Longitudinal Data Analysis, including Categorical Outcomes

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Advantages of Mixed-effects Regression Models
(MRM; aka multilevel, hierarchical linear, linear mixed models)

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 ⇒ methods for testing specific determinants of this structure
4. MRM can be extended to higher-level models ⇒ repeated observations within individuals within clusters
5. Generalizations for non-normal data

Mixed-effects Regression models aka

- random-effects models
- random-coefficient models
- multilevel models
- hierarchical linear models

Useful for analyzing

- Clustered data
  - subjects (level-1) within clusters (level-2)
    - e.g., clinics, hospitals, families, worksites, schools, classrooms, city wards
- Longitudinal data
  - repeated obs. (level-1) within subjects (level-2)

		cluster variables		*subject variables*		
cluster	subject	tx group	size	outcome	sex	age
1	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	n_1	.	.	.	.	.
2	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	n_2	.	.	.	.	.
.	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	$n_.$	.	.	.	.	.
N	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	n_N	.	.	.	.	.

$i = 1 \ldots N$ clusters
$j = 1 \ldots n_i$ subjects in cluster i

		time-invariant variables			*time-varying variables*	
subject	time	tx group	sex	age	outcome	dose
1	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	n_1	.	.	.	.	.
2	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	n_2	.	.	.	.	.
.	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	$n_.$	.	.	.	.	.
N	1	.	.	.	.	.
	$\vdots$	.	.	.	.	.
	n_N	.	.	.	.	.

$i = 1 \ldots N$ subjects
$j = 1 \ldots n_i$ timepoints for subject i

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

$\boldsymbol{y}_i = n_i \times 1$ response vector for individual i

$\boldsymbol{X}_i = n_i \times p$ design matrix for the fixed effects

$\boldsymbol{\beta} = p \times 1$ vector of unknown fixed parameters

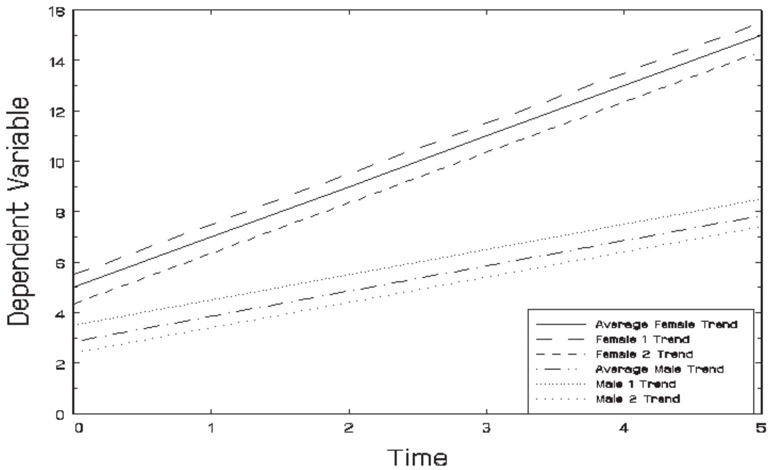
$\boldsymbol{Z}_i = n_i \times r$ design matrix for the random effects

$\boldsymbol{\upsilon}_i = r \times 1$ vector of unknown random effects $\sim \mathcal{N}(0, \boldsymbol{\Sigma}_\upsilon)$

$\boldsymbol{\varepsilon}_i = n_i \times 1$ residual vector $\sim \mathcal{N}(0, \sigma^2 \boldsymbol{I}_{n_i})$

Random-intercepts Model

each subject is parallel to their group trend



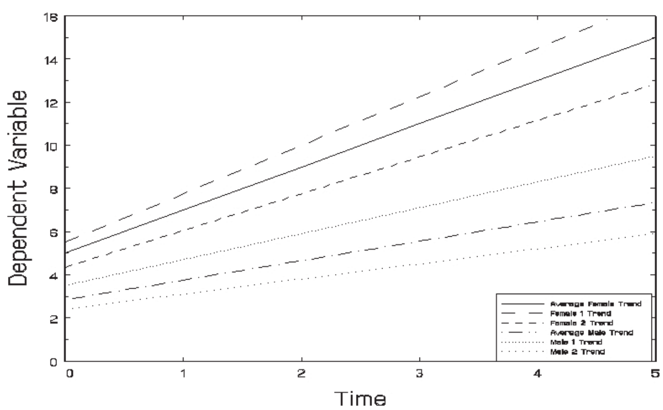
$$y = Time + Grp + (Grp \times Time) + Subj + Error$$

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

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

Random Intercepts and Trend Model

subjects deviate in terms of both intercept & slope



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

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

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

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

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

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

Estimation - EM algorithm

opposite process of "I do cocaine so I can work more, so I can do more cocaine, so I can work more, *etc.*, "

Effect of increasing cocaine use

Cocaine		*Work*	*Health*
do cocaine	$\rightarrow$	work more	declines
do more cocaine	$\rightarrow$	work more	declines more
do even more cocaine	$\rightarrow$	work even more	declines even more
...	...	...	...
do a ton of cocaine	$\rightarrow$	always working	death

Effect of EM estimation of parameters

M-Step (ML)		*E-Step (EB)*	*Estimation*
starting values $\boldsymbol{\beta}, \sigma^2, \boldsymbol{\Sigma}_\upsilon$	$\rightarrow$	estimate $\tilde{\boldsymbol{\upsilon}}_i$ $\boldsymbol{\Sigma}_{\upsilon\vert y_i}$	improves
re-estimate $\boldsymbol{\beta}, \sigma^2, \boldsymbol{\Sigma}_\upsilon$	$\rightarrow$	re-estimate $\tilde{\boldsymbol{\upsilon}}_i$ $\boldsymbol{\Sigma}_{\upsilon\vert y_i}$	improves more
re-re-estimate $\boldsymbol{\beta}, \sigma^2, \boldsymbol{\Sigma}_\upsilon$	$\rightarrow$	re-re-estimate $\tilde{\boldsymbol{\upsilon}}_i$ $\boldsymbol{\Sigma}_{\upsilon\vert y_i}$	improves even more
...	...	...	...
RE-estimate $\boldsymbol{\beta}, \sigma^2, \boldsymbol{\Sigma}_\upsilon$	$\rightarrow$	RE-estimate $\tilde{\boldsymbol{\upsilon}}_i$ $\boldsymbol{\Sigma}_{\upsilon\vert y_i}$	convergence

$\rightarrow$ EM is better than cocaine since EM leads to convergence and not death

EM solution - random intercepts model

- E-step (expectation - "Expected A Posteriori" or Empirical Bayes)

$$\tilde{\upsilon}_i \;=\; \rho_{n_i n_i} \left[\frac{1}{n_i} \sum_{j=1}^{n_i} y_{ij} - \boldsymbol{x}'_{ij}\boldsymbol{\beta} \right]$$

$$\sigma^2_{\upsilon|y_i} \;=\; \sigma^2_\upsilon (1 - \rho_{n_i n_i}) \qquad \text{where } \rho_{n_i n_i} = \frac{n_i r}{1 + (n_i - 1) r} \quad \text{and} \quad r = \frac{\sigma^2_\upsilon}{\sigma^2_\upsilon + \sigma^2}$$

- M-step (maximization - "Maximium Likelihood")

$$\hat{\boldsymbol{\beta}} \;=\; \left(\sum_i^N \boldsymbol{X}'_i \boldsymbol{X}_i \right)^{-1} \sum_i^N \boldsymbol{X}'_i (\boldsymbol{y}_i - \mathbf{1}_i \tilde{\upsilon}_i)$$

$$\hat{\sigma}^2_\upsilon \;=\; \frac{1}{N} \sum_i^N \tilde{\upsilon}_i{}^2 + \sigma^2_{\upsilon|y_i}$$

$$\hat{\sigma}^2 \;=\; (\sum_i^N n_i)^{-1} \sum_i^N (\boldsymbol{y}_i - \boldsymbol{X}_i \hat{\boldsymbol{\beta}} - \mathbf{1}_i \tilde{\upsilon}_i)' (\boldsymbol{y}_i - \boldsymbol{X}_i \hat{\boldsymbol{\beta}} - \mathbf{1}_i \tilde{\upsilon}_i) \;+\; n_i \sigma^2_{\upsilon|y_i}$$

- provide starting values for $\boldsymbol{\beta}$, σ^2_υ, and σ^2
- perform E-step, perform M-step, repeat early and often (until convergence)

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: `riesbydesc.do`

```
cd "u:\Stata_long\"
log using riesbydesc.log, replace
infile  id hamd intcpt week endog endweek ///
     using RIESBY.DAT.txt, clear
* remove observations with missing hamd
drop if mi(hamd)
summarize

* hamd descriptives across time by group
format hamd %6.2f
tabulate endog week, summarize(hamd) wrap

* reshape data to wide format
reshape wide hamd endweek, i(id) j(week)

* listwise deleted correlation matrix
corr hamd0 hamd1 hamd2 hamd3 hamd4 hamd5
* pairwise deleted correlation matrix
pwcorr hamd0 hamd1 hamd2 hamd3 hamd4 hamd5
log close
```

Partial list of `RIESBY.DAT.txt`

```
101 26  1  0  0  0
101 22  1  1  0  0
101 18  1  2  0  0
101  7  1  3  0  0
101  4  1  4  0  0
101  3  1  5  0  0
103 33  1  0  0  0
103 24  1  1  0  0
103 15  1  2  0  0
103 24  1  3  0  0
103 15  1  4  0  0
103 13  1  5  0  0
104 29  1  0  1  0
104 22  1  1  1  1
104 18  1  2  1  2
104 13  1  3  1  3
104 19  1  4  1  4
104  0  1  5  1  5
105 22  1  0  0  0
105 12  1  1  0  0
105 16  1  2  0  0
105 16  1  3  0  0
105 13  1  4  0  0
105  9  1  5  0  0
106 21  1  0  1  0
106 25  1  1  1  1
106 23  1  2  1  2
106 18  1  3  1  3
106 20  1  4  1  4
106  .  1  5  1  5
107 21  1  0  1  0
107 21  1  1  1  1
107 16  1  2  1  2
107 19  1  3  1  3
107  .  1  4  1  4
107  6  1  5  1  5
```



```
. summarize

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          id |       375    324.2507    145.2229        101        610
        hamd |       375    17.63733    7.190062          0         39
      intcpt |       375           1           0          1          1
        week |       375        2.48    1.683198          0          5
       endog |       375    .5466667    .4984825          0          1
-------------+--------------------------------------------------------
     endweek |       375       1.352    1.745534          0          5
```

```
. * hamd descriptives across time by group
. format hamd %6.2f

. tabulate endog week, summarize(hamd) wrap

           Means, Standard Deviations and Frequencies of hamd

           |                             week
     endog |         0          1          2          3          4          5 |     Total
-----------+------------------------------------------------------------------+----------
         0 |     22.79      20.48      17.00      15.34      12.62      11.22 |     16.60
           |      4.12       3.83       4.35       6.17       6.72       6.34 |      6.69
           |        28         29         28         29         29         27 |       170
-----------+------------------------------------------------------------------+----------
         1 |     24.00      23.00      19.30      17.28      14.47      12.58 |     18.50
           |      4.85       5.10       6.08       6.56       7.17       7.96 |      7.49
           |        33         34         37         36         34         31 |       205
-----------+------------------------------------------------------------------+----------
     Total |     23.44      21.84      18.31      16.42      13.62      11.95 |     17.64
           |      4.53       4.70       5.49       6.42       6.97       7.22 |      7.19
           |        61         63         65         65         63         58 |       375
```



