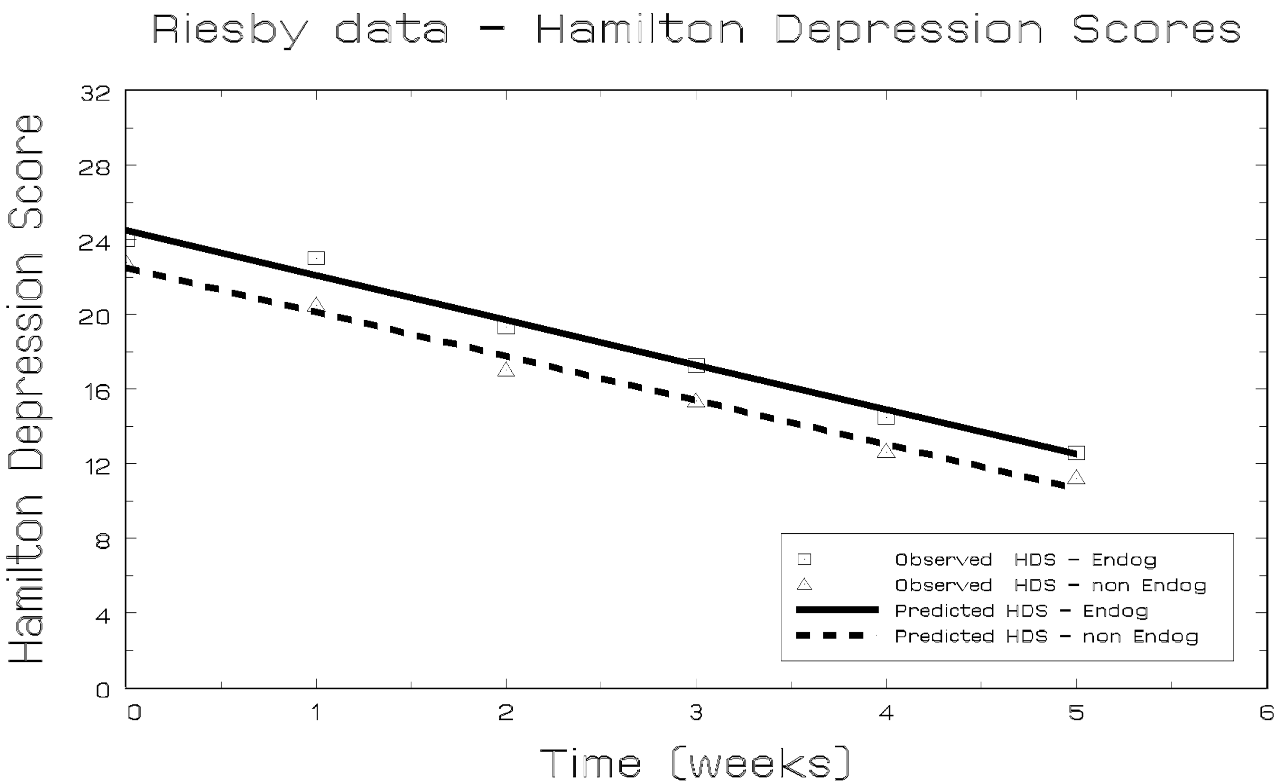
parameter	ML estimate	se	z	$p <$
NE int β_0	22.48	0.79	28.30	.0001
NE slope β_1	-2.37	0.31	-7.59	.0001
E int diff β_2	1.99	1.07	1.86	.063
E slope diff β_3	-0.03	0.42	-0.06	.95
$\sigma^2_{\upsilon_0}$	11.64	3.53		
$\sigma_{\upsilon_0 \upsilon_1}$	-1.40	1.00		
$\sigma^2_{\upsilon_1}$	2.08	0.50		
σ^2	12.22	1.11		

$\log L = -1107.47$

$\chi^2_2 = 4.1, p$ ns, *compared to model with* $\beta_2 = \beta_3 = 0$

$\sigma_{\beta_0 \beta_1}$ as corr between intercept and slope = -0.29

Riesby data - model fit by diagnosis



SAS MIXED code - in RIESBYM.SAS

```
PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL hamd = week endog endweek /SOLUTION;
RANDOM INTERCEPT week /SUB=id TYPE=UN G GCORR;
TITLE2 'random trend model with group effects';
RUN;
```

SPSS MIXED code - in RIESBYM.SPS

```
* random trend model with group effects.
MIXED
hamd WITH week endog endweek
/FIXED = week endog endweek
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
```

```
* random trend model with group effects .
MIXED
  hamd  WITH week endog endweek
  /FIXED = week  endog endweek
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
 /RANDOM INTERCEPT week  | SUBJECT(id) COVTYPE(UN) .
```

Mixed Model Analysis

Notes

Output Created		24-SEP-2007 10:18:06
Comments		
Input	Data	C:\mixdemo\riesby.sav
	Active Dataset	DataSet1
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	396
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		MIXED hamd WITH week endog endweek /FIXED = week endog endweek /METHOD = ML /PRINT = SOLUTION TESTCOV /RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
Resources	Elapsed Time	0:00:00.05
	Processor Time	0:00:00.06

```
[DataSet1] C:\mixdemo\riesby.sav
```

Model Dimension[b]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables
Fixed Effects	Intercept	1		1	
	week	1		1	
	endog	1		1	
	endweek	1		1	
Random Effects	Intercept + week[a]	2	Unstructured	3	id
Residual				1	
Total		6		8	

a. As of version 11.5, the syntax rules for the RANDOM subcommand have changed. Your command syntax may yield results that differ from those produced by prior versions. If you are using SPSS 11 syntax, please consult the current syntax reference guide for more information.

b. Dependent Variable: hamd.

Information Criteria[a]

-2 Log Likelihood	2214.929
Akaike's Information Criterion (AIC)	2230.929
Hurvich and Tsai's Criterion (AICC)	2231.323
Bozdogan's Criterion (CAIC)	2270.345
Schwarz's Bayesian Criterion (BIC)	2262.345

The information criteria are displayed in smaller-is-better forms.

a. Dependent Variable: hamd.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	61.598	800.624	.000
week	1	61.020	57.562	.000
endog	1	63.211	3.458	.068
endweek	1	62.701	.004	.949

a. Dependent Variable: hamd.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	22.476263	.794346	61.598	28.295	.000	20.888182	24.064344
week	-2.365687	.311810	61.020	-7.587	.000	-2.989186	-1.742189
endog	1.988021	1.069048	63.211	1.860	.068	-.148162	4.124203
endweek	-.027056	.419473	62.701	-.064	.949	-.865383	.811272

a. Dependent Variable: hamd.

