Repeated Measures Analysis

Correlated Data Analysis, Multilevel data analysis, Clustered data, Hierarchical linear modeling

- Examples
- Intraclass correlation
- Hierarchical linear models
- Random effects, random coefficients and Linear Mixed modeling
- Generalized linear mixed models, random effects in logistic and Poisson regression
- Estimation by Maximum likelihood with random effects
- Estimation by Generalized Estimating Equations
- Marginal versus conditional models

Examples of Hierarchical Data

- Cross-over study: Pancreatic enzymes examined in patients after being given 4 different types of pills at different times to examine which one is best at effecting enzymes. Repeated measures within individual patients. (from VGMS)
- Group randomized trials: Families randomized into health-improvement intervention group or control. Measure fruit/vegetable intake of all members of each family (baseline and 6 months). Randomization at family level, measurements taken on individuals within family. Family members are clustered within family.
- Longitudinal measurements: Quality of life measurements taken at baseline, 1, 3, 6, 9, 12, 18, 24 months in a CHD trial. Researchers want to know if there are differences in QOL trajectories after taking Drug A versus Drug B.
- Alcoholism treatment study relating engaging in treatment to abstinence. Patients were sampled from over 40 clinics across the country. Patients are nested within clinics. Accounting for potential clinic level effects may change results found for individual level relationships.
- Math Achievement measured on children within schools. Interested in examining whether individual or school factors are associated with achievement levels. Kids are nested within schools.

Hierarchical Data

Two characterizing features of hierarchical data

- Correlation among observations within units
- Predictor variables at the different levels of the hierarchy

Level 1 is nested in Level 2 is nested in Level 3, etc.

Level 1 is finest unit of analysis

Level 2 is next unit of aggregation

…

What are the level 1 and level 2 units (and potential covariates) for the different examples?

Pancreatic Enzyme Supplements Example

Lack of digestive enzymes in the intestine can cause bowel absorption problems. This will be indicated by excess fat in the feces. Pancreatic enzyme supplements can be given to ameliorate the problem. Does the supplement form make a difference? (Graham, Enzyme replacement therapy of exocrine pancreatic insufficiency in man. NEJM, 296: 1314-17, 1977 But note: sex information made up for illustration.)

Study design involved administering 4 different forms of the supplement (powder, tablet, capsule, coated capsule) to 6 patients. Each patient was given each of the 4 different pancreatic enzyme supplements (over time) and tested.

personid	gender	none	tablet	capsule	coated
1	M	44.5	7.3	3.4	12.4
2	F	33	21	23.1	25.4
3	M	19.1	5	11.8	22
4	M	9.4	4.6	4.6	5.8
5	F	71.3	23.3	25.6	68.2
6	F	51.2	38	36	52.6

WIDE Format versus LONG FORMAT

This dataset above is in what is called WIDE format. Wide format refers to data where the repeated measures are across columns and there is only one row per person. Many softwares, including both SAS and Stata, require the data to be converted to LONG format for analyses. Long format is where there are multiple rows per person corresponding to the different repeated measures.

personid	p	gender	fat
1	capsule	M	3.4
1	coated	M	12.4
1	none	M	44.5
1	tablet	M	7.3
2	capsule	F	23.1
2	coated	F	25.4
2	none	F	33
2	tablet	F	21
...			

WIDE Format versus LONG FORMAT

Stata code:

```
rename none fatnone
rename tablet fattablet
rename capsule fatcapsule
rename coated fatcoated
reshape long fat@, i(personid) j(p none tablet capsule coated) string
encode p, gen(pilltype)
```

SAS code:

```
proc transpose data = fecalfat out = long;
     by personid gender;
     var none tablet capsule coated;
run;

data long1;
     set long (rename = (col1 = fat _NAME_ = pilltype));
run;
```

Pancreatic Enzyme Example-WRONG ANALYSIS

Let Y_{ij} be the excreted fat for the *j*th pilltype administered to the *i*th patient

$Y_{ij} = \mu_j + e_{ij}$

$Y_{ij} = \beta_0 + \beta_1$ pilltype1 + β_2 pilltype2 + $\beta_3$pilltype3 + e_{ij} (pilltype 4 is the reference)

THE WRONG ANALYSIS would then be to assume $e_{ij} \sim$ i.i.d.N(0, σ^2). This is wrong because we do not expect the (e_{i1}, e_{i2}, e_{i3}, e_{i4}) to be independent across pilltype since they are coming from the same individual *i*.

If we model the errors as i.i.d, the method is wrongly assuming there are 24 independent people in this study with 6 of them assigned to each of the treatment groups.

Pancreatic Enzyme Example-WRONG ANALYSIS

```
proc glm data = long1;
            class pilltype;
            model fat = pilltype/solution;
            estimate "all compared to none" pilltype 1 1 -3 1;
run;

Dependent Variable: fat
                                        Sum of
Source                      DF         Squares     Mean Square    F Value    Pr > F
Model                        3     2008.601667      669.533889       1.86    0.1687
Error                       20     7193.363333      359.668167
Corrected Total             23     9201.965000

R-Square     Coeff Var      Root MSE      fat Mean
0.218280      73.57874      18.96492      25.77500

Source                      DF     Type III SS     Mean Square    F Value    Pr > F
pilltype                     3     2008.601667      669.533889       1.86    0.1687

                                          Standard
Parameter                   Estimate           Error    t Value    Pr > |t|
all compared to none     -49.2333333      26.8204462      -1.84      0.0813

                                          Standard
Parameter                 Estimate           Error    t Value    Pr > |t|
Intercept             16.53333333 B      7.74239591       2.14      0.0453
pilltype  capsule       0.88333333 B     10.94940130       0.08      0.9365
pilltype  coated       14.53333333 B     10.94940130       1.33      0.1994
pilltype  none         21.55000000 B     10.94940130       1.97      0.0631
pilltype  tablet        0.00000000 B       .                .         .
```