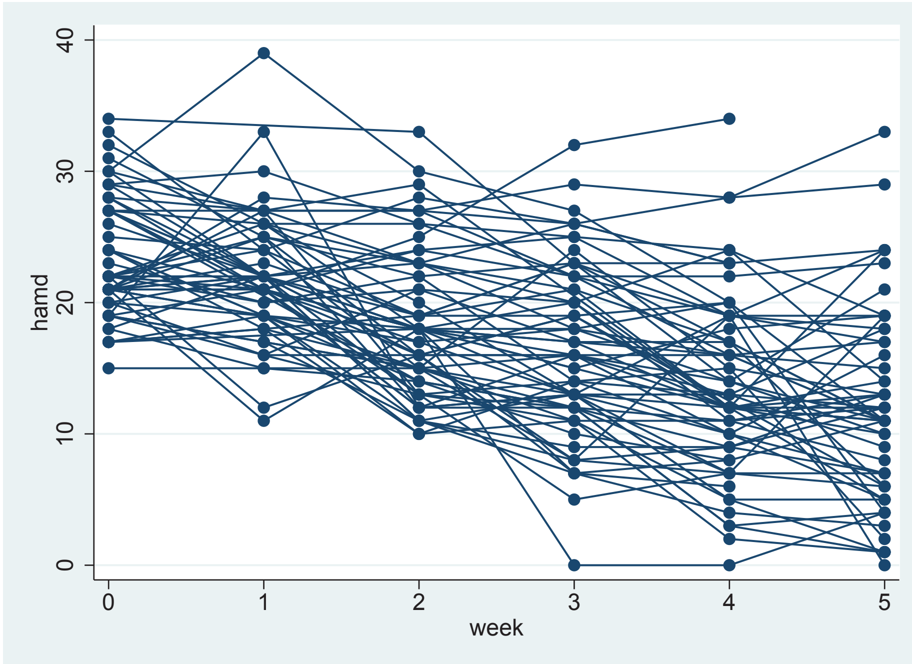
```
. * reshape data to wide format
. reshape wide hamd endweek, i(id) j(week)
(note: j = 0 1 2 3 4 5)

Data                               long   ->   wide
-----------------------------------------------------------------------------
Number of obs.                      375   ->      66
Number of variables                   6   ->      15
j variable (6 values)              week   ->   (dropped)
xij variables:
                                   hamd   ->   hamd0 hamd1 ... hamd5
                                endweek   ->   endweek0 endweek1 ... endweek5
-----------------------------------------------------------------------------
```

```
. * listwise deleted correlation matrix
. corr hamd0 hamd1 hamd2 hamd3 hamd4 hamd5
(obs=46)

             |    hamd0    hamd1    hamd2    hamd3    hamd4    hamd5
-------------+------------------------------------------------------
       hamd0 |   1.0000
       hamd1 |   0.4939   1.0000
       hamd2 |   0.4176   0.4925   1.0000
       hamd3 |   0.4445   0.5132   0.7310   1.0000
       hamd4 |   0.3034   0.3474   0.6803   0.7796   1.0000
       hamd5 |   0.2211   0.2273   0.5272   0.6227   0.7230   1.0000

. * pairwise deleted correlation matrix
. pwcorr hamd0 hamd1 hamd2 hamd3 hamd4 hamd5

             |    hamd0    hamd1    hamd2    hamd3    hamd4    hamd5
-------------+------------------------------------------------------
       hamd0 |   1.0000
       hamd1 |   0.4930   1.0000
       hamd2 |   0.4101   0.4943   1.0000
       hamd3 |   0.3331   0.4123   0.7378   1.0000
       hamd4 |   0.2268   0.3082   0.6685   0.8170   1.0000
       hamd5 |   0.1838   0.2179   0.4608   0.5681   0.6543   1.0000
```


Plots of longitudinal data: riesbyplot.do

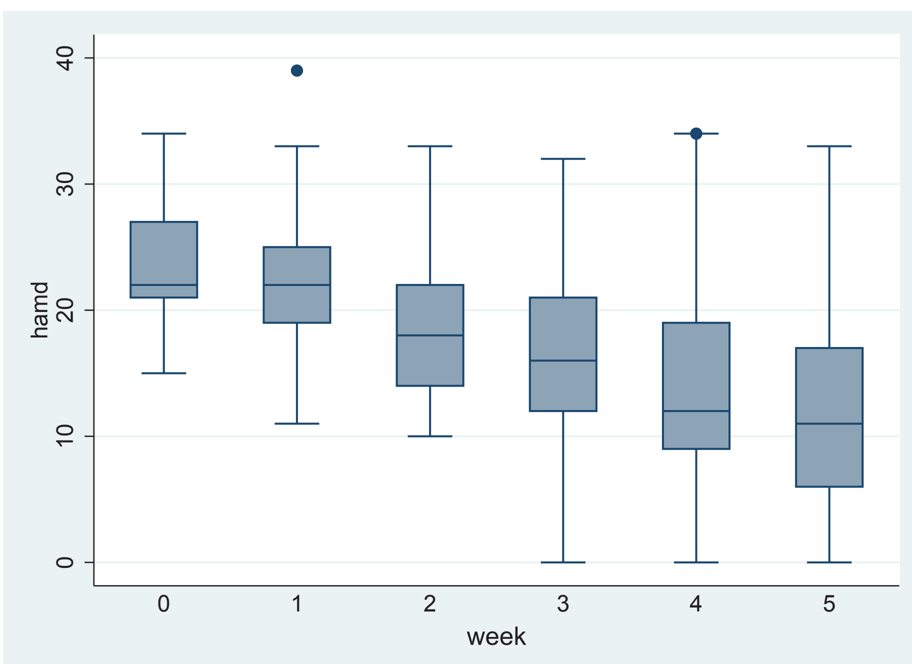
```
cd "u:\Stata_long\"
log using riesbyplot.log, replace
infile  id hamd intcpt week endog endweek ///
     using RIESBY.DAT.txt, clear
* remove observations with missing hamd
drop if mi(hamd)
summarize
```

```
* spaghetti plot
twoway connected hamd week, connect(L)
```

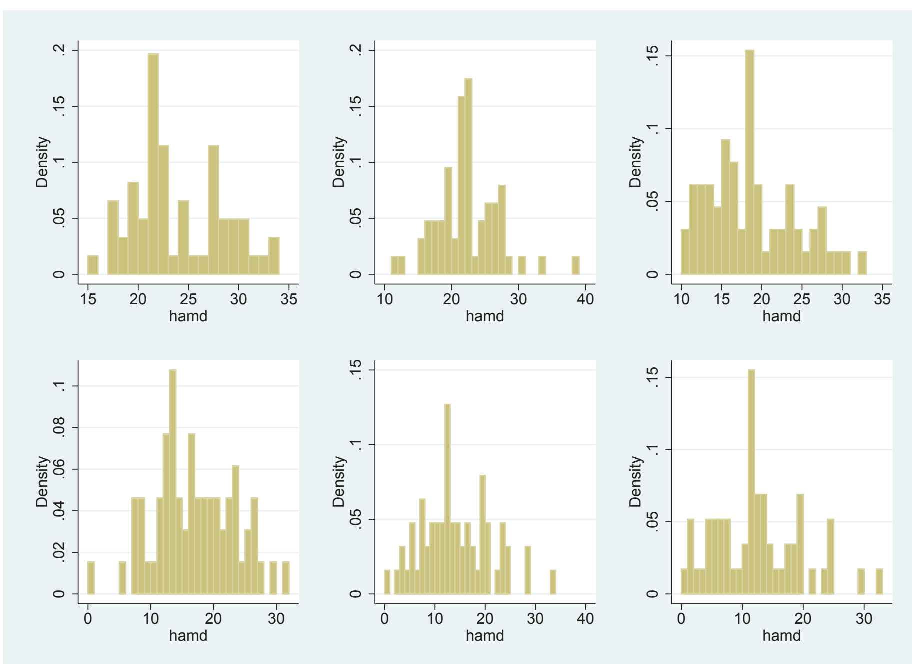


- increasing variance across time
- general linear decline over time

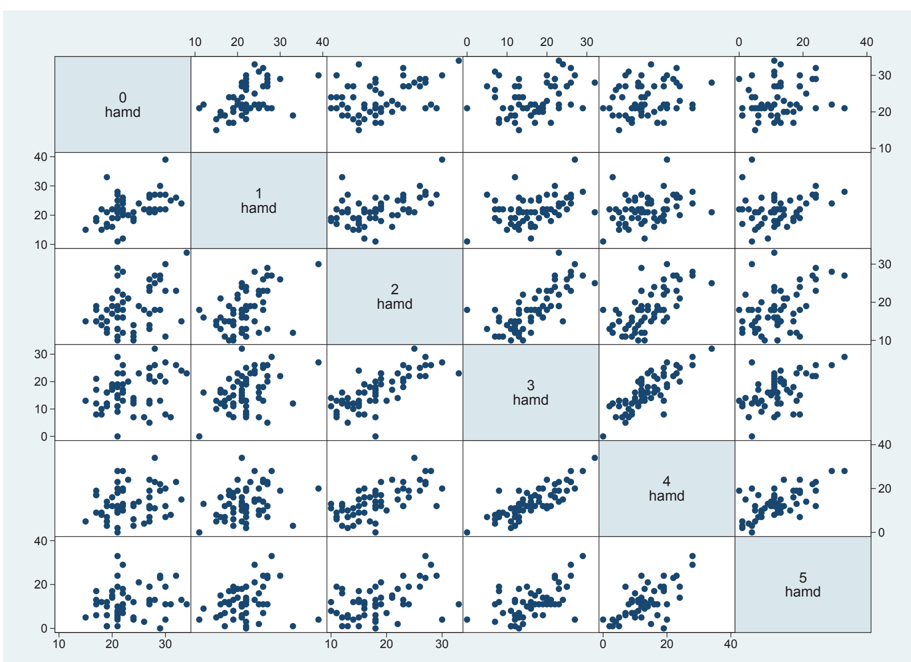

```
* boxplots across weeks
graph box hamd, over(week) b1title("week")
```



```
* histograms of hamd across weeks
twoway histogram hamd if week==0, width(1) name(hamd0)
twoway histogram hamd if week==1, width(1) name(hamd1)
twoway histogram hamd if week==2, width(1) name(hamd2)
twoway histogram hamd if week==3, width(1) name(hamd3)
twoway histogram hamd if week==4, width(1) name(hamd4)
twoway histogram hamd if week==5, width(1) name(hamd5)
graph combine hamd0 hamd1 hamd2 hamd3 hamd4 hamd5
```

```
* reshape data to wide format
reshape wide hamd endweek, i(id) j(week)

* matrix plot of hamd across weeks
graph matrix hamd0 hamd1 hamd2 hamd3 hamd4 hamd5
```

SAS descriptive statistics: riesbydesc.sas

```
* Descriptive statistics for Riesby dataset;

DATA one;
  INFILE 'c:\SAS_long\RIESBY.DAT.txt';
  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';

* Descriptives;
PROC MEANS;
RUN;
```


The SAS System

The MEANS Procedure

Variable	N	Mean	Std Dev	Minimum	Maximum
id	396	323.9696970	146.5491634	101.0000000	610.0000000
HamD	375	17.6373333	7.1900625	0	39.0000000
Intcpt	396	1.0000000	0	1.0000000	1.0000000
Week	396	2.5000000	1.7099856	0	5.0000000
Endog	396	0.5606061	0.4969412	0	1.0000000
EndWeek	396	1.4040404	1.7827255	0	5.0000000

```
* get the data in multivariate format for a matrix plot;
PROC SORT; BY id;RUN;
DATA t0;SET one; IF week=0; hamd_0 = hamd; RUN;
DATA t1;SET one; IF week=1; hamd_1 = hamd; RUN;
DATA t2;SET one; IF week=2; hamd_2 = hamd; RUN;
DATA t3;SET one; IF week=3; hamd_3 = hamd; RUN;
DATA t4;SET one; IF week=4; hamd_4 = hamd; RUN;
DATA t5;SET one; IF week=5; hamd_5 = hamd; RUN;
DATA comp (KEEP=id hamd_0-hamd_5 Endog);
     MERGE t0 t1 t2 t3 t4 t5; BY id;
RUN;

* get a sorted dataset by group;
DATA SortData;
     SET comp;
PROC SORT;
BY Endog;
RUN;
```



```
* Descriptives across time by group;
PROC MEANS DATA=SortData;
VAR hamd_0-hamd_5;
BY Endog; FORMAT Endog Endog. ;
RUN;

* Pairwise deleted correlation matrix;
PROC CORR DATA=comp;
VAR hamd_0-hamd_5;
RUN;

* Listwise deleted correlation matrix;
PROC CORR NOMISS DATA=comp;
VAR hamd_0-hamd_5;
RUN;
```

The SAS System

------------------------------------- Endog=NonEndog --------------------------------------

The MEANS Procedure

Variable	N	Mean	Std Dev	Minimum	Maximum
hamd_0	28	22.7857143	4.1218222	15.0000000	33.0000000
hamd_1	29	20.4827586	3.8323873	11.0000000	27.0000000
hamd_2	28	17.0000000	4.3461349	10.0000000	28.0000000
hamd_3	29	15.3448276	6.1718014	0	26.0000000
hamd_4	29	12.6206897	6.7210426	0	28.0000000
hamd_5	27	11.2222222	6.3387291	1.0000000	29.0000000

--------------------------------------- Endog=Endog ---------------------------------------

Variable	N	Mean	Std Dev	Minimum	Maximum
hamd_0	33	24.0000000	4.8476799	17.0000000	34.0000000
hamd_1	34	23.0000000	5.0990195	15.0000000	39.0000000
hamd_2	37	19.2972973	6.0821454	10.0000000	33.0000000
hamd_3	36	17.2777778	6.5622780	7.0000000	32.0000000
hamd_4	34	14.4705882	7.1657235	2.0000000	34.0000000
hamd_5	31	12.5806452	7.9572784	0	33.0000000

The SAS System

The CORR Procedure

6 Variables: hamd_0 hamd_1 hamd_2 hamd_3 hamd_4 hamd_5

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
hamd_0	61	23.44262	4.53330	1430	15.00000	34.00000
hamd_1	63	21.84127	4.69800	1376	11.00000	39.00000
hamd_2	65	18.30769	5.48556	1190	10.00000	33.00000
hamd_3	65	16.41538	6.41505	1067	0	32.00000
hamd_4	63	13.61905	6.97097	858.00000	0	34.00000
hamd_5	58	11.94828	7.21942	693.00000	0	33.00000