Covariance Parameters

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Residual		12.218475	1.119248	10.917	.000	10.210439	14.621420
Intercept + week [subject = id]	UN (1,1)	11.641202	3.359113	3.466	.001	6.612724	20.493460
	UN (2,1)	-1.401608	1.016046	-1.379	.168	-3.393022	.589806
	UN (2,2)	2.077069	.516252	4.023	.000	1.276105	3.380769

a. Dependent Variable: hamd.

Examination of HD across all weeks - quadratic trend

$$\underset{n_i \times 1}{\underset{\boldsymbol{y}_i}{\begin{bmatrix} HD_{i1} \\ HD_{i2} \\ \dots \\ HD_{in_i} \end{bmatrix}}} = \underset{n_i \times p}{\underset{\boldsymbol{X}_i}{\begin{bmatrix} 1 & WEEK_{i1} & WEEK_{i1}^2 \\ 1 & WEEK_{i2} & WEEK_{i2}^2 \\ \dots & \dots & \dots \\ 1 & WEEK_{in_i} & WEEK_{in_i}^2 \end{bmatrix}}} \underset{p \times 1}{\underset{\boldsymbol{\beta}}{\begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{bmatrix}}}$$

$$+ \underset{n_i \times r}{\underset{\boldsymbol{Z}_i}{\begin{bmatrix} 1 & WEEK_{i1} & WEEK_{i1}^2 \\ 1 & WEEK_{i2} & WEEK_{i2}^2 \\ \dots & \dots & \dots \\ 1 & WEEK_{in_i} & WEEK_{in_i}^2 \end{bmatrix}}} \underset{r \times 1}{\underset{\boldsymbol{\upsilon}_i}{\begin{bmatrix} \upsilon_{0i} \\ \upsilon_{1i} \\ \upsilon_{2i} \end{bmatrix}}} + \underset{n_i \times 1}{\underset{\boldsymbol{\varepsilon}_i}{\begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \dots \\ \varepsilon_{in_i} \end{bmatrix}}}$$

where $\max(n_i) = 6$, and $\boldsymbol{X}_i' = \boldsymbol{Z}_i' = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 & 4 & 5 \\ 0 & 1 & 4 & 9 & 16 & 25 \end{bmatrix}$

Within-subjects and between-subjects components

Within-subjects model

$$
\begin{aligned}
HD_{ij} &= b_{0i} + b_{1i} Time_{ij} + b_{2i} Time_{ij}^2 + E_{ij} \\
y_{ij} &= b_{0i} + b_{1i} x_{ij} + b_{2i} x_{ij}^2 + \varepsilon_{ij}
\end{aligned}
$$

$$
\begin{aligned}
b_{0i} &= \text{week 0 HD level for patient } i \\
b_{1i} &= \text{weekly linear change in HD for patient } i \\
b_{2i} &= \text{weekly quadratic change in HD for patient } i
\end{aligned}
$$

Between-subjects models

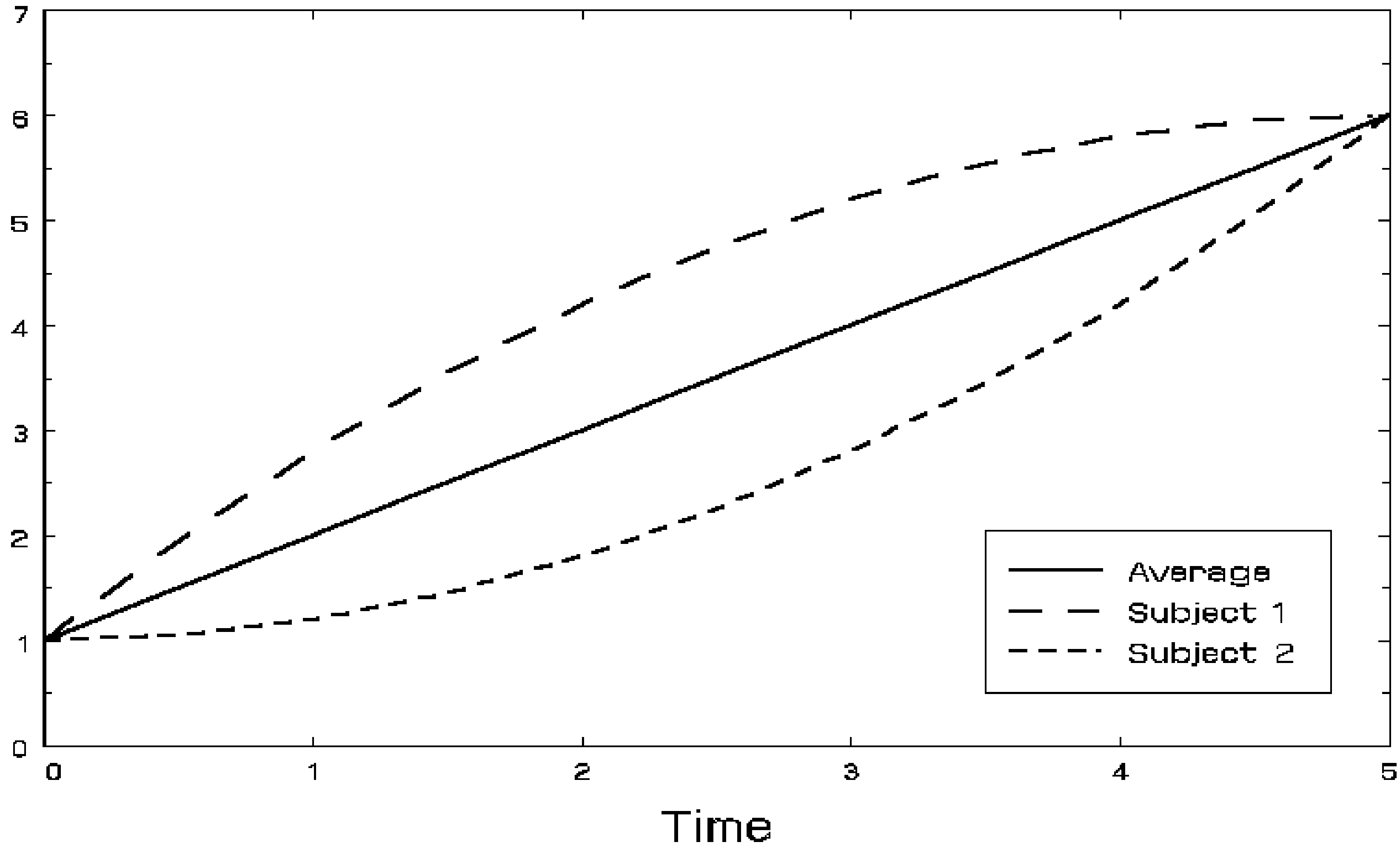
$$
\begin{aligned}
b_{0i} &= \beta_0 + \upsilon_{0i} \\
b_{1i} &= \beta_1 + \upsilon_{1i} \\
b_{2i} &= \beta_2 + \upsilon_{2i}
\end{aligned}
$$