Pancreatic Enzyme Example-WRONG ANALYSIS

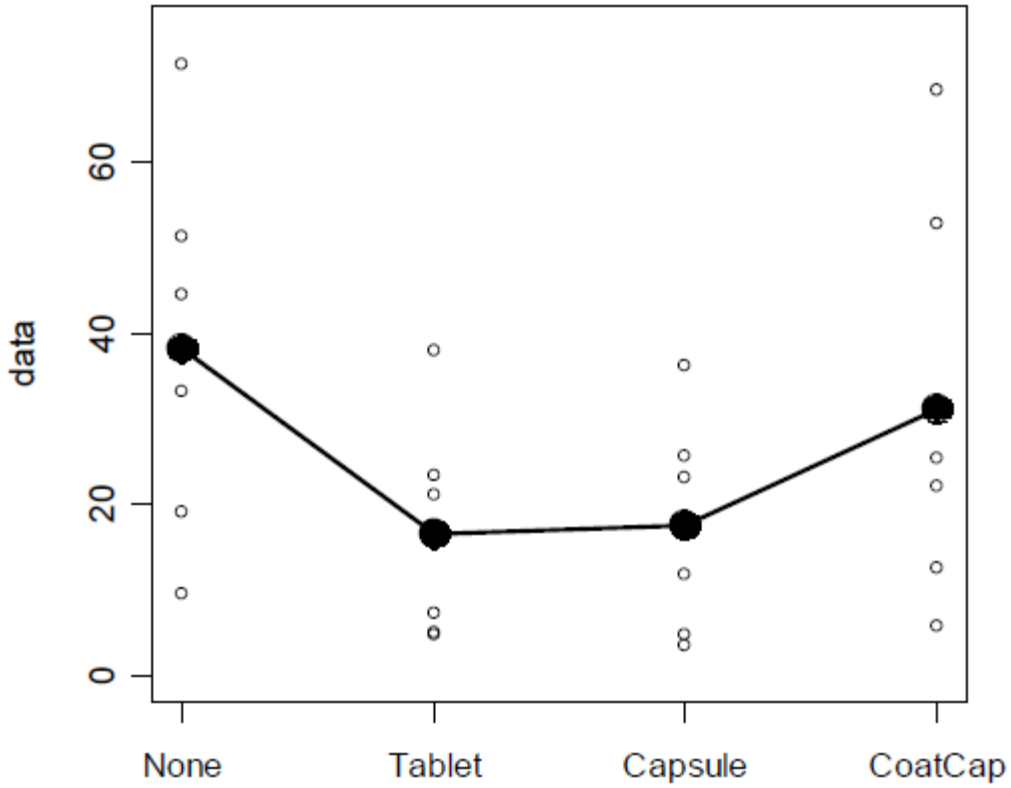
USING THE WRONG ANALYSIS:

We get MSE = σ^2 = 359.6 and

NONSIGNIFICANT pilltype effect (p = 0.1687)

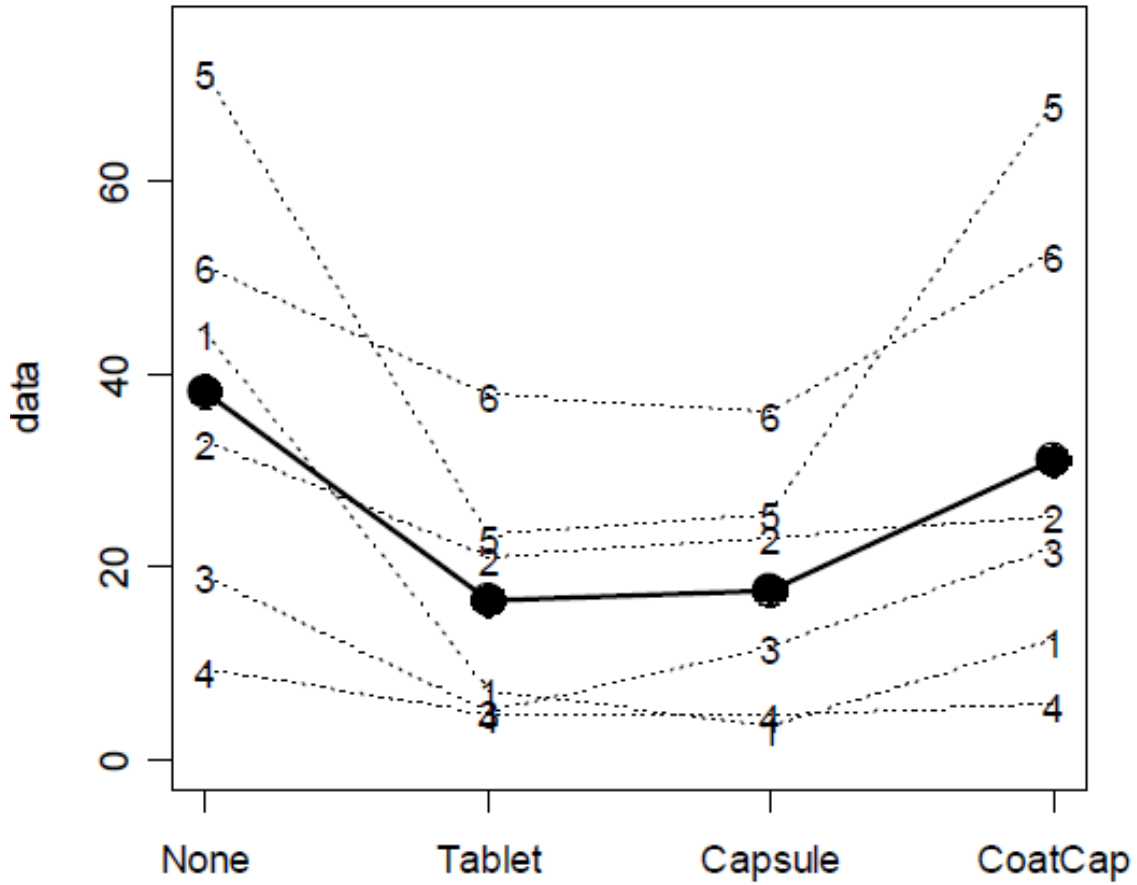
Fitted model:

Y_ij = beta0 + beta1*capsule + beta2*coated + beta3*none + e_ij



Pancreatic Enzyme Example-WRONG ANALYSIS

However, the data are NOT independent across pill types.



Some of the variability in fat measurement can be explained by person to person variability.

Pancreatic Enzyme Example-Fixed Effects Model

The previous wrong analysis does not take into account the potentially different effect of each subject (or consequently the correlation found between observations on the same person). We expect some people to have across the board higher fat excretion and some to have lower. To account for this, we introduce a subject effect in the model which simultaneously raises or lowers all measurements on that person.

How do we set up the model using linear regression techniques we have learned?