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	hamd_0	hamd_1	hamd_2	hamd_3	hamd_4	hamd_5
hamd_0	1.00000	0.49299	0.41007	0.33310	0.22677	0.18382
		<.0001	0.0011	0.0093	0.0869	0.1876
	61	58	60	60	58	53
hamd_1	0.49299	1.00000	0.49433	0.41229	0.30825	0.21792
	<.0001		<.0001	0.0009	0.0157	0.1100
	58	63	62	62	61	55
hamd_2	0.41007	0.49433	1.00000	0.73777	0.66854	0.46076
	0.0011	<.0001		<.0001	<.0001	0.0003
	60	62	65	64	62	57
hamd_3	0.33310	0.41229	0.73777	1.00000	0.81701	0.56809
	0.0093	0.0009	<.0001		<.0001	<.0001
	60	62	64	65	62	57
hamd_4	0.22677	0.30825	0.66854	0.81701	1.00000	0.65435
	0.0869	0.0157	<.0001	<.0001		<.0001
	58	61	62	62	63	55
hamd_5	0.18382	0.21792	0.46076	0.56809	0.65435	1.00000
	0.1876	0.1100	0.0003	<.0001	<.0001	
	53	55	57	57	55	58

The SAS System

The CORR Procedure

6 Variables: hamd_0 hamd_1 hamd_2 hamd_3 hamd_4 hamd_5

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
hamd_0	46	23.15217	4.40690	1065	15.00000	33.00000
hamd_1	46	21.82609	4.92298	1004	11.00000	39.00000
hamd_2	46	18.06522	5.17430	831.00000	10.00000	30.00000
hamd_3	46	16.60870	6.30512	764.00000	0	29.00000
hamd_4	46	13.45652	6.77809	619.00000	0	28.00000
hamd_5	46	12.15217	7.57178	559.00000	0	33.00000

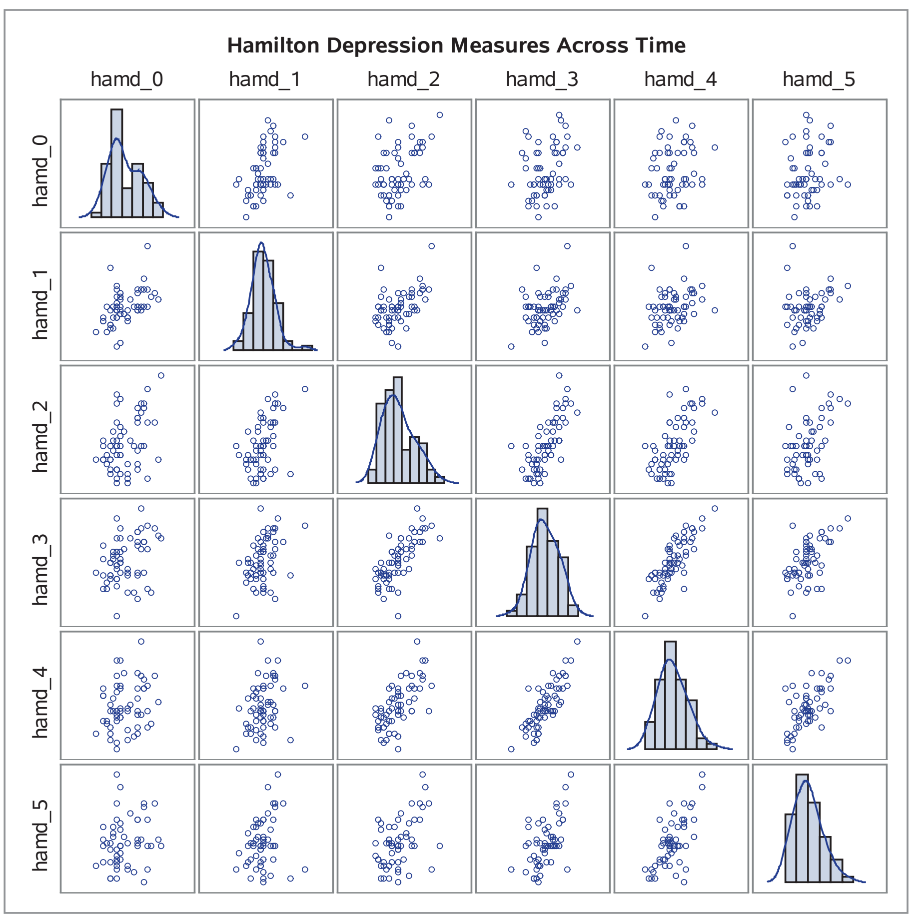
Pearson Correlation Coefficients, N = 46
Prob > |r| under H0: Rho=0

	hamd_0	hamd_1	hamd_2	hamd_3	hamd_4	hamd_5
hamd_0	1.00000	0.49393	0.41764	0.44446	0.30339	0.22106
		0.0005	0.0039	0.0020	0.0404	0.1398
hamd_1	0.49393	1.00000	0.49248	0.51322	0.34740	0.22727
	0.0005		0.0005	0.0003	0.0180	0.1288
hamd_2	0.41764	0.49248	1.00000	0.73099	0.68027	0.52724
	0.0039	0.0005		<.0001	<.0001	0.0002
hamd_3	0.44446	0.51322	0.73099	1.00000	0.77956	0.62268
	0.0020	0.0003	<.0001		<.0001	<.0001
hamd_4	0.30339	0.34740	0.68027	0.77956	1.00000	0.72302
	0.0404	0.0180	<.0001	<.0001		<.0001
hamd_5	0.22106	0.22727	0.52724	0.62268	0.72302	1.00000
	0.1398	0.1288	0.0002	<.0001	<.0001	

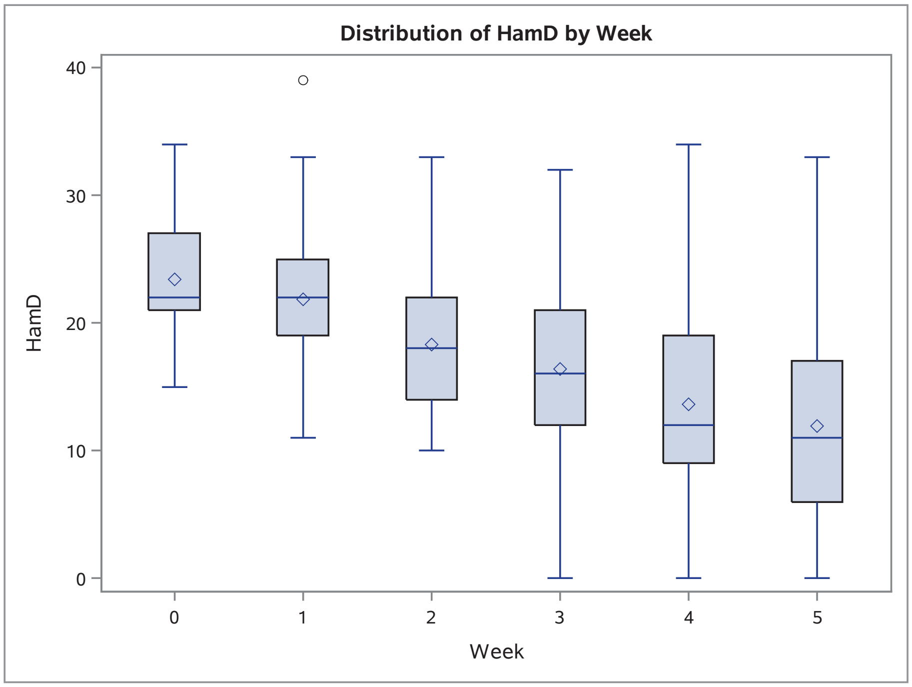
SAS plots of longitudinal data: riesbyplot.sas

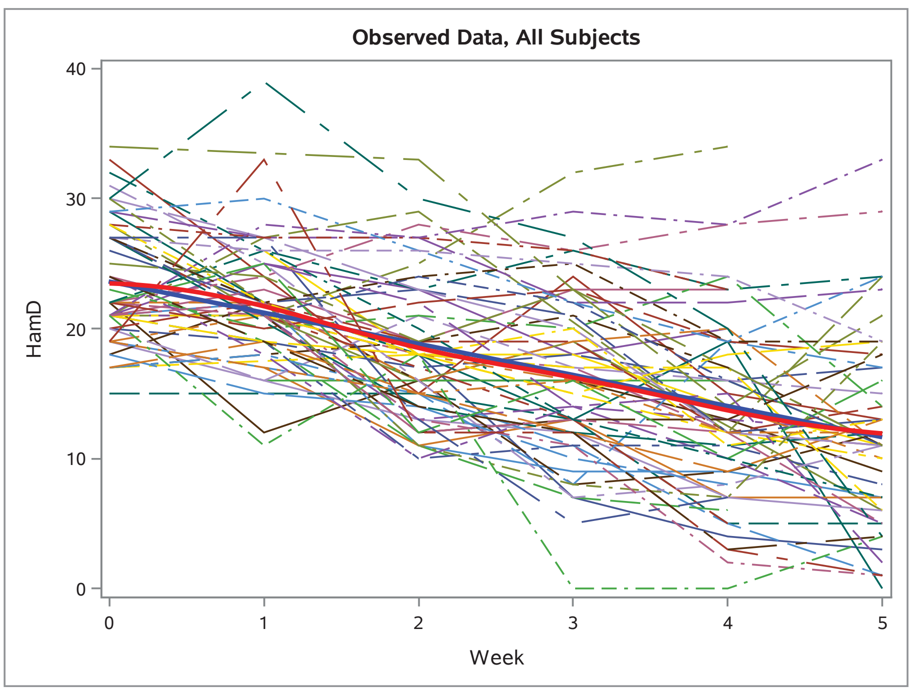
```
* Spaghetti plots and more for the Riesby dataset;

DATA one;
  INFILE 'u:\SAS_long\RIESBY.DAT.txt';
  INPUT id HamD Intcpt Week Endog EndWeek ;

* get the data in multivariate format for a matrix plot;
PROC SORT; BY id;RUN;
DATA t0;SET one; IF week=0; hamd_0 = hamd; RUN;
DATA t1;SET one; IF week=1; hamd_1 = hamd; RUN;
DATA t2;SET one; IF week=2; hamd_2 = hamd; RUN;
DATA t3;SET one; IF week=3; hamd_3 = hamd; RUN;
DATA t4;SET one; IF week=4; hamd_4 = hamd; RUN;
DATA t5;SET one; IF week=5; hamd_5 = hamd; RUN;
DATA comp (KEEP=id hamd_0-hamd_5);
     MERGE t0 t1 t2 t3 t4 t5; BY id;
RUN;

* get a sorted dataset by Week for Box plots;
DATA SortData;
     SET one;
PROC SORT;
BY Week;
RUN;
```

```
* plot specifications;
OPTIONS ORIENTATION=LANDSCAPE; ODS GRAPHICS ON;
ODS PDF FILE="u:\SAS_long\RIESBYplot2.pdf";

* matrix plot;
  TITLE 'Hamilton Depression Measures Across Time';
  PROC SGSCATTER DATA=comp;
  MATRIX hamd_0-hamd_5 / DIAGONAL=(HISTOGRAM KERNEL);

* box plots across time;
  TITLE 'Box Plot for Hamilton Depression Measures Across Time';
  PROC BOXPLOT DATA=SortData;
  PLOT HamD*Week / BOXSTYLE=SCHEMATIC;

* spaghetti, regression, and spline plots;
  TITLE 'Observed Data, All Subjects';
  PROC SGPLOT NOAUTOLEGEND DATA=one;
  * observed trends;
  SERIES X=Week Y=HamD / GROUP = id LINEATTRS = (THICKNESS=1);
  *overall linear ;
  REG X=Week Y=HamD / NOMARKERS LINEATTRS = (COLOR=BLUE PATTERN=1 THICKNESS=3);
  *overall spline;
  PBSPLINE X=Week Y=HamD / NOMARKERS LINEATTRS = (COLOR=RED THICKNESS=3);

ODS PDF CLOSE; ODS GRAPHICS OFF;
```

Box Plot for Hamilton Depression Measures Across Time





Examination of HD across all weeks

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

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

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

Within-subjects and between-subjects components

Within-subjects model

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

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

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 change
υ_{0i} = individual deviation from average intercept
υ_{1i} = individual deviation from average weekly change