$$
\begin{aligned}
\beta_0 &= \text{average week 0 } HD \text{ level} \\
\beta_1 &= \text{average } HD \text{ weekly linear change} \\
\beta_2 &= \text{average } HD \text{ weekly quadratic change} \\
\upsilon_{0i} &= \text{individual deviation from average intercept} \\
\upsilon_{1i} &= \text{individual deviation from average linear change} \\
\upsilon_{2i} &= \text{individual deviation from average quadratic change}
\end{aligned}
$$

parameter	ML estimate	se	z	$p <$
β_0	23.76	0.55	43.04	.0001
β_1	-2.63	0.48	-5.50	.0001
β_2	0.05	0.09	0.58	.56
$\sigma^2_{\upsilon_0}$	10.44	3.58		
$\sigma_{\upsilon_0\upsilon_1}$	-0.92	2.42		
$\sigma^2_{\upsilon_1}$	6.64	2.75		
$\sigma_{\upsilon_0\upsilon_2}$	-0.11	0.42		
$\sigma_{\upsilon_1\upsilon_2}$	-0.94	0.48		
$\sigma^2_{\upsilon_2}$	0.19	0.09		
σ^2	10.52	1.10		

$\log L = -1103.82$

$\chi^2_4 = 11.4, p < 0.025$, compared to model with $\beta_2 = \sigma^2_{\upsilon_2} = \sigma_{\upsilon_0\upsilon_2} = \sigma_{\upsilon_1\upsilon_2} = 0$
$\chi^2_3 = 11.0, p < 0.02$, compared to model with $\sigma^2_{\upsilon_2} = \sigma_{\upsilon_0\upsilon_2} = \sigma_{\upsilon_1\upsilon_2} = 0$
$\sigma_{\upsilon_1\upsilon_2}$ as corr between linear and quadratic terms = -0.83



Average linear and individual quadratic trends

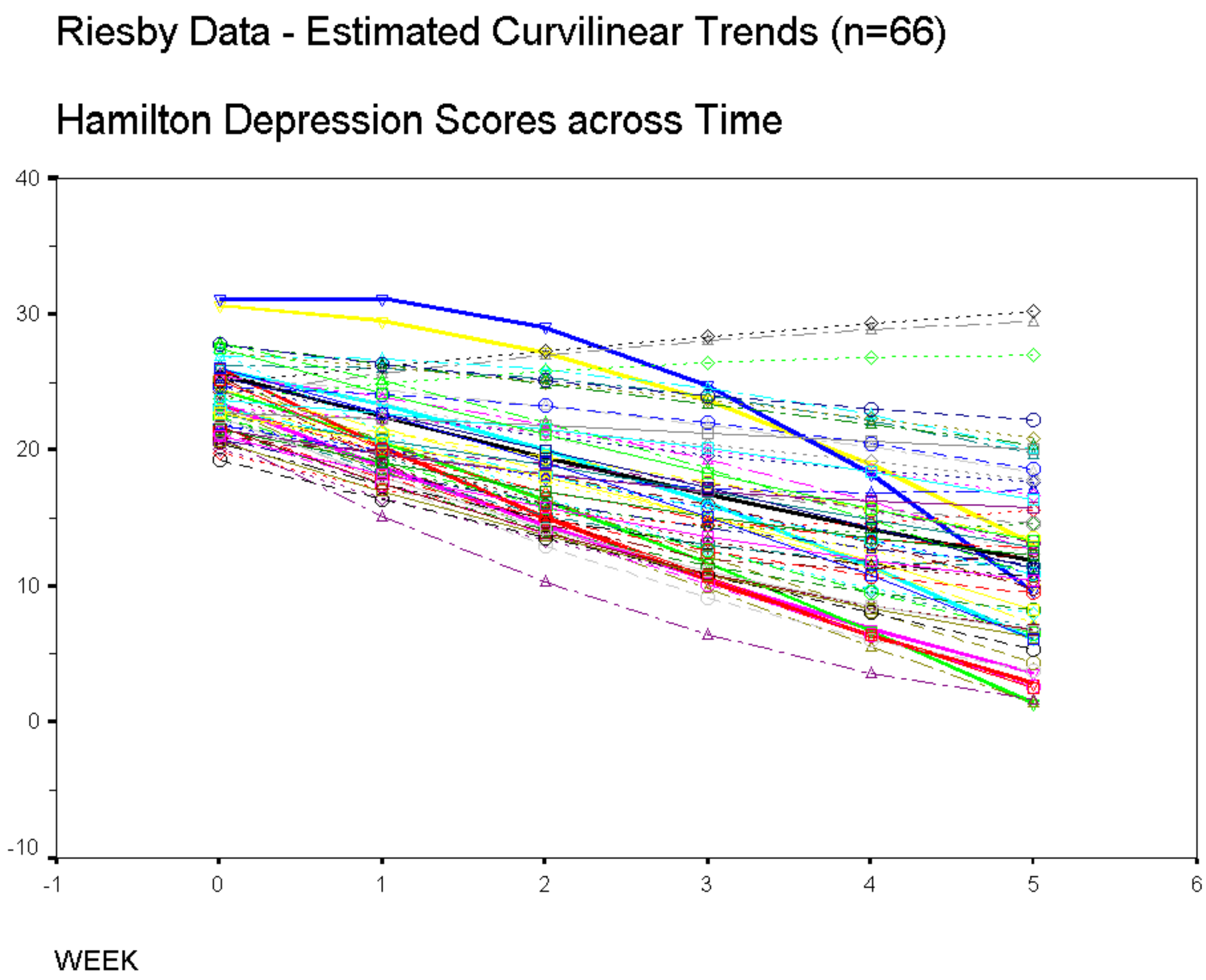
Observed (pairwise) and estimated variance-covariance matrix

$$\Sigma_{\boldsymbol{y}} = \begin{bmatrix} 20.55 & & & & & \\ 10.50 & 22.07 & & & & \\ 10.20 & 12.74 & 30.09 & & & \\ 9.69 & 12.43 & 25.96 & 41.15 & & \\ 7.17 & 10.10 & 25.56 & 36.54 & 48.59 & \\ 6.02 & 7.39 & 18.25 & 26.31 & 32.93 & 52.12 \end{bmatrix}$$