$Y_{ij} = \beta_0 + \beta_1 *(\text{person}=2) + ... + \beta_5*(\text{person}=6) + \beta_6*\text{capsule} + \beta_7 *\text{coated} + \beta_8*\text{none} + \varepsilon_{ij}$

Stata:

```
. regress fat ib(last).pilltype i.personid
```

Pancreatic Enzyme Example-Fixed Effects Model

SAS:

```
proc glm data = long1;
       class pilltype personid;
       model fat = pilltype personid/solution;
       estimate "all compared to none" pilltype 1 1 -3 1;
run;
```

Source	DF	Type III SS	Mean Square	F Value	Pr > F
pilltype	3	2008.601667	669.533889	6.26	0.0057

Parameter	Estimate	Standard Error	t Value	Pr > |t|
all compared to none	-49.2333333	14.6286629	-3.37	0.0042

Parameter		Estimate		Standard Error	t Value	Pr > |t|
Intercept		35.20833333	B	6.33439684	5.56	<.0001
pilltype	capsule	0.88333333	B	5.97212661	0.15	0.8844
pilltype	coated	14.53333333	B	5.97212661	2.43	0.0279
pilltype	none	21.55000000	B	5.97212661	3.61	0.0026
pilltype	tablet	0.00000000	B	.	.	.
personid	1	-27.55000000	B	7.31433144	-3.77	0.0019
personid	2	-18.82500000	B	7.31433144	-2.57	0.0212
personid	3	-29.97500000	B	7.31433144	-4.10	0.0009
personid	4	-38.35000000	B	7.31433144	-5.24	<.0001
personid	5	2.65000000	B	7.31433144	0.36	0.7222
personid	6	0.00000000	B	.	.	.

Pancreatic Enzyme Example-Fixed Effects Model

Person-specific intercepts:

Person 1: $b_{01} = \beta_0$

Person 2: $b_{02} = \beta_0 + \beta_1$

…

Person 6: $b_{06} = \beta_0 + \beta_5$

Potential problem: If we collect data from hundreds or thousands individuals, this fixed-effects model will include a huge number of predictors – very inefficient!

Solution: Make a distributional assumption for μ_{0i}'s so that we only need to estimate the parameters that determine the shape of the assumed distribution. Which distribution comes to our mind first?

Introduce Subject Random Effects

Suppose we are mainly interested in the relationship between fat measure and pilltype, and less interested in the person-specific averages.

As before, let Y_{ij} be the excreted fat for the *j*th pilltype administered to the *i*th patient. But now we split the error term into a subject specific effect b_i and a residual error effect e^*_{ij}.

$$Y_{ij} = \mu_j + e_{ij} = \mu_j + b_i + e^*_{ij}$$

We now assume $b_i \sim_{iid} N\left(0, \sigma^2_{subject}\right)$ and $e^*_{ij} \sim_{iid} N(0, \sigma^2)$.

Treating b_i as a random effect (rather than a fixed term) is interpreted as the individuals in our study being some random sample from a larger population of subjects which we wish to make inference. We would treat subjects as fixed effects (i.e. as in the previous slide), if we were interested in making inference about the 6 specific people.

Fitting Random Effects Model – SAS (1)

```
proc mixed data = long1;
     class pilltype personid;
     model fat = pilltype / solution;
     random intercept / subject = personid;  ** person specific random effects;
     estimate "all compared to none" pilltype 1 1 -3 1;
run;
```

```
Dependent Variable           fat
Covariance Structure         Variance Components
Subject Effect               personid            ← level 2 unit identifier
Estimation Method            REML                ← estimation method (alternative: MLE)
Residual Variance Method     Profile
Fixed Effects SE Method      Model-Based
Degrees of Freedom Method    Containment

Dimensions
Covariance Parameters            2
Columns in X                     5               ← number of fixed effects
Columns in Z Per Subject         1               ← 1 random effect (random intercept)
Subjects                         6
Max Obs Per Subject              4

Covariance Parameter Estimates
Cov Parm      Subject     Estimate
Intercept     personid      252.67      ← estimated σ²_subject
Residual                    107.00      ← estimated σ²
```

Fitting Random Effects Model – SAS (2)

Fit Statistics

-2 Res Log Likelihood	169.1
AIC (smaller is better)	173.1
AICC (smaller is better)	173.8
BIC (smaller is better)	172.7

Solution for Fixed Effects

Effect	NAME OF FORMER VARIABLE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		16.5333	7.7424	5	2.14	0.0858
pilltype	capsule	0.8833	5.9721	15	0.15	0.8844
pilltype	coated	14.5333	5.9721	15	2.43	0.0279
pilltype	none	21.5500	5.9721	15	3.61	0.0026
pilltype	tablet	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
pilltype	3	15	6.26	0.0057

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
all compared to none	-49.2333	14.6287	15	-3.37	0.0042

Fitting Random Effects Model – SAS (3)

Notice the error degrees of freedom are now 15 rather than 20 as in WRONG ANALYSIS, why?

Also notice that the previous error variance of 359.6 has been split into subject-to-subject variance 252.67 plus true error variance 107. Notice that because the error variance is smaller, the p-values for pilltype are more significant. (more details in next slides)

Also notice that the point estimates for each pilltype is the same as those in fixed-effects model.

Fitting Random Effects Model – Stata

```
. xtmixed fat ib(last).pilltype || personid:, variance reml
Mixed-effects REML regression                   Number of obs      =        24
Group variable: personid                        Number of groups   =         6
                                                Obs per group: min =         4
                                                               avg =       4.0
                                                               max =         4
                                                Wald chi2(3)       =     18.77
Log restricted-likelihood = -84.555945          Prob > chi2        =    0.0003
------------------------------------------------------------------------------
         fat |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    pilltype |
           1 |   .8833336   5.972126     0.15   0.882    -10.82182    12.58849
           2 |   14.53333   5.972126     2.43   0.015     2.828181    26.23848
           3 |      21.55   5.972126     3.61   0.000     9.844849    33.25515
             |
       _cons |   16.53333   7.742398     2.14   0.033     1.358512    31.70815
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
personid: Identity           |
                  var(_cons) |   252.6695     176.99      64.01811     997.247
-----------------------------+------------------------------------------------
               var(Residual) |   106.9989   39.07045      52.30755    218.8739
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =    12.52 Prob >= chibar2 = 0.0002
```