Stata example: riesbymu.do

```
cd "u:\Stata_long\"
log using riesbymu.log, replace
infile  id hamd intcpt week endog endweek ///
     using RIESBY.DAT.txt, clear
* remove observations with missing hamd
drop if mi(hamd)
summarize

* random intercept model
mixed hamd week  || id: , mle

* random intercept and trend model
mixed hamd week  || id: week, covariance(unstructured) mle
```



```
. * random intercept model
. mixed hamd week  || id: , mle

Mixed-effects ML regression                     Number of obs     =        375
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          4
                                                              avg =        5.7
                                                              max =          6

                                                Wald chi2(1)      =     309.80
Log likelihood = -1142.5944                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        hamd |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.375652   .1349712   -17.60   0.000     -2.64019   -2.111113
       _cons |   23.55177    .638549    36.88   0.000     22.30024    24.80331
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                  var(_cons) |   16.15554   3.410245      10.68176    24.43431
-----------------------------+------------------------------------------------
               var(Residual) |   19.03753   1.531582      16.26039    22.28899
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 114.52        Prob >= chibar2 = 0.0000
```

- Random intercept model implies a compound symmetry (CS) structure for $\Sigma_{\boldsymbol{y}_i}$
- variance $= 19.04 + 16.16 = 35.2$ at every timepoint
- covariance $= 16.16$ for all pairwise associations of repeated measures

Intraclass correlation (ICC)

$$ICC = \frac{16.16}{16.16 + 19.04} = .46$$

- average pairwise correlation of repeated measures $= .46$
- proportion of (unexplained) variation at the subject level is 46%

```
. * random intercept and trend model
. mixed hamd week  || id: week, covariance(unstructured) mle

Log likelihood = -1109.5188                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        hamd |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.377067   .2086458   -11.39   0.000    -2.786005   -1.968129
       _cons |   23.57695   .5455452    43.22   0.000      22.5077     24.6462
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                  var(week) |   2.078992   .5165809      1.277465    3.383424
                 var(_cons) |    12.6293    3.52744      7.305228    21.83359
           cov(week,_cons) |  -1.420933   1.037669     -3.454727     .612862
-----------------------------+------------------------------------------------
              var(Residual) |   12.21663   1.119004      10.20902    14.61904
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 180.67                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```


Model comparisons - Likelihood Ratio (LR) tests

- comparing random intercept model to simple linear regression

  `LR test vs.  linear model:  chibar2(01) = 114.52 Prob >= chibar2 = 0.0000`

  $H_0 : \sigma_\upsilon^2 = 0, \quad H_A : \sigma_\upsilon^2 > 0 \quad \Rightarrow$ one-sided test

  `chibar2(01)` refers to a 50:50 mixture of a χ_0^2 and a χ_1^2 distribution; chi-bar square distribution; p-value is obtained from χ_1^2, but is halved

- comparing random trend to simple linear regression

  ```
  LR test vs. linear model: chi2(3) = 180.67        Prob > chi2 = 0.0000
  Note: LR test is conservative and provided only for reference.
  ```

  $H_0 : \sigma_{\upsilon_0}^2 = \sigma_{\upsilon_1}^2 = \sigma_{\upsilon_{01}} = 0$

- comparing random trend to random intercept model

  $H_0 : \sigma^2_{\upsilon_1} = \sigma_{\upsilon_{01}} = 0$

  need `chibar2(12)`, 50:50 mixture of a χ^2_1 and a χ^2_2 distribution; p-value is obtained from the average of χ^2_1 and χ^2_2 (i.e., q and $q-1$, where q is the number of (co)variance parameters in the null)

  random intercept model: `Log likelihood = -1142.5944`
  random trend model: `Log likelihood = -1109.5188`

  LR $\chi^2 = -2 \times (-1142.59 - (-1109.52)) = 66.14$; in `Stata`

```
. display chi2tail(1, 66.14)
4.200e-16

. display chi2tail(2, 66.14)
4.344e-15

. display .5*chi2tail(1, 66.14) + .5*chi2tail(2, 66.14)
2.382e-15
```


Heterogeneity in intercepts and slopes

Intercept heterogeneity expressed as 95% plausible value range

$$\hat{\beta}_0 \pm 1.96 \times \hat{\sigma}_{\upsilon_0} \;=\; 23.58 \pm 1.96 \times \sqrt{12.63} \;=\; (16.61, 30.55)$$

Slope heterogeneity expressed as 95% plausible value range

$$\hat{\beta}_1 \pm 1.96 \times \hat{\sigma}_{\upsilon_1} \;=\; -2.38 \pm 1.96 \times \sqrt{2.08} \;=\; (-5.21, 0.45)$$

$\Rightarrow$ A great deal of subject heterogeneity in terms of initial level of depression and change over time in depression (the mean response doesn't tell the whole story)

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
observed	23.44	21.84	18.31	16.42	13.62	11.95
estimated	$\hat{\beta}_0$	$\hat{\beta}_0 + \hat{\beta}_1$	$\hat{\beta}_0 + 2\hat{\beta}_1$	$\hat{\beta}_0 + 3\hat{\beta}_1$	$\hat{\beta}_0 + 4\hat{\beta}_1$	$\hat{\beta}_0 + 5\hat{\beta}_1$
	23.58	21.21	18.82	16.45	14.07	11.69

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

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

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

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

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

Stata mata file: riesby_mataest.do

```
* Riesby random intercept and trend model
cd "u:\Stata_long\"
log using riesby_mataest.log, replace
mata
/* beta estimates and covariate matrix for intercept and week */
beta = (23.57695 \  -2.377067 )
xmat = (1, 0 \
        1, 1 \
        1, 2 \
        1, 3 \
        1, 4 \
        1, 5)
xbeta = xmat*beta
/* estimate means across time */
xbeta
```



```
/* variance-covariance estimates */
vare = 12.21663
varu = (12.6293, -1.420933 \
      -1.420933,  2.078992)
zmat = xmat
vary = zmat * varu * zmat' + vare * I(6)
vary

/* get CIs for int and slope */
int_lo = beta[1,1] - invnormal(.975)*sqrt(varu[1,1])
int_hi = beta[1,1] + invnormal(.975)*sqrt(varu[1,1])
int_lo, int_hi
slope_lo = beta[2,1] - invnormal(.975)*sqrt(varu[2,2])
slope_hi = beta[2,1] + invnormal(.975)*sqrt(varu[2,2])
slope_lo, slope_hi

/* end mata session */
end
log close
```

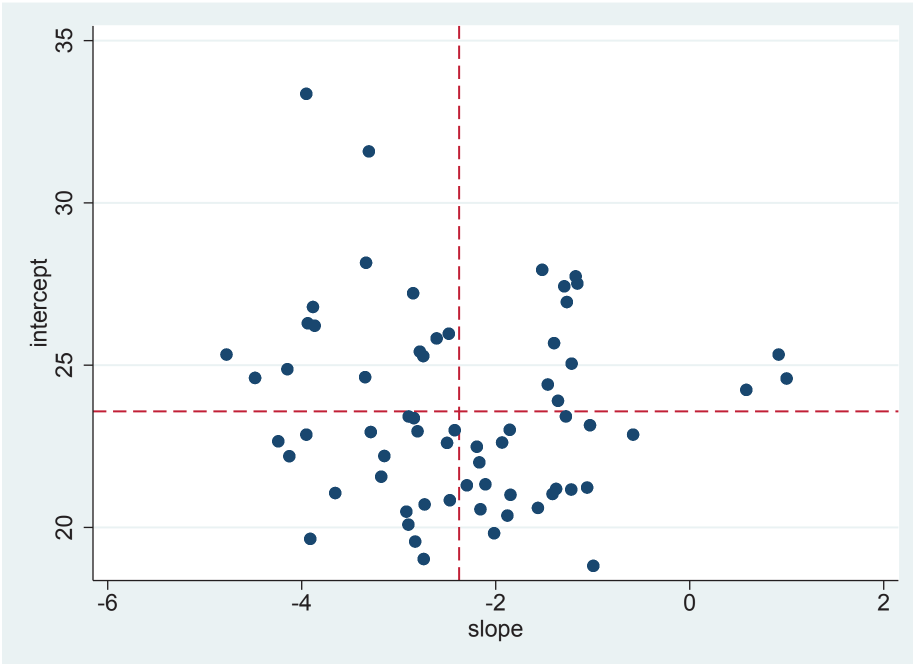
Empirical Bayes estimates of random effects: from `riesbymu.do`

```
* obtain the random effects for each subject
predict u1 u0, reffects

* list the random effects for the first few subjects
by id, sort: generate tolist = (_n==1)
list id u0 u1 in 1/30 if tolist

     +-----------------------------+
     |  id          u0          u1 |
     |-----------------------------|
  1. | 101    1.029755   -2.103769 |
  7. | 103    3.639485   -.4744411 |
 13. | 104    2.639233   -1.489337 |
 19. | 105    -3.01689    .2199695 |
 25. | 106    .3248745    1.019122 |
 30. | 107   -.6143847    -.428573 |
     +-----------------------------+
```

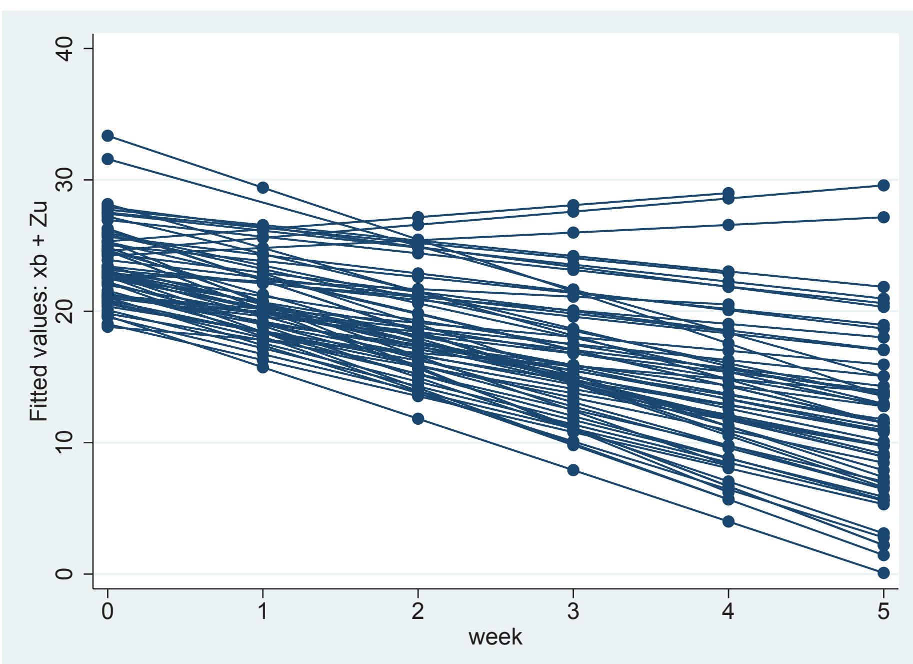


```
* add random and fixed effects together, list out a few
generate intercept = _b[_cons] + u0
generate slope = _b[week] + u1
list id intercept slope in 1/30 if tolist

     +----------------------------+
     |  id   interc~t       slope |
     |----------------------------|
  1. | 101    24.6067   -4.480836 |
  7. | 103   27.21643   -2.851508 |
 13. | 104   26.21618   -3.866404 |
 19. | 105   20.56006   -2.157098 |
 25. | 106   23.90182   -1.357945 |
 30. | 107   22.96256    -2.80564 |
     +----------------------------+
```

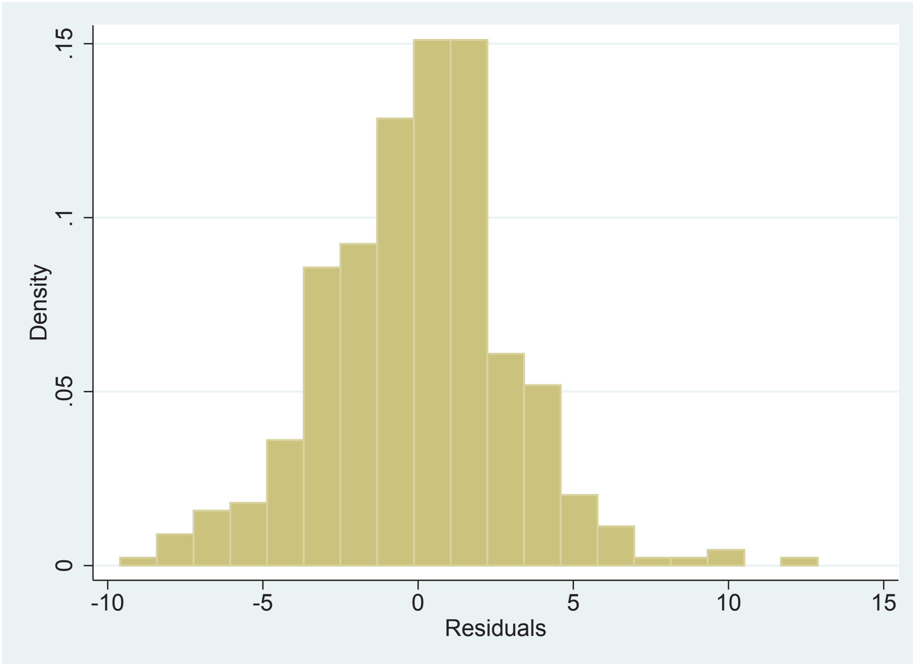
```
* plot subjects intercepts and slopes
local yref = _b[_cons]
local xref = _b[week]
twoway scatter intercept slope, yline(‘yref’, lpattern(dash)) ///
       xline(‘xref’, lpattern(dash))
```