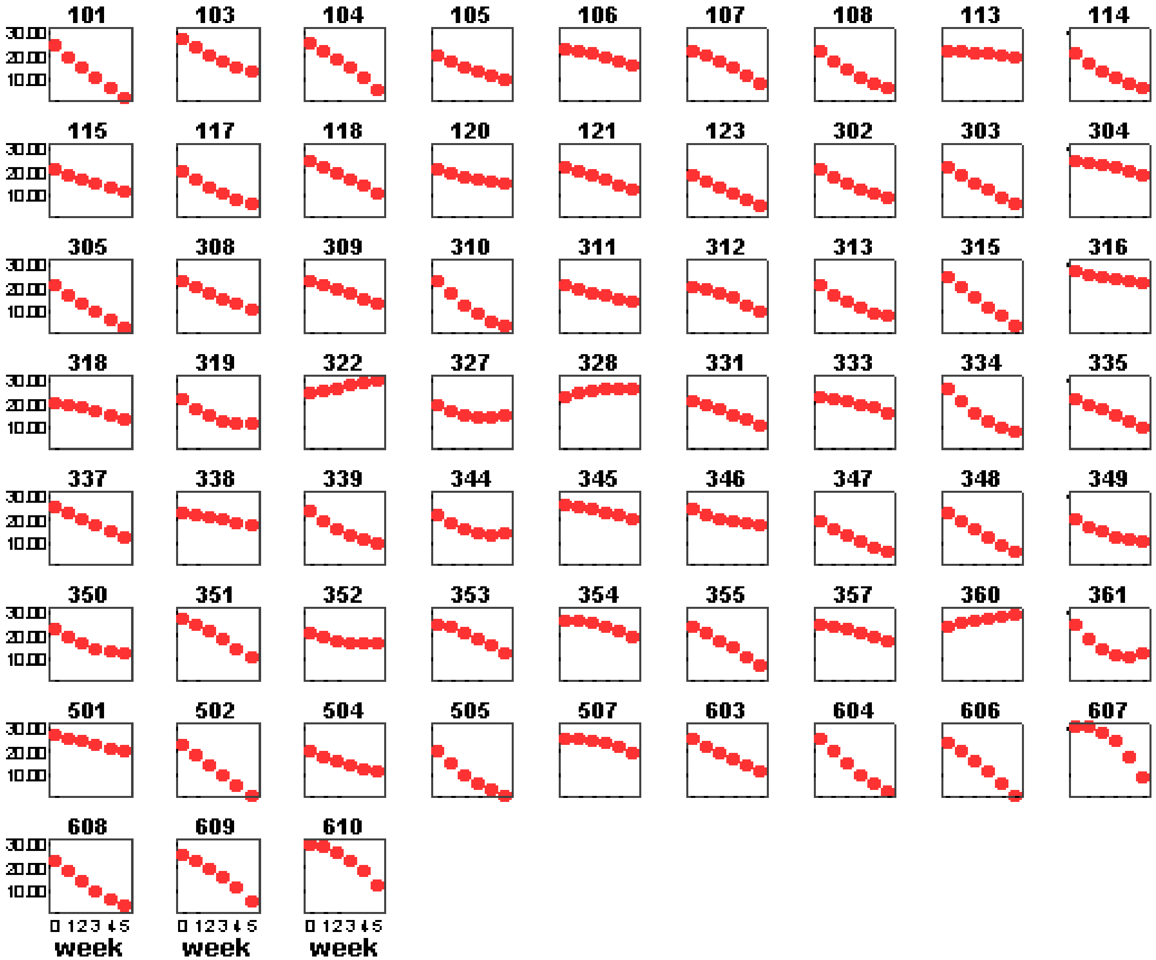
$$\begin{aligned} \hat{\Sigma}_{\boldsymbol{y}} &= \boldsymbol{Z}\hat{\boldsymbol{\Sigma}}_v\boldsymbol{Z}' + \hat{\sigma}^2\boldsymbol{I} \\ &= \begin{bmatrix} 20.96 & & & & & \\ 9.41 & 23.86 & & & & \\ 8.16 & 15.57 & 31.07 & & & \\ 6.68 & 16.08 & 23.11 & 38.31 & & \\ 4.98 & 14.88 & 23.26 & 30.12 & 45.98 & \\ 3.06 & 11.97 & 20.98 & 30.09 & 39.29 & 59.11 \end{bmatrix} \end{aligned}$$

where $\quad \boldsymbol{Z}' = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 1 & 2 & 3 & 4 & 5 \\ 0 & 1 & 4 & 9 & 16 & 25 \end{bmatrix} \qquad \hat{\boldsymbol{\Sigma}}_v = \begin{bmatrix} 10.44 & -0.92 & -0.11 \\ -0.92 & 6.64 & -0.94 \\ -0.11 & -0.94 & 0.19 \end{bmatrix}$

Empirical Bayes estimates of Subject Trends



Empirical Bayes estimates of Subject Trends



SAS MIXED code in RIESBYM.SAS

```
PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL hamd = week week*week /SOLUTION;
RANDOM INTERCEPT week week*week /SUB=id TYPE=UN G GCORR;
TITLE2 'random quadratic trend model';
RUN;
```

SPSS MIXED code in RIESBYM.SPS

```
* compute time squared .
COMPUTE week2 = week*week .
EXECUTE .
* random quadratic trend model .
MIXED
hamd WITH week week2
/FIXED = week week2
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT week week2 | SUBJECT(id) COVTYPE(UN) .
```

```
* compute time squared .
COMPUTE week2 = week*week .
EXECUTE .

* random quadratic trend model .
MIXED
  hamd  WITH week week2
  /FIXED = week  week2
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
 /RANDOM INTERCEPT week week2  | SUBJECT(id) COVTYPE(UN) .
```

Mixed Model Analysis

Notes

Output Created		24-SEP-2007 10:20:14
Comments		
Input	Data	C:\mixdemo\riesby.sav
	Active Dataset	DataSet1
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	396
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		MIXED hamd WITH week week2 /FIXED = week week2 /METHOD = ML /PRINT = SOLUTION TESTCOV /RANDOM INTERCEPT week week2 | SUBJECT(id) COVTYPE(UN) .
Resources	Elapsed Time	0:00:00.06
	Processor Time	0:00:00.09

```
[DataSet1] C:\mixdemo\riesby.sav
```

Model Dimension[b]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables
Fixed Effects	Intercept	1		1	
	week	1		1	
	week2	1		1	
Random Effects	Intercept + week + week2[a]	3	Unstructured	6	id
Residual				1	
Total		6		10	

a. As of version 11.5, the syntax rules for the RANDOM subcommand have changed. Your command syntax may yield results that differ from those produced by prior versions. If you are using SPSS 11 syntax, please consult the current syntax reference guide for more information.

b. Dependent Variable: hamd.