Fitting Random Effects Model – Stata

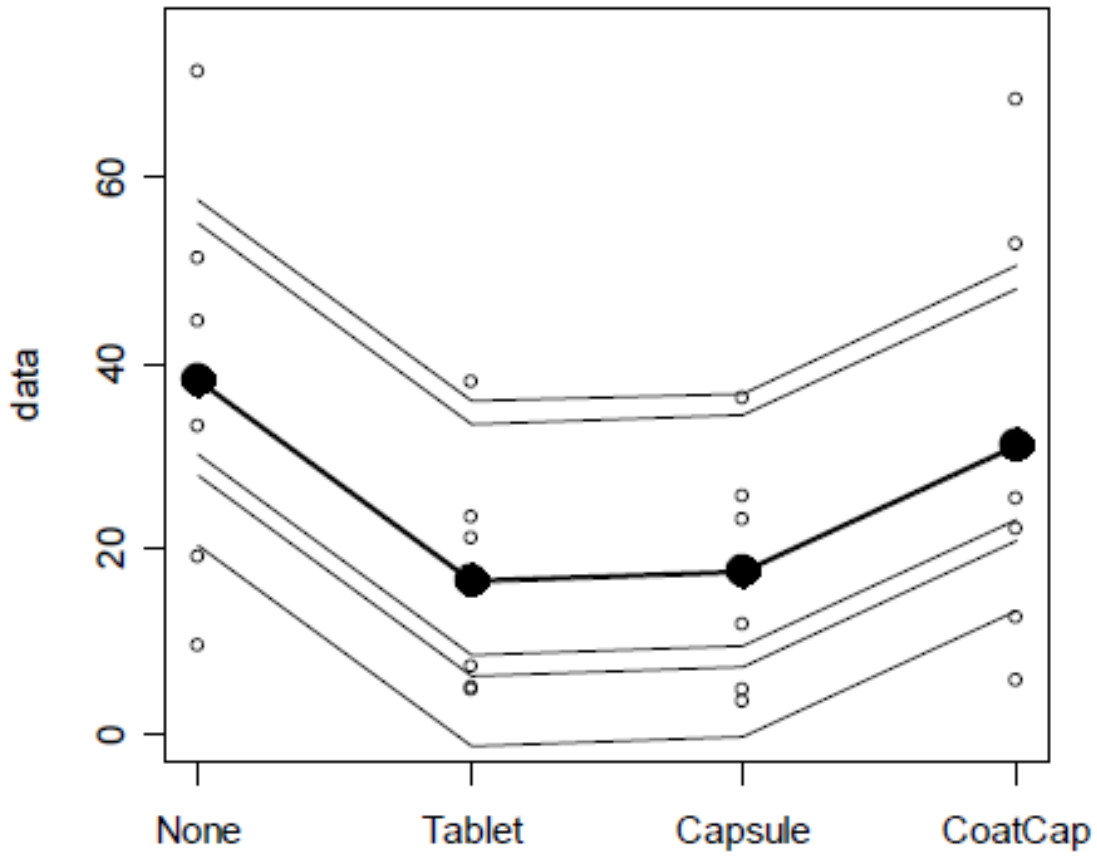
```
. test 1.pilltype 2.pilltype 3.pilltype           // joint test for pilltype effect
 ( 1)  [fat]1.pilltype = 0
 ( 2)  [fat]2.pilltype = 0
 ( 3)  [fat]3.pilltype = 0
           chi2(  3) =   18.77
         Prob > chi2 =    0.0003

. lincom 1.pilltype+2.pilltype-3*3.pilltype       // all compared to none
 ( 1)  [fat]1.pilltype + [fat]2.pilltype - 3*[fat]3.pilltype = 0
------------------------------------------------------------------------------
         fat |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |  -49.23334   14.62866    -3.37   0.001    -77.90498   -20.56169
------------------------------------------------------------------------------

. contrast {pilltype 1 1 -3 1}                 // available in Stata 12
Contrasts of marginal linear predictions
Margins      : asbalanced
-----------------------------------------------
             |         df        chi2     P>chi2
-------------+---------------------------------
fat          |
    pilltype |          1       11.33     0.0008
-----------------------------------------------
-------------------------------------------------------------
             |   Contrast   Std. Err.     [95% Conf. Interval]
-------------+-----------------------------------------------
fat          |
    pilltype |
         (1) |  -49.23334   14.62866     -77.90498   -20.56169
-------------------------------------------------------------
```

Fitting Random Effects Model

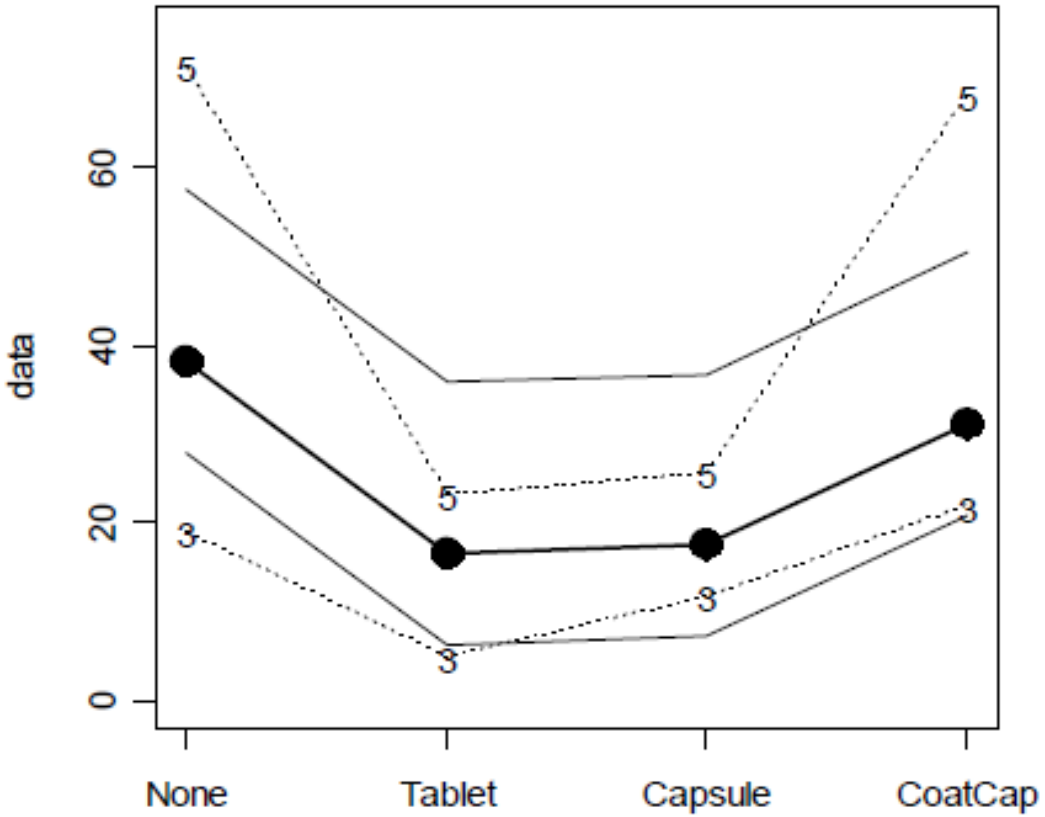
The uncertainty about how treatment will work NOW can be estimated by considering the deviation between the observed values for a person and the expected value for that person. The variance of the e_{ij}^{*} in the new model is the variability AFTER accounting for person to person variability.