```
* generate an estimated spaghetti plot
predict fithamd, fitted
sort id week
twoway connected fithamd week, connect(L)
```



```
* residual plot
predict resids, residuals
twoway histogram resids
```



SAS example: from `riesbym.sas`

```
TITLE1 'Analysis of Riesby data - HDRS scores across time';

DATA ONE;
  INFILE 'c:\SAS_long\RIESBY.DAT.txt';
  INPUT ID HamD Intcpt Week Endog EndWeek ;

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';
```

Analysis of Riesby data - HDRS scores across time
Random trend model

The Mixed Procedure

Model Information

Data Set	WORK.ONE
Dependent Variable	HamD
Covariance Structure	Unstructured
Subject Effect	ID
Estimation Method	ML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
ID	66	101 103 104 105 106 107 108 113 114 115 117 118 120 121 123 302 303 304 305 308 309 310 311 312 313 315 316 318 319 322 327 328 331 333 334 335 337 338 339 344 345 346 347 348 349 350 351 352 353 354 355 357 360 361 501 502 504 505 507 603 604 606 607 608 609 610

Dimensions

Covariance Parameters	4
Columns in X	2
Columns in Z Per Subject	2
Subjects	66
Max Obs Per Subject	6

Number of Observations

Number of Observations Read	396
Number of Observations Used	375
Number of Observations Not Used	21

Iteration History

Iteration	Evaluations	-2 Log Like	Criterion
0	1	2399.71226762	
1	2	2219.30726751	0.00031526
2	1	2219.04369935	0.00000794
3	1	2219.03751634	0.00000001

Convergence criteria met.

Estimated G Matrix

Row	Effect	ID	Col1	Col2
1	Intercept	101	12.6280	-1.4197
2	Week	101	-1.4197	2.0779

Estimated G Correlation Matrix

Row	Effect	ID	Col1	Col2
1	Intercept	101	1.0000	-0.2771
2	Week	101	-0.2771	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error	Z Value	Pr Z
UN(1,1)	ID	12.6280	3.5272	3.58	0.0002
UN(2,1)	ID	-1.4197	1.0372	-1.37	0.1711
UN(2,2)	ID	2.0779	0.5162	4.03	<.0001
Residual		12.2177	1.1191	10.92	<.0001

Fit Statistics

-2 Log Likelihood	2219.0
AIC (smaller is better)	2231.0
AICC (smaller is better)	2231.3
BIC (smaller is better)	2244.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	180.67	<.0001

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	23.5769	0.5455	65	43.22	<.0001
Week	-2.3771	0.2086	65	-11.39	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Week	1	65	129.84	<.0001

SAS example: from `riesbym2.sas`

```
OPTIONS NOCENTER;
TITLE1 'analysis of riesby data - empirical bayes estimates';

DATA one;
  INFILE 'c:\SAS_long\riesby.dat.txt';
  INPUT id hamd intcpt week endog endweek ;

PROC MIXED METHOD=ML COVTEST;
  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';
  RUN;

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



```
analysis of riesby data - empirical bayes estimates
random trend model
```

Obs	Effect	id	Estimate	StdErr Pred	DF	tValue	Probt
1	Intercept	101	1.0290	2.0432	243	0.50	0.6150
2	week	101	-2.1035	0.6995	243	-3.01	0.0029
3	Intercept	103	3.6392	2.0432	243	1.78	0.0761
4	week	103	-0.4743	0.6995	243	-0.68	0.4983
5	Intercept	104	2.6386	2.0432	243	1.29	0.1978
6	week	104	-1.4891	0.6995	243	-2.13	0.0343
7	Intercept	105	-3.0167	2.0432	243	-1.48	0.1411
8	week	105	0.2199	0.6995	243	0.31	0.7535
9	Intercept	106	0.3253	2.0868	243	0.16	0.8763
10	week	106	1.0189	0.8492	243	1.20	0.2314
11	Intercept	107	-0.6145	2.0435	243	-0.30	0.7639
12	week	107	-0.4285	0.7495	243	-0.57	0.5680
13	Intercept	108	-2.0124	2.0432	243	-0.98	0.3257
14	week	108	-0.8032	0.6995	243	-1.15	0.2520
15	Intercept	113	-0.7157	2.0868	243	-0.34	0.7319
16	week	113	1.7931	0.8492	243	2.11	0.0358
17	Intercept	114	-3.0895	2.4736	243	-1.25	0.2129
18	week	114	-0.5436	0.7853	243	-0.69	0.4894

```
/* 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;
RUN;
```



```
analysis of riesby data - empirical bayes estimates
random trend model
```

Obs	id	hamd_0	hamd_1	hamd_2	hamd_3	hamd_4	hamd_5
1	101	26	22	18	7	4	3
2	103	33	24	15	24	15	13
3	104	29	22	18	13	19	0
4	105	22	12	16	16	13	9
5	106	21	25	23	18	20	.
6	107	21	21	16	19	.	6
7	108	21	22	11	9	9	7
8	113	21	23	19	23	23	.
9	114	.	17	11	13	7	7
10	115	.	16	16	16	16	11
11	117	19	16	13	12	7	6
12	118	.	26	18	18	14	11
13	120	20	19	17	18	16	17
14	121	20	22	19	19	12	14
15	123	15	15	15	13	5	5
16	302	18	22	16	8	9	12
17	303	21	21	13	14	10	5
18	304	21	27	29	.	12	24

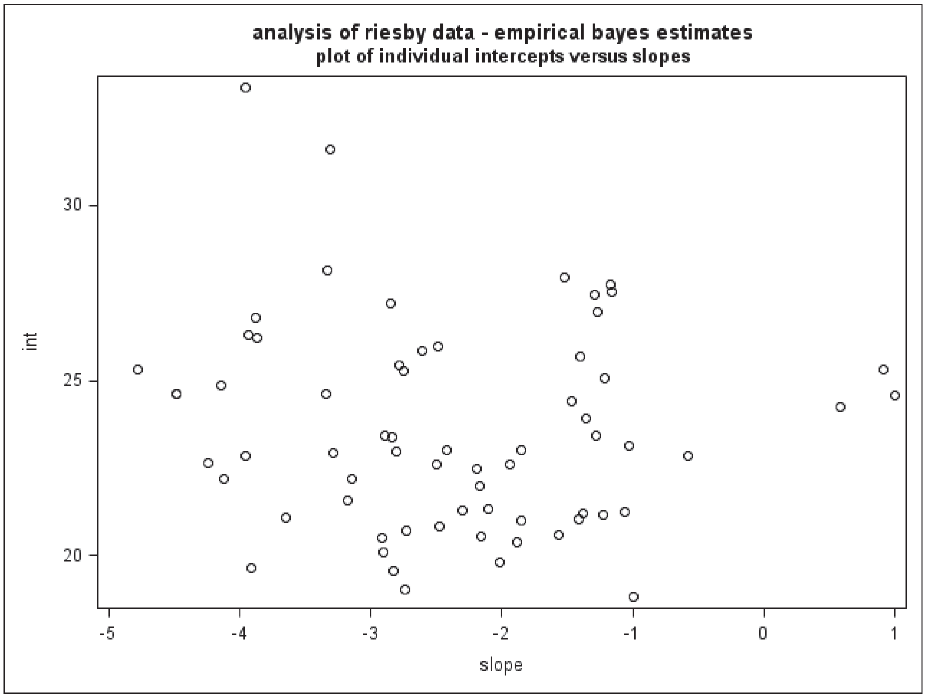
```
/* extract the intercepts and slopes for each person */
/* and compute the estimated hamd values across time */
PROC SORT DATA=randest; BY id;
DATA randest2 (KEEP=id intdev slopedev int slope hdest_0-hdest_5);

     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;
RUN;
```



```
analysis of riesby data - empirical bayes estimates
random trend model
```

Obs	id	hdest_0	hdest_1	hdest_2	hdest_3	hdest_4	hdest_5
1	101	24.6059	20.1253	15.6448	11.1642	6.6837	2.2031
2	103	27.2161	24.3646	21.5132	18.6618	15.8104	12.9590
3	104	26.2155	22.3493	18.4831	14.6169	10.7508	6.8846
4	105	20.5602	18.4030	16.2458	14.0886	11.9314	9.7742
5	106	23.9022	22.5440	21.1858	19.8276	18.4694	17.1113
6	107	22.9624	20.1568	17.3512	14.5456	11.7399	8.9343
7	108	21.5645	18.3843	15.2040	12.0238	8.8435	5.6632
8	113	22.8612	22.2772	21.6931	21.1091	20.5251	19.9410
9	114	20.4874	17.5667	14.6460	11.7253	8.8046	5.8838
10	115	21.0060	19.1583	17.3106	15.4629	13.6152	11.7675
11	117	20.0882	17.1882	14.2883	11.3883	8.4884	5.5884
12	118	25.4181	22.6361	19.8540	17.0719	14.2899	11.5078
13	120	21.1695	19.9480	18.7265	17.5051	16.2836	15.0621
14	121	22.6175	20.6830	18.7485	16.8140	14.8795	12.9450
15	123	19.0273	16.2849	13.5426	10.8003	8.0580	5.3156
16	302	20.8385	18.3656	15.8927	13.4198	10.9469	8.4740
17	303	22.2019	19.0539	15.9060	12.7581	9.6101	6.4622
18	304	25.0481	23.8303	22.6126	21.3948	20.1771	18.9594

```
PROC SGPLOT  DATA=randest2;
     SCATTER X=slope Y=int;
     TITLE2 'plot of individual intercepts versus slopes';
RUN;
```



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

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

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

from `riesbymu.do`

```
* model with endog & endweek
mixed hamd week endog endweek || id: week, covariance(unstructured)
lincom endog + 5*endweek
```

```
Mixed-effects ML regression                     Number of obs     =        375
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          4
                                                              avg =        5.7
                                                              max =          6

                                                Wald chi2(3)      =     134.15
Log likelihood = -1107.4646                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        hamd |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.365687   .3118099    -7.59   0.000    -2.976824   -1.754551
       endog |   1.988021   1.069048     1.86   0.063    -.1072754    4.083317
     endweek |  -.0270557   .4194729    -0.06   0.949    -.8492075    .7950961
       _cons |   22.47626   .7943462    28.30   0.000     20.91937    24.03315
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.077071    .516252      1.276107    3.380772
                  var(_cons) |   11.64121   3.359115      6.612731    20.49347
            cov(week,_cons) |   -1.40161   1.016047     -3.393025    .5898043
-----------------------------+------------------------------------------------
               var(Residual) |   12.21847   1.119248      10.21044    14.62142
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 175.51               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

. lincom endog + 5*endweek

 ( 1)  [hamd]endog + 5*[hamd]endweek = 0

------------------------------------------------------------------------------
        hamd |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.852742   1.868687     0.99   0.321    -1.809817    5.515302
------------------------------------------------------------------------------
```

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

Linear Transforms: `lincom in Stata`

Fixed part of model:

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

in terms of the Endogenous group effect

$$(\hat{\beta}_2 + \hat{\beta}_3 Week) Endog$$

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

$$\hat{\beta}_2 + 5\hat{\beta}_3$$

$H_0 : \beta_2 + 5\beta_3 = 0$; null that groups are equivalent at the study's end

$$z = \frac{\hat{\beta}_2 + 5\hat{\beta}_3}{SE(\hat{\beta}_2 + 5\hat{\beta}_3)}$$

Linear Transforms: from `riesbym2.sas`

```
PROC MIXED METHOD=ML COVTEST;
  CLASS id;
  MODEL hamd = week ENDOG ENDWEEK /SOLUTION;
  RANDOM INTERCEPT week /SUB=id TYPE=UN G GCORR;
  ESTIMATE 'grp diff at week 5' endog 1 endweek 5;
```

```
                                         Estimates

                                         Standard
Label                     Estimate          Error       DF     t Value     Pr > |t|

grp diff at week 5          1.8527         1.8685      243        0.99       0.3224
```


Riesby data - model fit by diagnosis

	wk 0	wk 1	wk 2	wk 3	wk 4	wk 5
Non-Endogenous group ($DX_i = 0$)						
N	28	29	28	29	29	27
observed	22.8	20.5	17.0	15.3	12.6	11.2
estimated	$\hat{\beta}_0$	$\hat{\beta}_0 + \hat{\beta}_1$	$\hat{\beta}_0 + 2\hat{\beta}_1$	$\hat{\beta}_0 + 3\hat{\beta}_1$	$\hat{\beta}_0 + 4\hat{\beta}_1$	$\hat{\beta}_0 + 5\hat{\beta}_1$
	22.5	20.1	17.7	15.4	13.0	10.6
Endogenous group ($DX_i = 1$)						
N	33	34	37	36	34	31
observed	24.0	23.0	19.3	17.3	14.5	12.6
estimated	$(\hat{\beta}_0 + \hat{\beta}_2)$	$(\hat{\beta}_0 + \hat{\beta}_2)$ $+(\hat{\beta}_1 + \hat{\beta}_3)$	$(\hat{\beta}_0 + \hat{\beta}_2)$ $+2(\hat{\beta}_1 + \hat{\beta}_3)$	$(\hat{\beta}_0 + \hat{\beta}_2)$ $+ 3(\hat{\beta}_1 + \hat{\beta}_3)$	$(\hat{\beta}_0 + \hat{\beta}_2)$ $+4(\hat{\beta}_1 + \hat{\beta}_3)$	$(\hat{\beta}_0 + \hat{\beta}_2)$ $+ 5(\hat{\beta}_1 + \hat{\beta}_3)$
	24.5	22.1	19.7	17.3	14.9	12.5