Information Criteria[a]

-2 Log Likelihood	2207.648
Akaike's Information Criterion (AIC)	2227.648
Hurvich and Tsai's Criterion (AICC)	2228.252
Bozdogan's Criterion (CAIC)	2276.917
Schwarz's Bayesian Criterion (BIC)	2266.917

The information criteria are displayed in smaller-is-better forms.

a. Dependent Variable: hamd.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	64.040	1852.370	.000
week	1	63.384	30.206	.000
week2	1	64.046	.340	.562

a. Dependent Variable: hamd.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	23.760249	.552061	64.040	43.039	.000	22.657394	24.863105
week	-2.632576	.478997	63.384	-5.496	.000	-3.589661	-1.675490
week2	.051481	.088347	64.046	.583	.562	-.125010	.227973

a. Dependent Variable: hamd.

Covariance Parameters

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Residual		10.515981	1.106086	9.507	.000	8.556955	12.923507
Intercept + week + week2 [subject = id]	UN (1,1)	10.440212	3.586158	2.911	.004	5.325079	20.468809
	UN (2,1)	-.915381	2.407566	-.380	.704	-5.634124	3.803363
	UN (2,2)	6.638061	2.761282	2.404	.016	2.937385	15.001051
	UN (3,1)	-.112173	.420857	-.267	.790	-.937037	.712691
	UN (3,2)	-.936480	.488042	-1.919	.055	-1.893025	.020066
	UN (3,3)	.193738	.093635	2.069	.039	.075132	.499581

a. Dependent Variable: hamd.

Time-varying Covariates - WS and BS effects

Section 4.5.2 in Hedeker & Gibbons (2006), Longitudinal Data Analysis, Wiley.

Examination of HD across 4 weeks by plasma drug-levels

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

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

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

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

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

Between-subjects models

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

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

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*

$^*p < 0.05$

Model with time-varying covariate X_{ij}

Within-subjects model

$$Y_{ij} = b_{0i} + b_{1i}T_{ij} + b_{2i}X_{ij} + E_{ij}$$

Between-subjects models

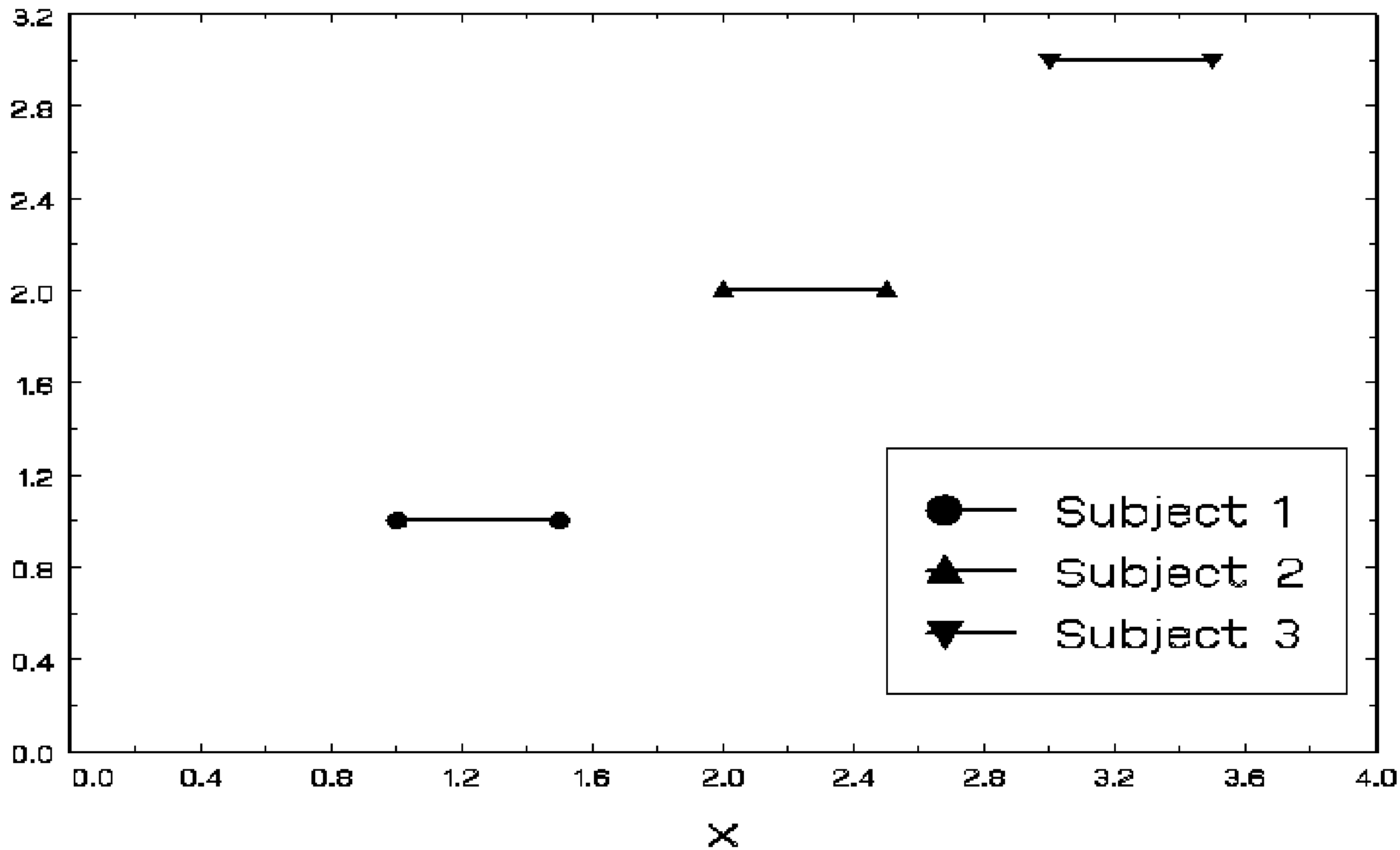
$$\begin{aligned} b_{0i} &= \beta_0 + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \upsilon_{1i} \\ b_{2i} &= \beta_2 \end{aligned}$$