*. Why the fitted lines are parallel?

Fitting Random Effects Model

This variability is calculated within each person and then (averaged) across individuals. Plot below shows the data and expected values for Person 5 and Person 3. The variance is 107. This is MUCH SMALLER than that in WRONG ANALYSIS. Hence tests for treatment differences are more powerful since the treatment differences (i.e. mean change in fat across different treatments) are compared to an uncertainty of 107 rather than 359.



Fitting Random Effects Model

Notice that the standard errors are much smaller than those in WRONG ANALYSIS, because here they are constructed using 107 rather than 359 as the estimate for σ^2. Recall that the estimated standard errors are $\sigma^2(X'X)^{-1}$.

Predict Random Effects

We can predict (not estimate) the random intercepts for each person by adding `solution` option in the `random` statement.

```
...; random intercept / subject = personid solution; run;
```

Solution for Random Effects

Effect	personid	Estimate	Std Err Pred	DF	t Value	Pr > |t|
Intercept	1	-8.0254	7.8911	15	-1.02	0.3253
Intercept	2	-0.1356	7.8911	15	-0.02	0.9865
Intercept	3	-10.2182	7.8911	15	-1.29	0.2149
Intercept	4	-17.7914	7.8911	15	-2.25	0.0395
Intercept	5	19.2835	7.8911	15	2.44	0.0274
Intercept	6	16.8872	7.8911	15	2.14	0.0492

In Stata, use:

```
. predict varname, reffects
```

Predict Random Effects

To predict b_i, we can use:

$$\widetilde{b_i} = E\left(b_i|\underline{Y_i}\right)$$

which is called best linear unbiased prediction (BLUP). In the random intercept model,

$$\widetilde{b_i} = E\left(b_i|\underline{Y_i}\right) = \frac{n_i\ \sigma^2_{subject}}{n_i\ \sigma^2_{subject} + \sigma^2}(\overline{Y_i} - \mu)$$

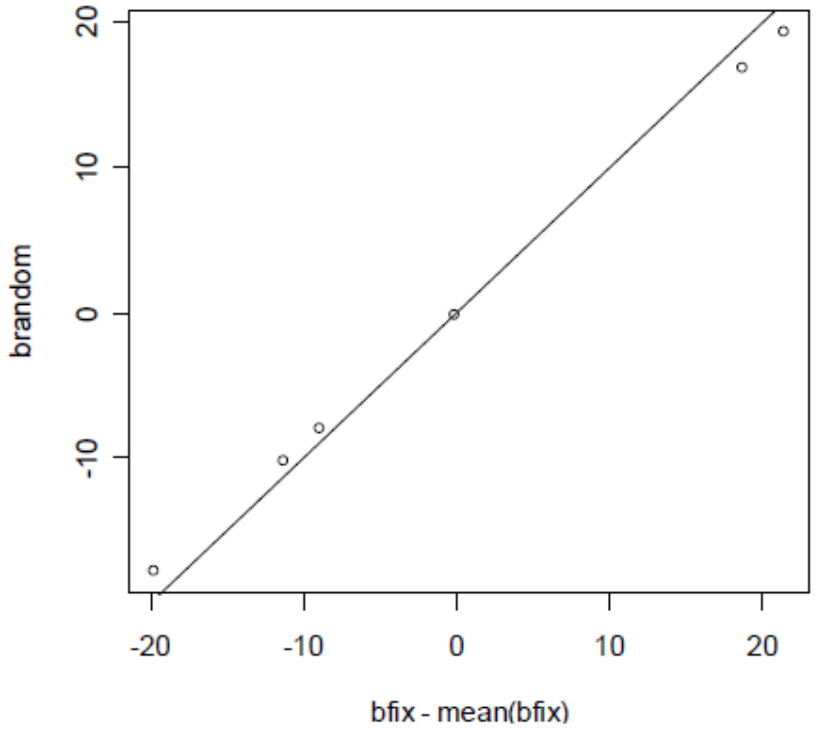
which is known as "shrinkage estimator" – weighted derivation of $\overline{Y_i}$ and μ.

Define: $\mu_i = E(Y_{ij}|b_i) = \mu + b_i$.

When $\sigma^2_{subject} \to \infty, \widehat{\mu_i} = \overline{Y_i}$;

$\sigma^2 \to \infty, \qquad \widehat{\mu_i} = \hat{\mu}$.

Random Effects vs Fixed Effects



The random effects are “shrunk”, i.e. smaller (closer to zero) than the fixed effects estimates. In this example with balanced data (i.e. same number of observations within subject), the standard errors are same using two methods.

Using fixed subject effect, we cannot then test for subject level covariates since completely confounded

Correlation Within Subjects

The subject specific random effects in the model induce a correlation between observation within a person.

$$
\begin{aligned}
Corr(Y_{ij}, Y_{ij'}) &= Corr(\mu_j + b_i + e^*_{ij}, \mu_{j'} + b_i + e^*_{ij'}) \\
&= Corr(b_i + e^*_{ij}, b_i + e^*_{ij'}) \\
&= \frac{Cov(b_i + e^*_{ij}, b_i + e^*_{ij'})}{sqrt(Var(b_i + e^*_{ij}))sqrt(Var(b_i + e^*_{ij}))} \\
&= \frac{Cov(b_i, b_i)}{sqrt(\sigma^2_{subject} + \sigma^2)sqrt(\sigma^2_{subject} + \sigma^2)} \\
&= \frac{\sigma^2_{subject}}{\sigma^2_{subject} + \sigma^2}
\end{aligned}
$$

This correlation is known as the “intraclass correlation” sometimes denoted ρ_I.