Model estimates by diagnosis: riesby_mataest2.do

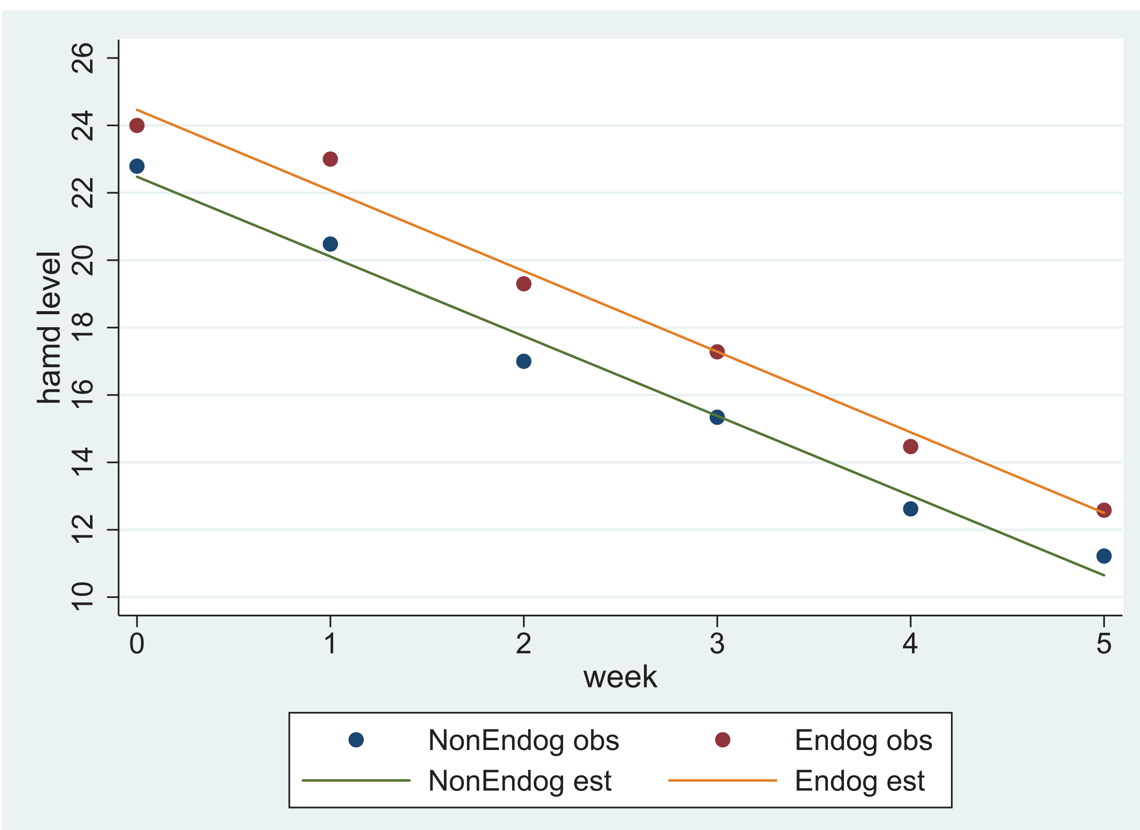
```
* Riesby random int and trend model with endog & endweek
cd "u:\Stata_long\"
log using riesby_mataest2.log, replace
mata
/* beta estimates and covariate matrices for both groups */
beta = (22.47626 \  -2.365687 \ 1.988021 \ -0.0270557 )
xmat0 =(1, 0, 0, 0  \
        1, 1, 0, 0  \
        1, 2, 0, 0  \
        1, 3, 0, 0  \
        1, 4, 0, 0  \
        1, 5, 0, 0 )
xmat1 =(1, 0, 1, 0  \
        1, 1, 1, 1  \
        1, 2, 1, 2  \
        1, 3, 1, 3  \
        1, 4, 1, 4  \
        1, 5, 1, 5 )
xbeta0 = xmat0*beta
xbeta1 = xmat1*beta
/* mean estimates across time */
xbeta0, xbeta1
/* end mata session */
end
```



```
: /* mean estimates across time */
: xbeta0, xbeta1
                1             2
    +---------------------------+
  1 |    22.47626    24.464281  |
  2 |   20.110573   22.0715383  |
  3 |   17.744886   19.6787956  |
  4 |   15.379199   17.2860529  |
  5 |   13.013512   14.8933102  |
  6 |   10.647825   12.5005675  |
    +---------------------------+
```

Stata example: riesby_obsest_plot.do

```
* graphing observed and estimated means
* observed means from riesbydesc.log
* estimated means from riesby_mataest2.log
input obs_est week hamd_end0 hamd_end1
1  0 22.79      24.00
1  1 20.48      23.00
1  2 17.00      19.30
1  3 15.34      17.28
1  4 12.62      14.47
1  5 11.22      12.58
2  0 22.47626    24.464281
2  1 20.110573   22.0715383
2  2 17.744886   19.6787956
2  3 15.379199   17.2860529
2  4 13.013512   14.8933102
2  5 10.647825   12.5005675
end
twoway (scatter hamd_end0 hamd_end1 week if obs_est==1)  ///
       (line    hamd_end0 hamd_end1 week if obs_est==2), ///
       ylabel(10(2)26) xlabel(0(1)5) ///
       legend(label(1 "observed") label(2 "estimated")) ///
       ytitle("hamd level", size(medium)) ///
       xtitle("week", size(medium))
```

from riesbymu.do

```
* model with just endog & week
mixed hamd week endog   || id: week, covariance(unstructured) mle


Mixed-effects ML regression                     Number of obs      =       375
Group variable: id                              Number of groups   =        66

                                                Obs per group:
                                                              min =          4
                                                              avg =        5.7
                                                              max =          6

                                                Wald chi2(2)       =    134.13
Log likelihood = -1107.4667                     Prob > chi2        =    0.0000

------------------------------------------------------------------------------
        hamd |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.380637   .2085862   -11.41   0.000    -2.789459   -1.971816
       endog |   1.956503    .950826     2.06   0.040     .0929184    3.820088
       _cons |   22.49344   .7483852    30.06   0.000     21.02663    23.96025
------------------------------------------------------------------------------
```



```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.077392   .5162788      1.276368    3.381126
                  var(_cons) |   11.64177   3.359196      6.613137    20.49418
            cov(week,_cons) |  -1.402036    1.01611     -3.393576    .5895036
-----------------------------+------------------------------------------------
               var(Residual) |   12.21833   1.119219      10.21034    14.62121
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 175.52                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

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

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

b_{0i} = week 0 HD level for patient i
b_{1i} = weekly linear change in HD for patient i
b_{2i} = weekly quadratic change in HD for patient i

Between-subjects models

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

β_0 = average week 0 HD level
β_1 = average HD weekly linear change
β_2 = average HD weekly quadratic change
υ_{0i} = individual deviation from average intercept
υ_{1i} = individual deviation from average linear change
υ_{2i} = individual deviation from average quadratic change

from `riesbymu.do`

```
* model with quadratic effect of week
generate week2 = week*week
mixed hamd week week2 || id: week week2, covariance(unstructured) mle


Mixed-effects ML regression                     Number of obs     =        375
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          4
                                                              avg =        5.7
                                                              max =          6

                                                Wald chi2(2)      =     133.39
Log likelihood = -1103.8239                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        hamd |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.632576   .4789971    -5.50   0.000    -3.571393   -1.693758
       week2 |   .0514812   .0883472     0.58   0.560    -.1216761    .2246385
       _cons |   23.76025   .5520611    43.04   0.000     22.67823    24.84227
------------------------------------------------------------------------------
```



```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   6.638071   2.761359      2.937326     15.0014
                  var(week2) |    .193738   .0936361      .0751309    .4995873
                  var(_cons) |   10.44021   3.586247      5.324992    20.46915
            cov(week,week2) |  -.9364809   .4880525     -1.893046    .0200844
            cov(week,_cons) |   -.915378   2.407786     -5.634552    3.803796
           cov(week2,_cons) |   -.112174   .4208953     -.9371136    .7127656
-----------------------------+------------------------------------------------
               var(Residual) |   10.51598   1.106092      8.556942    12.92352
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 191.92                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Expressing random effect variance-covariance matrix as std devs and correlations

```
mixed hamd week week2 || id: week week2, covariance(unstructured) mle stddev
```

```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   sd(week) |   2.576445   .5358854      1.713863    3.873164
                  sd(week2) |   .4401568   .1063667      .2741001    .7068149
                  sd(_cons) |   3.231132   .5549522      2.307594    4.524285
           corr(week,week2) |  -.8257918   .0850313       -.93525   -.5722005
           corr(week,_cons) |  -.1099575   .2648525     -.5620729    .3927526
          corr(week2,_cons) |  -.0788733   .3108909      -.599385     .488518
-----------------------------+------------------------------------------------
               sd(Residual) |   3.242835    .170544      2.925225     3.59493
------------------------------------------------------------------------------
```

$\Rightarrow$ Large negative association between the linear and quadratic trend components

Testing of quadratic trend (co)variance parameters

from `riesbymu.do`

```
mixed hamd week week2 || id: week, covariance(unstructured) mle
...
Log likelihood =  -1109.313
```

vs

```
mixed hamd week week2 || id: week week2, ///
covariance(unstructured) mle
....
Log likelihood = -1103.8239
```

$H_0 : \sigma^2_{\upsilon_2} = \sigma_{\upsilon_0 \upsilon_2} = \sigma_{\upsilon_1 \upsilon_2} = 0$

LR $\chi^2_3 = -2 \times (-1109.313 - (-1103.8239)) = 10.98$

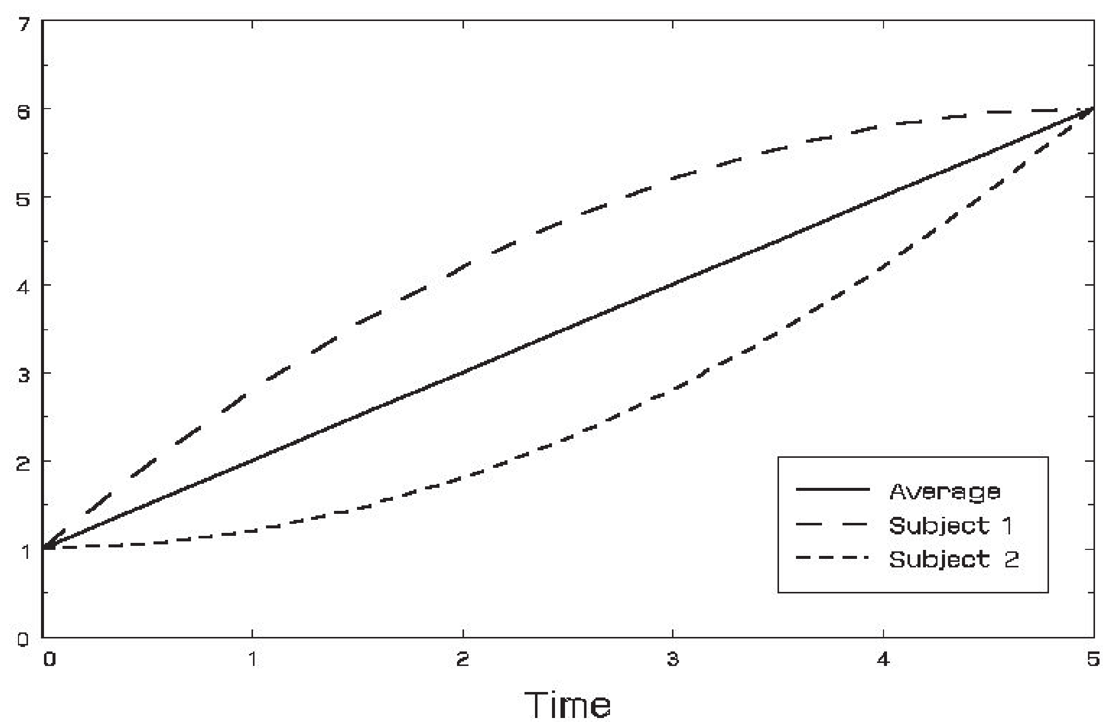
need `chibar2(23)`, 50:50 mixture of a χ^2_2 and a χ^2_3 distribution; p-value is obtained from the average of χ^2_2 and χ^2_3 (i.e., q and $q-1$, where q is the number of (co)variance parameters in the null)

in `Stata`

```
display .5*chi2tail(2, 10.98) + .5*chi2tail(3, 10.98)
.00798118
```

reject $H_0 : \sigma^2_{\upsilon_2} = \sigma_{\upsilon_0\upsilon_2} = \sigma_{\upsilon_1\upsilon_2} = 0$