Is the effect of X_{ij} purely within-subjects? What about

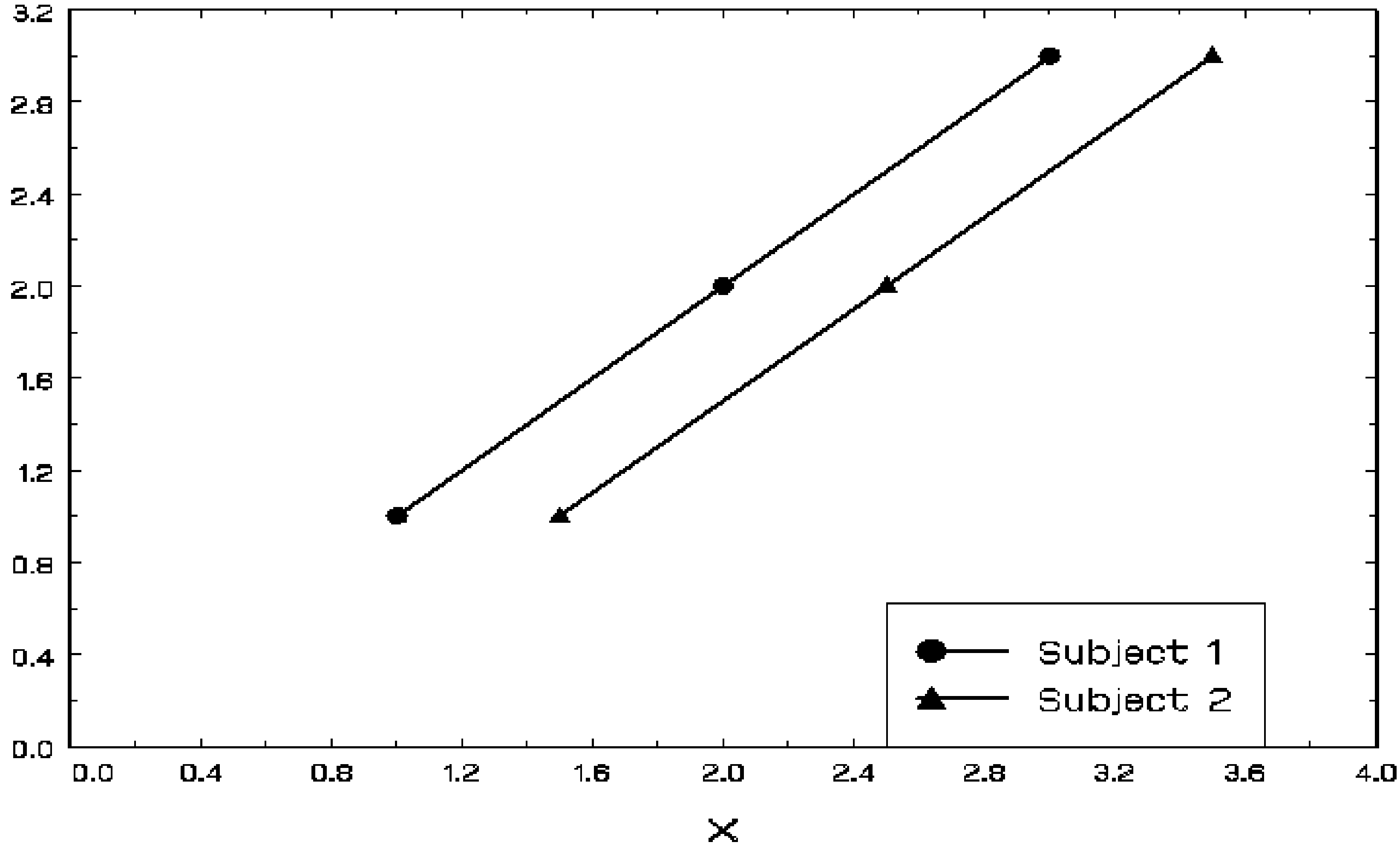
$$\begin{aligned} X_{ij} &= X_{ij} + \bar{X}_i - \bar{X}_i \\ &= \bar{X}_i + (X_{ij} - \bar{X}_i) \end{aligned}$$

$\bar{X}_i$ is between-subjects component of X

$X_{ij} - \bar{X}_i$ is within-subjects component of X



Time-varying covariate effects: purely between-subjects



Time-varying covariate effects: purely within-subjects

Model with decomposition of time-varying covariate X_{ij}

Within-subjects model

$$Y_{ij} = b_{0i} + b_{1i}T_{ij} + b_{2i}(X_{ij} - \bar{X}_i) + E_{ij}$$

Between-subjects models

$$\begin{aligned} b_{0i} &= \beta_0 + \beta_{BS}\bar{X}_i + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \upsilon_{1i} \\ b_{2i} &= \beta_{WS} \end{aligned}$$

Notice, effect of X is now $\beta_{BS}\bar{X}_i + \beta_{WS}(X_{ij} - \bar{X}_i)$

β_{BS} = effect of $\bar{X}_i$ on $\bar{Y}_i$ BS or "cross-sectional"

β_{WS} = effect of $(X_{ij} - \bar{X}_i)$ on $(Y_{ij} - \bar{Y}_i)$ WS or "longitudinal"

Model with only X_{ij} assumes equal BS and WS effects ($\beta_{BS} = \beta_{WS}$)