Including Subject Specific Covariates

Recall we know the gender of each patient. So we may expect that part of the reason there is variability in the b_i in our model is that there are differences due to gender.

$$Y_{ij} = \mu_j + b_i + e_{ij} \text{ -- LEVEL 1}$$

$$b_i = \beta_0 + \beta_1 female + \delta_i \text{ -- LEVEL 2}$$

where we assume $\delta_i \sim_{iid} N\left(0, \sigma^2_{subject}\right)$ and $e_{ij} \sim_{iid} N(0, \sigma^2)$.

NOTICE that this 2-level model can be collapsed into a single equation:

$$Y_{ij} = \mu_j + (\beta_0 + \beta_1 female + \delta_i) + e_{ij}$$

where the $\beta_0 + \beta_1 female$ can get folded into the regular fixed regression part of the model, and now δ_i represents the subject to subject variability found after accounting for the fixed differences between males and females.

So the Level 2 covariates can be treated simply as regular fixed covariates.

Pancreas enzyme example - including gender

```
proc mixed data = long1;
     class pilltype personid gender;
     model fat = pilltype gender/solution ddfm=bw;
     random intercept / subject = personid solution;
     estimate "all compared to none" pilltype 1 1 -3 1;
run;
```

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
Intercept	personid	57.8536
Residual		107.00

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
pilltype	3	15	6.26	0.0057
gender	1	4	12.51	0.0241

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
all compared to none	-49.2333	14.6287	15	-3.37	0.0042

Pancreas enzyme example - including gender

Solution for Fixed Effects

Effect	NAME OF FORMER VARIABLE	gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			3.2500	6.4479	4	0.50	0.6407
pilltype	capsule		0.8833	5.9721	15	0.15	0.8844
pilltype	coated		14.5333	5.9721	15	2.43	0.0279
pilltype	none		21.5500	5.9721	15	3.61	0.0026
pilltype	tablet		0	.	.	.	.
gender		F	26.5667	7.5101	4	3.54	0.0241
gender		M	0	.	.	.	.

Now the person level variance has decreased dramatically to 57.85 from 252.67 in previous model. But the Residual variance is unchanged.

We can say that $(252.67 - 57.85)/252.67 = 77\%$ of the overall subject-to-subject variability is explained by differences due to gender. Notice including gender has no effect on the within subject effect of pilltype. Generally there **can be changes** in the within subject effect when between subject covariates are included.

Denominator degrees of freedom

- For testing within subject covariates: $\sum_{i=1}^{N}(n_i - 1)$ − (# within subject covariates but don't count intercept)
- For testing between subject covariates: *N* - (# of between subject covariates + intercept)

where *N* is the number of groups (i.e. clusters) and n_i is the number of observations within group *i*.

For the pancreatic enzyme example, *N* = 6, n_i = 4, *i* = 1. . . 6, so we have:

- For testing within subject covariates (pilltype), d.f. = $[\sum_{i=1}^{6}(4 - 1)\ ] - 3 = 18 - 3 = 15$
- For testing between subject covariates (gender), d.f. = 6 − (1 + 1) = 4

NOTE: IF the denominator degrees of freedom are larger than 25 then (similar to the t test which is well approximated by normal for larger n), it doesn't really matter exactly what they are since the F-distribution is well approximated by the Chi-square distribution for larger n.

NOTE: Stata uses the Chi-square test instead of F-test, in which the d.f. is simply the number of parameters being tested.

Outcomes at the individual level, covariates at the cluster level

Consider the following data representing age and gender standardized weight measurements (called indwt) on each member of 100 families. Family size ranges from 2 to 7 people - the NA's are just place holders for families with less than 7 members. The SES variable represents high (1) and low (0) social economic status.

famid	ses	indwt.1	indwt.2	indwt.3	indwt.4	indwt.5	indwt.6	indwt.7
1	0	-1.502010417	0.5544752668	0.21948023	-0.73089186	-0.06883068	NA	NA
2	0	-0.165649544	1.6845611290	-0.25421119	0.13671355	-0.54476531	-0.390195188	NA
3	0	0.107652186	-0.4094990408	-0.63696492	-1.12084914	NA	NA	NA
4	0	-0.552277153	0.3145029798	-1.46222496	NA	NA	NA	NA
5	0	-0.123146029	0.5977726803	-0.09794692	-0.24070294	-0.15363626	-1.258170451	0.5799855
.....								
.....								
95	1	1.678510357	-0.9638609547	NA	NA	NA	NA	NA
96	1	-1.962873583	-1.3636885934	0.74723714	-0.24008793	NA	NA	NA
97	1	-0.192067250	0.1974400504	NA	NA	NA	NA	NA
98	1	1.758464726	1.9870328896	2.66994629	-0.37149802	NA	NA	NA
99	1	0.963863621	0.4527053930	-0.87886858	-0.08271378	-0.12789991	NA	NA
100	1	-0.817236088	0.2732589261	-0.98071062	-0.86561513	NA	NA	NA

What is the association between SES and standardized weight?

Different Approaches

- Ignore the fact that people are sampled in clusters of families. In total there are 416 individuals who we have weights. Regress individual weights on SES. - Will tend to lead to overly optimistic results (standard errors too small)
- Create family level mean weights. There are 100 families. Regress mean family weight on SES. - If family sizes are about equal (gives equal weight to each mean) -- not a bad method for examining group level covariates but does not allow for individual level covariates
- Randomly pick one member of each family so then we have 100 independent individuals and then regress individual weight (of randomly chosen family member) on SES. - Throws away information (standard errors too large, less power)
- Use a multilevel model that utilizes all 416 individuals measurements while partitioning variance due to family differences not explained by SES. – Correct compromise between methods 1 and 2 above, correctly tests subject level covariates while also allowing the possibility of individual level covariates.

Results of Different Approaches: Family Weight Data

Data were simulated under a few different scenarios which varied by how much of the family level variability was explained by SES. Overall in each scenario, the percent of total variability was fixed in the weight measurements that is coming from the family level clusters to be 0.80. In other words, 80% of variability in weight can be explained by family differences, while only .01, .02, or .05 of those differences can be explained by family SES.