$\Rightarrow$ taken together with the non-significant result for testing β_2 (coefficient for fixed quadratic effect), evidence for curvilinearity at the individual level, but not at the population level



Average linear and individual quadratic trends

Observed (pairwise) and estimated variance-covariance matrix

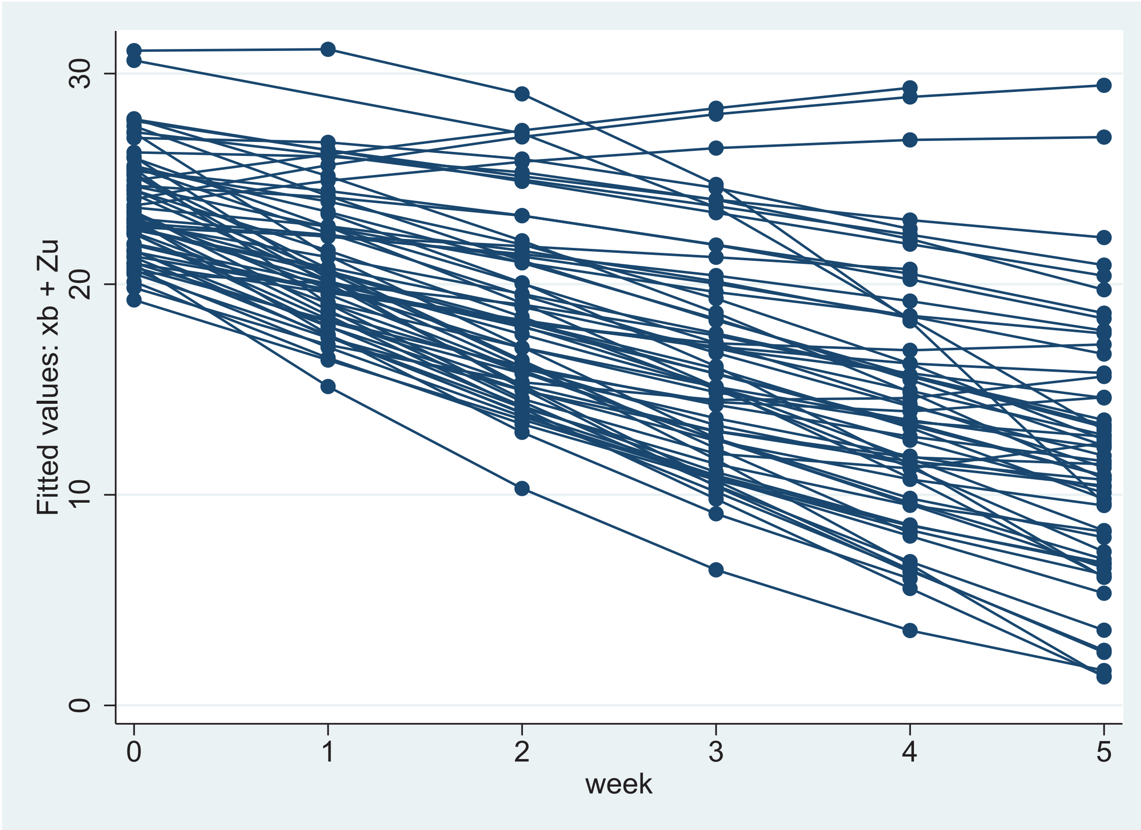
$$\Sigma_{\boldsymbol{y}} = \begin{bmatrix} 20.55 & & & & & \\ 10.50 & 22.07 & & & & \\ 10.20 & 12.74 & 30.09 & & & \\ 9.69 & 12.43 & 25.96 & 41.15 & & \\ 7.17 & 10.10 & 25.56 & 36.54 & 48.59 & \\ 6.02 & 7.39 & 18.25 & 26.31 & 32.93 & 52.12 \end{bmatrix}$$

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

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

Empirical Bayes estimates of Subject Trends: from `riesbymu.do`

```
* model with quadratic effect of week
generate week2 = week*week
mixed hamd week week2 || id: week week2, covariance(unstructured) mle

* generate an estimated spaghetti plot (quadratic model)
predict fithamd_quad, fitted
sort id week
twoway connected fithamd_quad week, connect(L)
```



Time-varying Covariates - WS and BS effects

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

Within-subjects and between-subjects components

Within-subjects model

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

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

Between-subjects models

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

β_0 = average week 2 HD level for drug-free patients
β_1 = average HD weekly improvement
β_2 = average HD difference for unit change in $\ln IMI$
β_3 = average HD difference for unit change in $\ln DMI$
υ_{0i} = individual intercept deviation from model
υ_{1i} = individual slope deviation from model

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

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

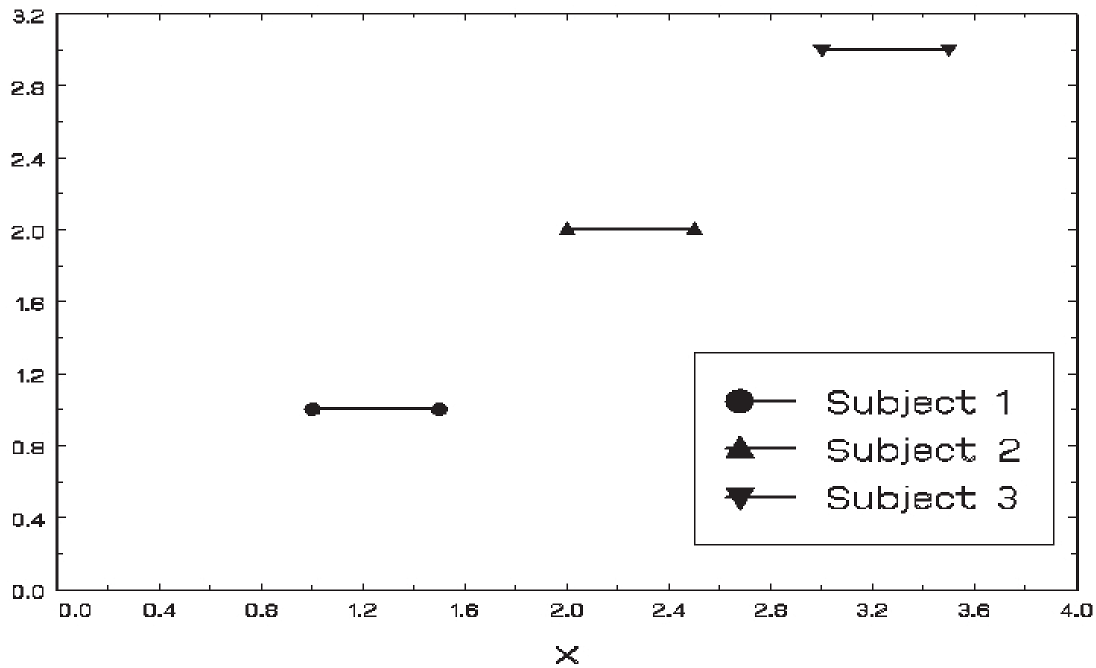
Between-subjects models

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

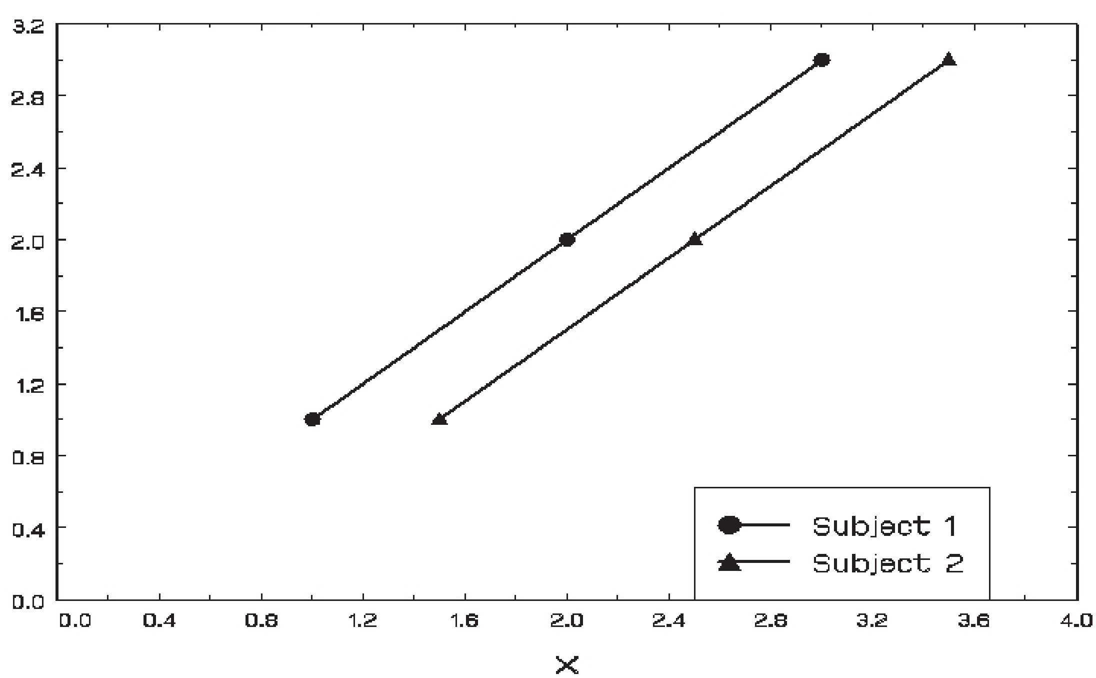
Is the effect of X_{ij} purely within-subjects? What about

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

$\bar{X}_i$ 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 ($\beta_{BS} = \beta_{WS}$)

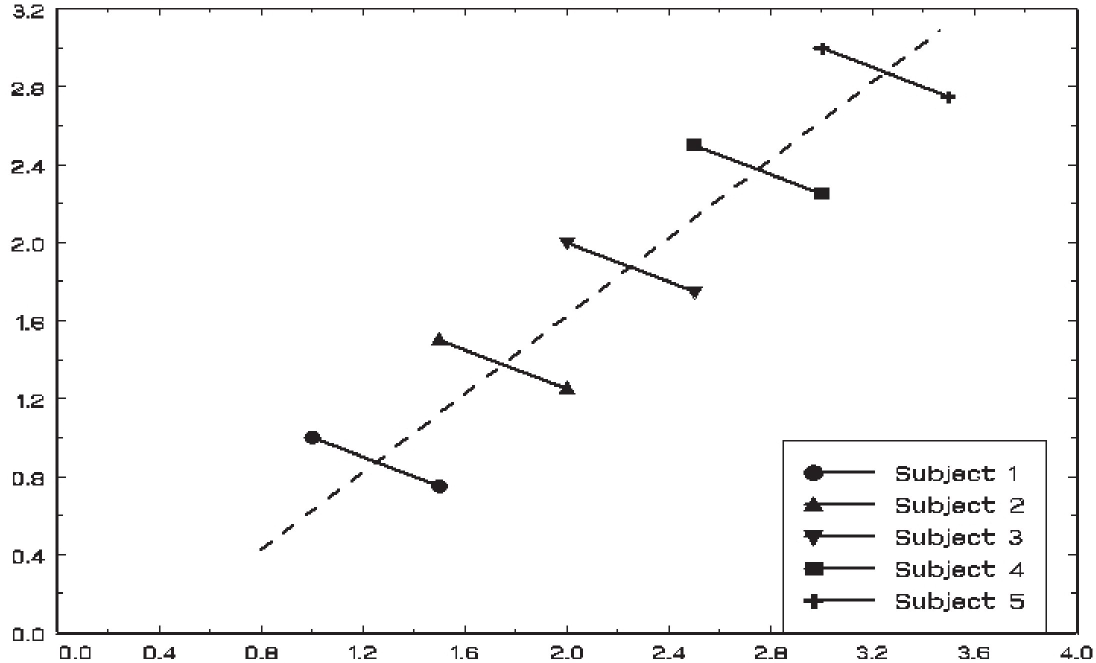
suppose $\beta_{BS} = \beta_{WS} = \beta^*$, then in the model with decomposition,

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

Alternative decomposition of time-varying X_{ij}

Begg & Parides (2003). Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data. *Statistics in Medicine*, 22:2591-2602.