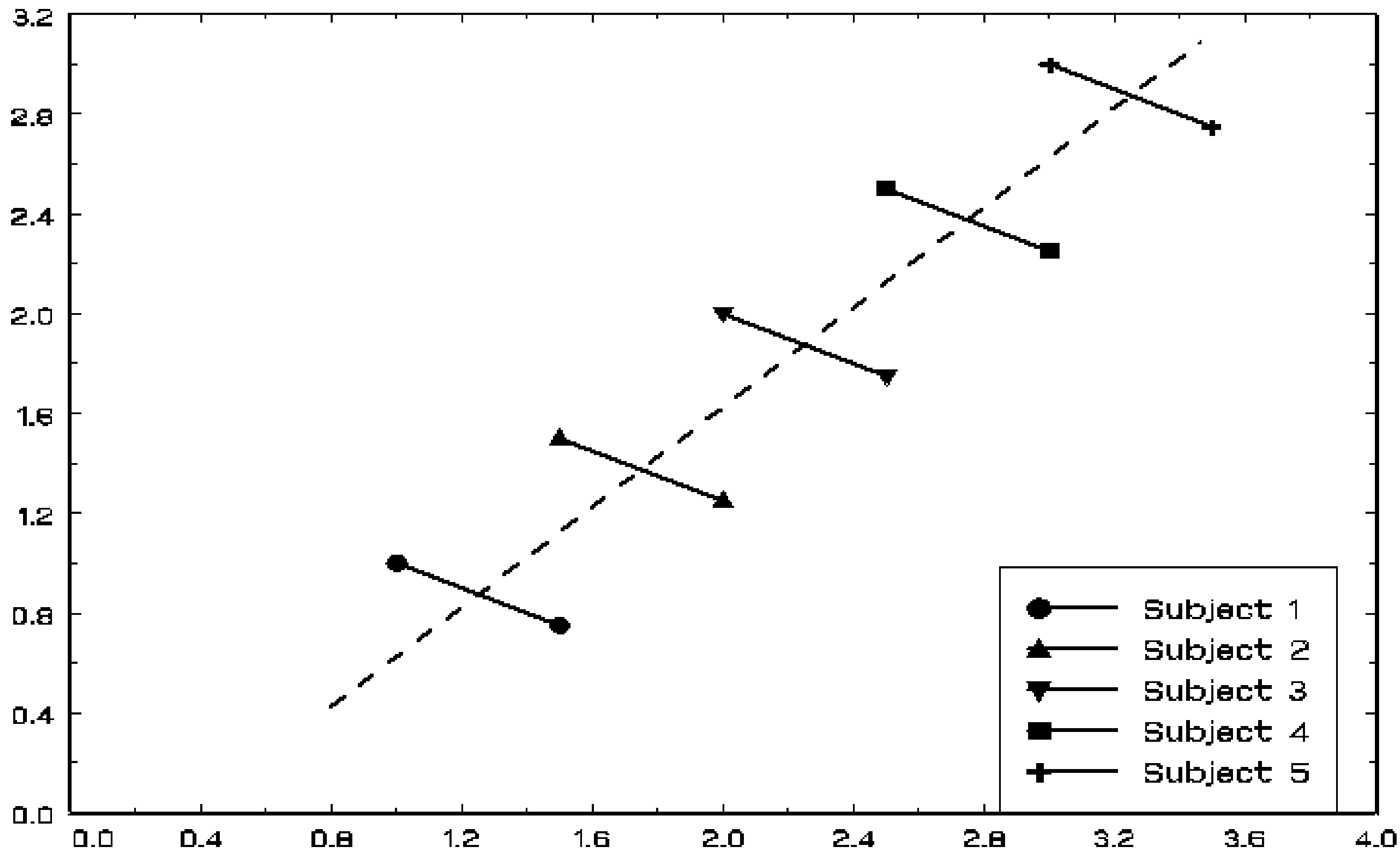
suppose $\beta_{BS} = \beta_{WS} = \beta^*$, then in the model with decomposition,

the effect of $X_{ij} \; = \; \beta^* \bar{X}_i + \beta^*(X_{ij} - \bar{X}_i) \; = \; \beta^* X_{ij}$

$\Rightarrow$ precisely what the model with only X_{ij} assumes

Equal WS and BS effects of X_{ij}?

- can be a dubious assumption
- needs to be tested (by comparing two models via LR test)
- there is no guarantee that β_{BS} and β_{WS} even agree on sign



Time-varying covariate effects: opposite sign WS and BS effects

parameter	estimate	se	$p <$
assuming BS=WS drug effects			
intercept	1.52	3.74	ns
slope	-1.97	0.28	.0001
ln IMI	0.63	0.82	ns
ln DMI	-1.97	0.60	.001
deviance = 1498.8			
relaxing BS=WS drug effects			
intercept	7.26	5.02	ns
slope	-2.03	0.29	.0001
ln IMI BS	-0.28	1.00	ns
ln DMI BS	-2.39	0.79	.003
ln IMI WS	2.37	1.46	ns
ln DMI WS	-1.74	1.00	ns
deviance = 1495.8			

$$X_2^2 = 1498.8 - 1495.8 = 3 \quad \Rightarrow \text{Accept } H_0 : \boldsymbol{\beta}_{BS} = \boldsymbol{\beta}_{WS}$$

SAS MIXED code - RIESBSWS.SAS

```
TITLE1 'partitioning BS and WS effects of drug levels';
DATA one; INFILE 'c:\mixdemo\riesbyt4.dat';
INPUT id hamdelt intcpt week sex endog lnimi lndmi ;

PROC SORT; BY id;
PROC MEANS NOPRINT; CLASS id; VAR lnimi lndmi;
OUTPUT OUT = two MEAN = mlnimi mlndmi;

DATA three; MERGE one two; BY id;
lnidev = lnimi - mlnimi; lnddev = lndmi - mlndmi;

PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL hamdelt = week lnimi lndmi /SOLUTION;
RANDOM INTERCEPT week /SUB=id TYPE=UN G GCORR;
TITLE2 'assuming bs=ws drug effects';

PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL hamdelt = week mlnimi mlndmi lnidev lnddev /SOLUTION;
RANDOM INTERCEPT week /SUB=id TYPE=UN G GCORR;
TITLE2 'relaxing bs=ws drug effects';
```

SPSS MIXED code - RIESBSWS.SPS - after opening RIESBYT4.SAV
(SPSS dataset with variables: id, hamdelt, week, lnimi, lndmi)

```
* assuming bs=ws drug effects .
MIXED
hamdelt WITH week lnimi lndmi
/FIXED = week lnimi lndmi
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .

* obtaining subject-level means of drug variables .
AGGREGATE
/OUTFILE=*
MODE=ADDVARIABLES
/BREAK=id
/lnimi_mean = MEAN(lnimi) /lndmi_mean = MEAN(lndmi).

* obtaining deviations to subject-level means of drug variables .
COMPUTE lnimi_dev = lnimi - lnimi_mean .
COMPUTE lndmi_dev = lndmi - lndmi_mean .
EXECUTE .
```

```
* relaxing bs=ws drug effects .
MIXED
hamdelt WITH week lnimi_mean lndmi_mean lnimi_dev lndmi_dev
/FIXED = week lnimi_mean lndmi_mean lnimi_dev lndmi_dev
/METHOD = ML
/PRINT = SOLUTION TESTCOV
/RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
```

```
GET
  FILE='C:\mixdemo\riesbyt4.sav'.
DATASET NAME DataSet2 WINDOW=FRONT.
DATASET ACTIVATE DataSet2.
DATASET CLOSE DataSet1.
MIXED
  hamdelt  WITH week lnimi lndmi
  /FIXED = week lnimi lndmi
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
 /RANDOM INTERCEPT week  | SUBJECT(id) COVTYPE(UN) .
```