N=100 families, total individuals n=416

% total variability from families	% family variability from ses	betaRE	pval	betaiid	pval	betaChoose1	pval	betaagg	pval
.8	.01	.296(.197)	.13	.401(.103)	<.0001	.35(.229)	.13	.292(.197)	.14
.8	.02	.369(.196)	.06	.474(.103)	<.0001	.42(.228)	.07	.366(.196)	.07
.8	.05	.514(.193)	.009	.62 (.101)	<.0001	.57(.226)	.014	.511(.193)	.009

Notice the similarity between betaRE and betaagg. Notice that betaiid is rejecting highly in all cases (standard errors are too small) and that betaChoose1 is slightly conservative (larger standard errors), but not much.

Random Intercepts

In fat enzyme example:

$$Y_{ij} = \beta_{0i} + \beta_1 * trt + e_{ij}$$
$$\beta_{0i} = \beta_0 + b_i$$

β_{0i} represent person specific intercept (based on trt reference of "tablet", the intercept is the person specific estimate for trt of type "tablet"). We used the within person variability of e_{ij} to test for treatment effect.

In family SES related to weight example:

$$Y_{ij} = \beta_{0i} + e_{ij}$$
$$\beta_{0i} = \beta_0 + \beta_1 * SES + b_i$$

β_{0i} represents family specific average weight. Variance of b_i represents deviation of family specific average weight from that expected based on their SES. We used the between person variability of b_i to test for SES effect.

Random Intercepts and Random Slopes

We have focused so far on taking into account clustering by including a random intercept into the model. It may also be of interest to examine whether the way that individual level covariates effect the outcome vary by cluster as well. This implies that slopes vary by cluster.

We will consider a now classic dataset from the 1982 ”High School and Beyond” survey on Math Achievement of 7185 students from 160 schools. The data was used in Bryk and Raudenbush’s first edition 1992 text *Hierarchal Linear Models*

- A step-by-step analysis of the data using SAS was done by Judith Singer in *Journal of Educational and Behavioral Statistics* and also can be found at http://www.ats.ucla.edu/stat/sas/seminars/sas_mlm/mlm_sas_seminar.htm
- A step-by-step analysis of the data using R was done by John Fox as an appendix to his text *An R and S-plus Companion to Applied Regression*

We want to examine whether the way a child’s own SES (*cses*) is related to his/her math achievement (*mathach*) varies by what school they are in. That is, can “contextual factors” (i.e. school level variability) moderate the relationship between SES and achievement.

Random Slope: Compare to Interaction Model

- Suppose we suspect the relationship between *mathach* and *cses* varies by school:
  - Our level 1 (student level) equation becomes:

    $$mathach_{ij} = \beta_{0i} + \beta_{1i}*cses_{ij} + e_{ij}$$

    note the subscript change from β_1 to β_{1i} for SES effect.
  - On level 2, we try to explain the variation of slopes of *cses* by school's SES (*meanses*) and sector status (*sector*).
    - Fixed effects: We can use a deterministic model,

      $$\beta_{1i} = \beta_{10} + \beta_{11}*meanses + \beta_{12}*sector$$

      i.e., *meanses* and *sector* can fully explain the variation of slopes. When we plug level 2 equation back to level 1, we get a fixed-effects model with *cses*, *meanses***cses*, and *sector***cses* as the predictors.

      We could also estimate school-specific slopes, which is equivalent to add *school***cses* interactions. But there will be too many predictors, since there are 160 levels for *school*.

Random Slope: Compare to Interaction Model (2)

- Random effects: If we think *meanses* and *sector* cannot fully explain the variation of slopes, we can include a random error term to level 2 equation for the unaccounted-for variation.

$$\beta_{1i} = \beta_{10} + \beta_{11}*meanses + \beta_{12}*sector + b_{1i}$$

where $b_{1i} \sim N(0, \sigma^2_{cses})$.

Plug level 2 equation back to level 1, we will get fixed effects for *cses*, *meanses***cses*, and *sector***cses*, and random slope term b_{1i} **cses*.

Random Intercept and Slope and Covariates at Both Levels

$$Y_{ij} = \beta_{0i} + \beta_{1i}X_{ij} + e_{ij}$$
$$\beta_{0i} = \alpha_{00} + \alpha_{01}W_i + \delta_{0i}$$
$$\beta_{1i} = \alpha_{10} + \alpha_{11}W_i + \delta_{1i}$$

where $e_{ij} \sim N(0, \sigma^2)$ and $\begin{pmatrix} \delta_{0i} \\ \delta_{1i} \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_{00} & \tau_{10} \\ \tau_{10} & \tau_{11} \end{pmatrix}\right]$

X_{ij} represents a Level 1 covariate, e.g. child specific social economic status (in Math Achievement example). The Level 1 equation assumes that in each cluster *i* that there is a linear relationship between the covariate and the outcome and this relationship is allowed to be different across clusters.

The Level 2 equations and the distribution of δ_{0i} and δ_{1i} provide information about how the intercept and slope of the Level 1 equation vary across clusters, e.g. the school's mean SES level as well as the type of school (private or public) may influence the intercept Math Achievement (β_{0i}) and may influence the way that a child's own SES relates to Math Achievement (β_{1i}).