Level-1: Within-subjects model

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

Level-2: Between-subjects model

$$\begin{aligned} a_{0i} &= \alpha_0 + \alpha_{BS\Delta}\bar{X}_i + \gamma_{0i} \\ a_{1i} &= \alpha_1 + \gamma_{1i} \\ a_{2i} &= \alpha_{WS} \end{aligned}$$

- Same model results and $\alpha_{WS} = \beta_{WS}$, but $\alpha_{BS\Delta} \neq \beta_{BS}$

  in previous model, effect of X
  $= \beta_{BS}\bar{X}_i + \beta_{WS}(X_{ij} - \bar{X}_i) = (\beta_{BS} - \beta_{WS})\bar{X}_i + \beta_{WS}X_{ij}$

$\rightarrow \alpha_{BS\Delta} = \beta_{BS} - \beta_{WS}$ difference between BS and WS effects

parameter	estimate	se	$p <$
assuming BS=WS drug effects			
intercept	1.52	3.74	.684
slope	-1.97	0.28	.001
ln IMI	0.63	0.82	.443
ln DMI	-1.97	0.60	.001
deviance = 1498.85			
relaxing BS=WS drug effects			
intercept	7.27	5.04	.149
slope	-2.02	0.29	.001
ln IMI BS	-0.31	1.00	.755
ln DMI BS	-2.37	0.80	.003
ln IMI WS	2.44	1.46	.093
ln DMI WS	-1.80	1.00	.072
deviance = 1495.77			

LR $X_2^2 = 1498.85 - 1495.77 = 3.08 \quad \Rightarrow$ Accept $H_0 : \boldsymbol{\beta}_{BS} = \boldsymbol{\beta}_{WS}$

Stata example: `riesby_BSWS.do`

```
cd "u:\Stata_long\"
log using riesby_BSWS.log, replace
infile id hamdelt intcpt week sex endog lnimi lndmi ///
       using RIESBYT4.DAT.txt, clear
egen lnimi_mean = mean(lnimi), by(id)
egen lndmi_mean = mean(lndmi), by(id)
gen lnimi_dev = lnimi - lnimi_mean
gen lndmi_dev = lndmi - lndmi_mean
summ
* assumming BS=WS effects
mixed hamdelt week lnimi lndmi  || id: week, covariance(unstructured) mle
* not assuming BS=WS effects: usual parameterization
mixed hamdelt week lnimi_mean lndmi_mean  lnimi_dev lndmi_dev ///
  || id: week, covariance(unstructured) mle
* not assuming BS=WS effects: alternative parameterization
mixed hamdelt week lnimi_mean lndmi_mean  lnimi lndmi ///
      || id: week, covariance(unstructured) mle
log close
```

```
. * not assuming BS=WS effects: usual parameterization
. mixed hamdelt week lnimi_mean lndmi_mean  lnimi_dev lndmi_dev ///
>   || id: week, covariance(unstructured) mle

Log likelihood = -747.88476
------------------------------------------------------------------------------
     hamdelt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.023795   .2917128    -6.94   0.000    -2.595541   -1.452048
  lnimi_mean |  -.3129397   1.003714    -0.31   0.755    -2.280182    1.654303
  lndmi_mean |  -2.366923   .7963101    -2.97   0.003    -3.927662   -.8061838
   lnimi_dev |   2.443656   1.456049     1.68   0.093    -.4101479     5.29746
   lndmi_dev |  -1.796511   .9986883    -1.80   0.072    -3.753905    .1608817
       _cons |    7.26606    5.03887     1.44   0.149    -2.609943    17.14206
------------------------------------------------------------------------------
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.825933   .9741771      1.437901    5.553855
                  var(_cons) |    20.3199   5.100869      12.42356    33.23512
            cov(week,_cons) |   .4983436   1.644257     -2.724341    3.721029
-----------------------------+------------------------------------------------
               var(Residual) |     10.376   1.358992      8.026838    13.41269
------------------------------------------------------------------------------
```



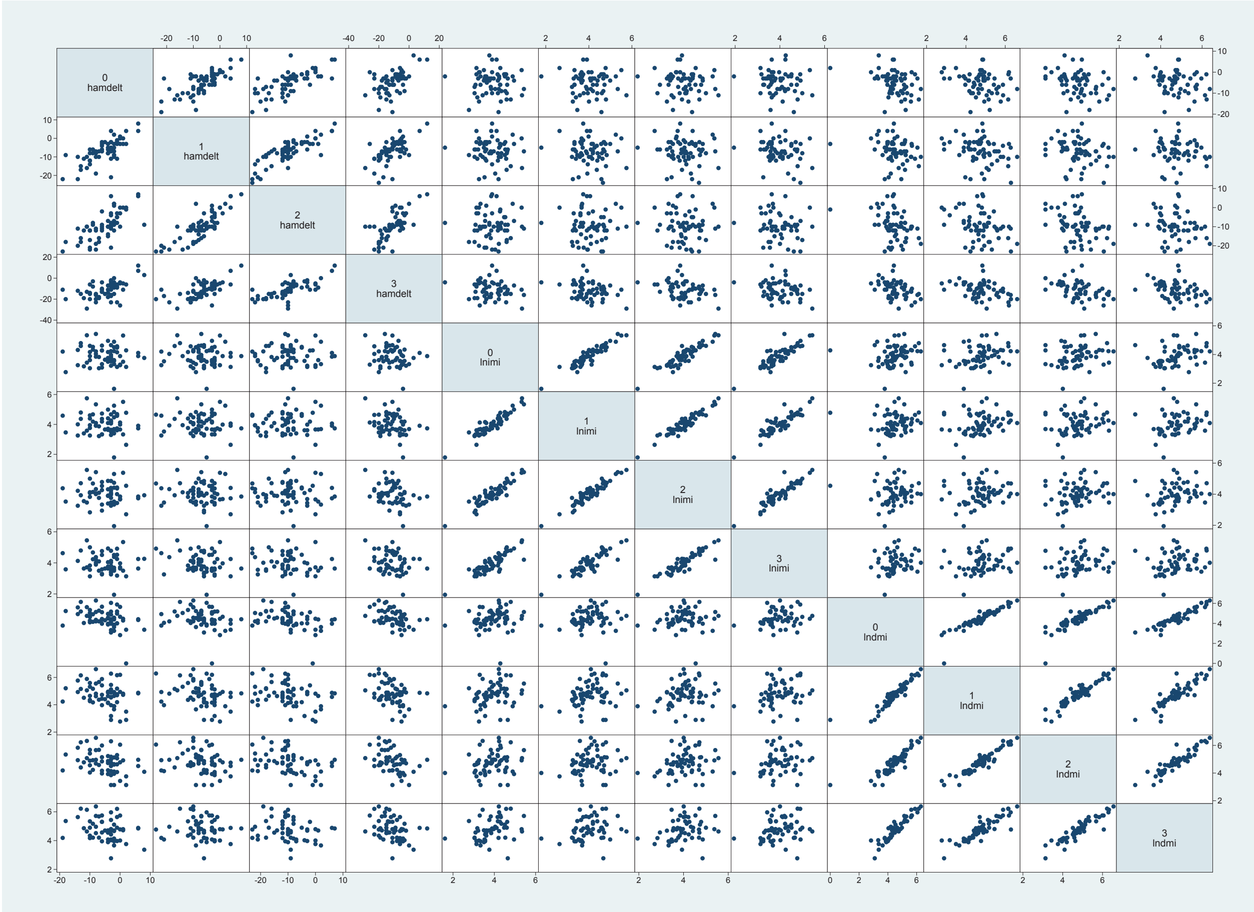
```
. * not assuming BS=WS effects: alternative parameterization
. mixed hamdelt week lnimi_mean lndmi_mean  lnimi lndmi ///
>   || id: week, covariance(unstructured) mle

Log likelihood = -747.88476
------------------------------------------------------------------------------
     hamdelt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -2.023795   .2917128    -6.94   0.000    -2.595541   -1.452048
  lnimi_mean |  -2.756596   1.790536    -1.54   0.124    -6.265982    .7527903
  lndmi_mean |  -.5704114   1.312089    -0.43   0.664    -3.142059    2.001236
       lnimi |   2.443656   1.456049     1.68   0.093    -.4101479     5.29746
       lndmi |  -1.796511   .9986883    -1.80   0.072    -3.753905    .1608817
       _cons |    7.26606    5.03887     1.44   0.149    -2.609943    17.14206
------------------------------------------------------------------------------
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.825933   .9741771      1.437901    5.553855
                  var(_cons) |    20.3199   5.100869      12.42356    33.23512
            cov(week,_cons) |   .4983436   1.644257     -2.724341    3.721029
-----------------------------+------------------------------------------------
               var(Residual) |     10.376   1.358992      8.026838    13.41269
------------------------------------------------------------------------------
```

SAS example: `riesbsws.sas`

```
TITLE1 'partitioning BS and WS effects of drug levels';
FILENAME Riesby HTTP "https://hedeker.people.uic.edu/RIESBYT4.DAT.txt";
DATA one; INFILE Riesby;  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';  RUN;
```


Stata example: `riesbyT4plot.do`

```
cd "u:\Stata_long\"
log using riesbyT4plot.log, replace
infile  id hamdelt intcpt week sex endog lnimi lndmi ///
       using RIESBYT4.DAT.txt, clear
reshape wide hamdelt lnimi lndmi, i(id) j(week)
summ
graph matrix hamdelt0 hamdelt1 hamdelt2 hamdelt3 ///
             lnimi0 lnimi1 lnimi2 lnimi3 ///
 lndmi0 lndmi1 lndmi2 lndmi3
log close
```



Partial listing: RIESBYT4.DAT.txt

101	-8	1	0	0	0	4.04305	4.20469
101	-19	1	1	0	0	3.93183	4.81218
101	-22	1	2	0	0	4.33073	4.96284
101	-23	1	3	0	0	4.36945	4.96284
103	-18	1	0	1	0	2.77259	5.23644
103	-9	1	1	1	0	3.46574	5.20949
103	-18	1	2	1	0	3.52636	5.34233
103	-20	1	3	1	0	3.58352	5.36129
104	-11	1	0	1	1	5.34233	4.75359
104	-16	1	1	1	1	5.74620	5.05625
104	-10	1	2	1	1	5.56452	5.08140
104	-29	1	3	1	1	5.45104	4.63473
105	-6	1	0	1	0	3.09104	4.35671
105	-6	1	1	1	0	3.33220	4.44265
105	-9	1	2	1	0	2.94444	4.17439
105	-13	1	3	1	0	3.29584	4.56435
106	2	1	0	0	1	4.29046	.00000
106	-3	1	1	0	1	4.77912	2.89037
106	-1	1	2	0	1	4.54329	3.13549

from riesby_BSWS.do

```
mixed hamdelt week lnimi lndmi  || id: week, covariance(unstructured) mle


Mixed-effects ML regression                     Number of obs     =        250
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          3
                                                              avg =        3.8
                                                              max =          4

                                                Wald chi2(3)      =      67.48
Log likelihood = -749.42283                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
     hamdelt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -1.966858   .2849741    -6.90   0.000    -2.525397   -1.408319
       lnimi |    .630078   .8211181     0.77   0.443    -.9792838     2.23944
       lndmi |  -1.966628   .6024592    -3.26   0.001    -3.147426   -.7858293
       _cons |   1.521352   3.742576     0.41   0.684    -5.813962    8.856666
------------------------------------------------------------------------------
```



```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.782405   .9691781       1.40581    5.506989
                  var(_cons) |   20.49971   5.126605      12.55677    33.46708
            cov(week,_cons) |   .8371648   1.614433     -2.327065    4.001395
-----------------------------+------------------------------------------------
               var(Residual) |    10.5278   1.385194      8.134691    13.62494
------------------------------------------------------------------------------
```

```
mixed hamdelt week lnimi lndmi if lndmi > 0 || id: week, ///
          covariance(unstructured) mle
```

```
Mixed-effects ML regression                     Number of obs     =        249
Group variable: id                              Number of groups  =         66

                                                Obs per group:
                                                              min =          2
                                                              avg =        3.8
                                                              max =          4

                                                Wald chi2(3)      =      66.61
Log likelihood = -746.64597                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
     hamdelt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        week |  -1.962411   .2849209    -6.89   0.000    -2.520846   -1.403976
       lnimi |   .7174779   .8272036     0.87   0.386    -.9038113    2.338767
       lndmi |   -2.30261   .6960158    -3.31   0.001    -3.666776   -.9384443
       _cons |   2.756865   3.945963     0.70   0.485     -4.97708    10.49081
------------------------------------------------------------------------------
```



```
------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
id: Unstructured             |
                   var(week) |   2.772006   .9661326      1.399985    5.488644
                  var(_cons) |   20.53147   5.123044      12.59004    33.48214
            cov(week,_cons) |        .72   1.611875     -2.439218    3.879218
-----------------------------+------------------------------------------------
               var(Residual) |   10.55963   1.388703      8.160312     13.6644
------------------------------------------------------------------------------
```

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
$\sigma^2_{\upsilon_0}$	20.50	5.12		20.53	5.12	
$\sigma_{\upsilon_0 \upsilon_1}$	0.84	1.61		0.72	1.61	
$\sigma^2_{\upsilon_1}$	2.78	0.97		2.77	0.97	
σ^2	10.53	1.39		10.56	1.39	