Mixed Model Analysis

Notes

Output Created		24-SEP-2007 10:27:36
Comments		
Input	Data	C:\mixdemo\riesbyt4.sav
	Active Dataset	DataSet2
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	250
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		MIXED hamdelt WITH week lnimi lndmi /FIXED = week lnimi lndmi /METHOD = ML /PRINT = SOLUTION TESTCOV /RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
Resources	Elapsed Time	0:00:00.05
	Processor Time	0:00:00.06

```
[DataSet2] C:\mixdemo\riesbyt4.sav
```

Model Dimension[b]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables
Fixed Effects	Intercept	1		1	
	week	1		1	
	lnimi	1		1	
	lndmi	1		1	
Random Effects	Intercept + week[a]	2	Unstructured	3	id
Residual				1	
Total		6		8	

a. As of version 11.5, the syntax rules for the RANDOM subcommand have changed. Your command syntax may yield results that differ from those produced by prior versions. If you are using SPSS 11 syntax, please consult the current syntax reference guide for more information.

b. Dependent Variable: hamdelt.

Information Criteria[a]

-2 Log Likelihood	1498.846
Akaike's Information Criterion (AIC)	1514.846
Hurvich and Tsai's Criterion (AICC)	1515.443
Bozdogan's Criterion (CAIC)	1551.017
Schwarz's Bayesian Criterion (BIC)	1543.017

The information criteria are displayed in smaller-is-better forms.

a. Dependent Variable: hamdelt.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	132.062	.165	.685
week	1	65.236	47.636	.000
lnimi	1	120.833	.589	.444
lndmi	1	128.053	10.656	.001

a. Dependent Variable: hamdelt.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	1.521353	3.742575	132.062	.406	.685	-5.881799	8.924505
week	-1.966858	.284974	65.236	-6.902	.000	-2.535951	-1.397764
lnimi	.630078	.821118	120.833	.767	.444	-.995565	2.255720
lndmi	-1.966628	.602459	128.053	-3.264	.001	-3.158691	-.774564

a. Dependent Variable: hamdelt.

Covariance Parameters

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Residual		10.527806	1.385195	7.600	.000	8.134692	13.624940
Intercept + week [subject = id]	UN (1,1)	20.499701	5.126601	3.999	.000	12.556759	33.467053
	UN (2,1)	.837165	1.614432	.519	.604	-2.327063	4.001394
	UN (2,2)	2.782404	.969178	2.871	.004	1.405809	5.506988

a. Dependent Variable: hamdelt.

```
AGGREGATE
  /OUTFILE=*
  MODE=ADDVARIABLES
  /BREAK=id
  /lnimi_mean = MEAN(lnimi) /lndmi_mean = MEAN(lndmi).

COMPUTE lnimi_dev = lnimi - lnimi_mean .
COMPUTE lndmi_dev = lndmi - lndmi_mean .
EXECUTE .

MIXED
  hamdelt  WITH week lnimi_mean lndmi_mean lnimi_dev lndmi_dev
  /FIXED = week lnimi_mean lndmi_mean lnimi_dev lndmi_dev
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
 /RANDOM INTERCEPT week  | SUBJECT(id) COVTYPE(UN) .
```

Mixed Model Analysis

Notes

Output Created		24-SEP-2007 10:27:37
Comments		
Input	Data	C:\mixdemo\riesbyt4.sav
	Active Dataset	DataSet2
	Filter	<none>
	Weight	<none>
	Split File	<none>
	N of Rows in Working Data File	250
Missing Value Handling	Definition of Missing	User-defined missing values are treated as missing.
	Cases Used	Statistics are based on all cases with valid data for all variables in the model.
Syntax		MIXED hamdelt WITH week lnimi_mean lndmi_mean lnimi_dev lndmi_dev /FIXED = week lnimi_mean lndmi_mean lnimi_dev lndmi_dev /METHOD = ML /PRINT = SOLUTION TESTCOV /RANDOM INTERCEPT week | SUBJECT(id) COVTYPE(UN) .
Resources	Elapsed Time	0:00:00.05
	Processor Time	0:00:00.06

```
[DataSet2] C:\mixdemo\riesbyt4.sav
```

Model Dimension[b]

		Number of Levels	Covariance Structure	Number of Parameters	Subject Variables
Fixed Effects	Intercept	1		1	
	week	1		1	
	lnimi_mean	1		1	
	lndmi_mean	1		1	
	lnimi_dev	1		1	
	lndmi_dev	1		1	
Random Effects	Intercept + week[a]	2	Unstructured	3	id
Residual				1	
Total		8		10	

a. As of version 11.5, the syntax rules for the RANDOM subcommand have changed. Your command syntax may yield results that differ from those produced by prior versions. If you are using SPSS 11 syntax, please consult the current syntax reference guide for more information.

b. Dependent Variable: hamdelt.

Information Criteria[a]

-2 Log Likelihood	1495.770
Akaike's Information Criterion (AIC)	1515.770
Hurvich and Tsai's Criterion (AICC)	1516.690
Bozdogan's Criterion (CAIC)	1560.984
Schwarz's Bayesian Criterion (BIC)	1550.984

The information criteria are displayed in smaller-is-better forms.

a. Dependent Variable: hamdelt.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	65.459	2.079	.154
week	1	67.305	48.131	.000
lnimi_mean	1	64.411	.097	.756
lndmi_mean	1	65.092	8.835	.004
lnimi_dev	1	183.024	2.817	.095
lndmi_dev	1	184.585	3.236	.074

a. Dependent Variable: hamdelt.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Intercept	7.266061	5.038868	65.459	1.442	.154	-2.795918	17.328039
week	-2.023795	.291713	67.305	-6.938	.000	-2.606007	-1.441582
lnimi_mean	-.312940	1.003713	64.411	-.312	.756	-2.317841	1.691962
lndmi_mean	-2.366923	.796310	65.092	-2.972	.004	-3.957221	-.776625
lnimi_dev	2.443656	1.456049	183.024	1.678	.095	-.429144	5.316457
lndmi_dev	-1.796511	.998688	184.585	-1.799	.074	-3.766822	.173800

a. Dependent Variable: hamdelt.

Covariance Parameters

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Residual		10.376008	1.358992	7.635	.000	8.026840	13.412693
Intercept + week [subject = id]	UN (1,1)	20.319887	5.100865	3.984	.000	12.423548	33.235094
	UN (2,1)	.498344	1.644257	.303	.762	-2.724340	3.721027
	UN (2,2)	2.825931	.974177	2.901	.004	1.437901	5.553853

a. Dependent Variable: hamdelt.