Level 2 Covariates for Slopes Lead to Interactions

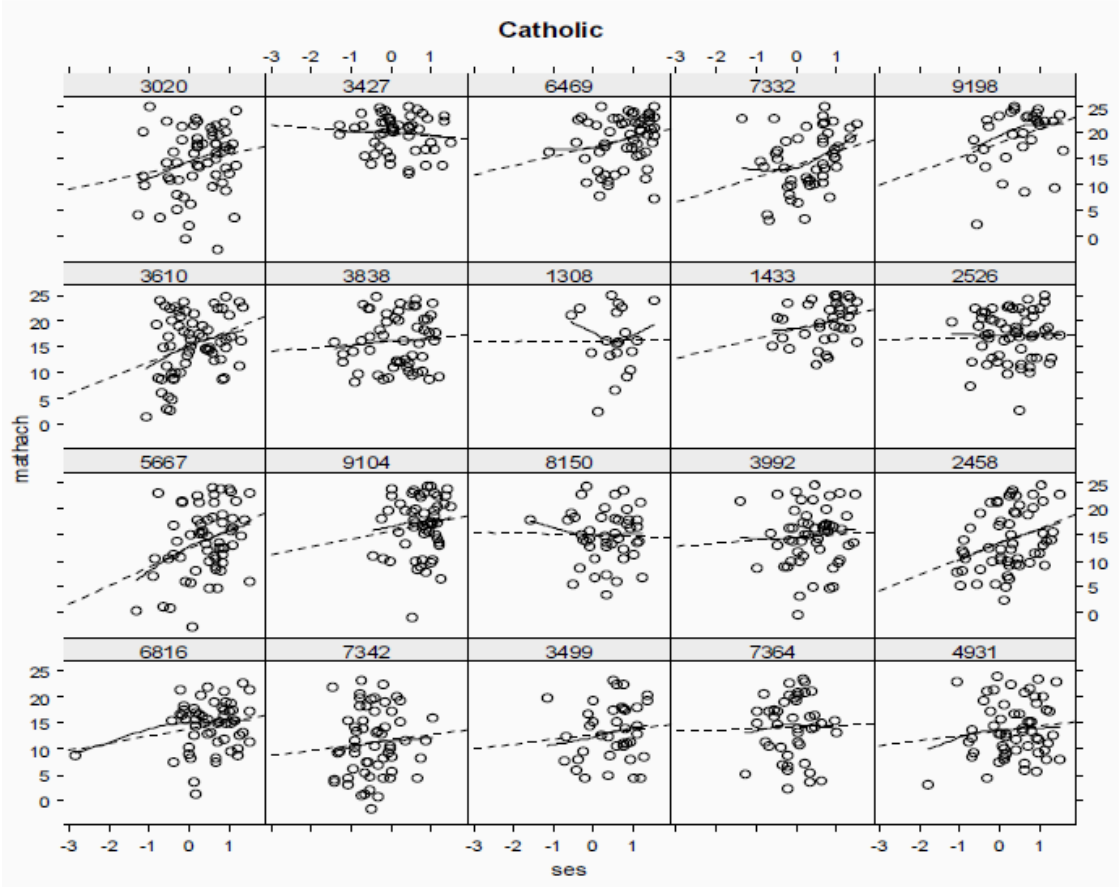
When we plug in the Level 2 equations into the Level 1 equation, we get

$$Y_{ij} = \alpha_{00} + \alpha_{01}W_i + \delta_{0i} + (\alpha_{10} + \alpha_{11}W_i + \delta_{1i})X_{ij} + e_{ij}$$
$$= (\alpha_{00} + \delta_{0i}) + (\alpha_{10} + \delta_{1i})X_{ij} + \alpha_{01}W_i + \alpha_{11}W_i * X_{ij} + e_{ij}$$

Notice, if the coefficient for the interaction term α_{11} is not significant this implies that the cluster level covariate W_i does not help explain differential slope relationship between X_{ij} and the outcome (but it does not exclude other source of variability among the slopes).

Examining Random Intercepts and Slopes

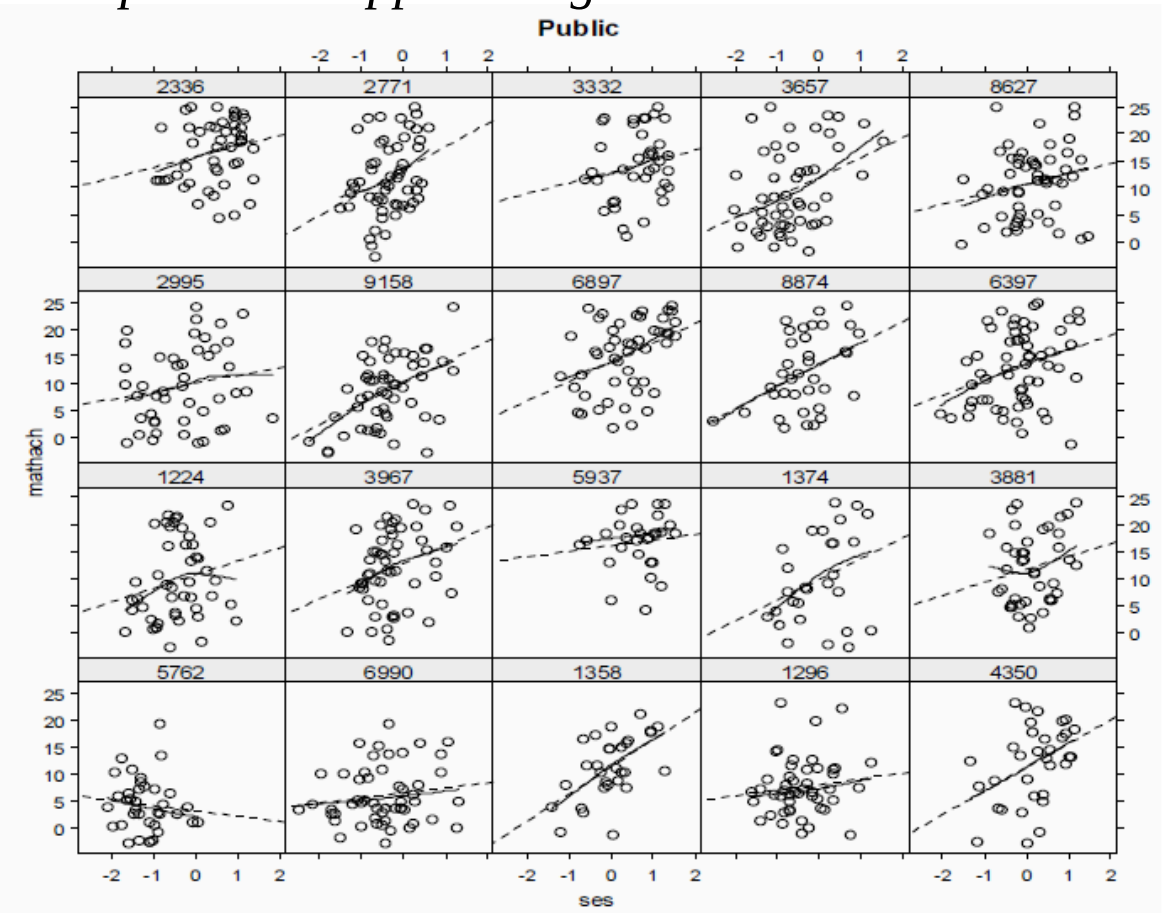
Math achievement example: from John Fox's appendix to *An R and S-PLUS Companion to Applied Regression*



Trellis display of math achievement by socio-economic status for 20 randomly selected Catholic schools. The broken lines give linear least-squares fits, the solid lines local-regression fits.

Examining Random Intercepts and Slopes

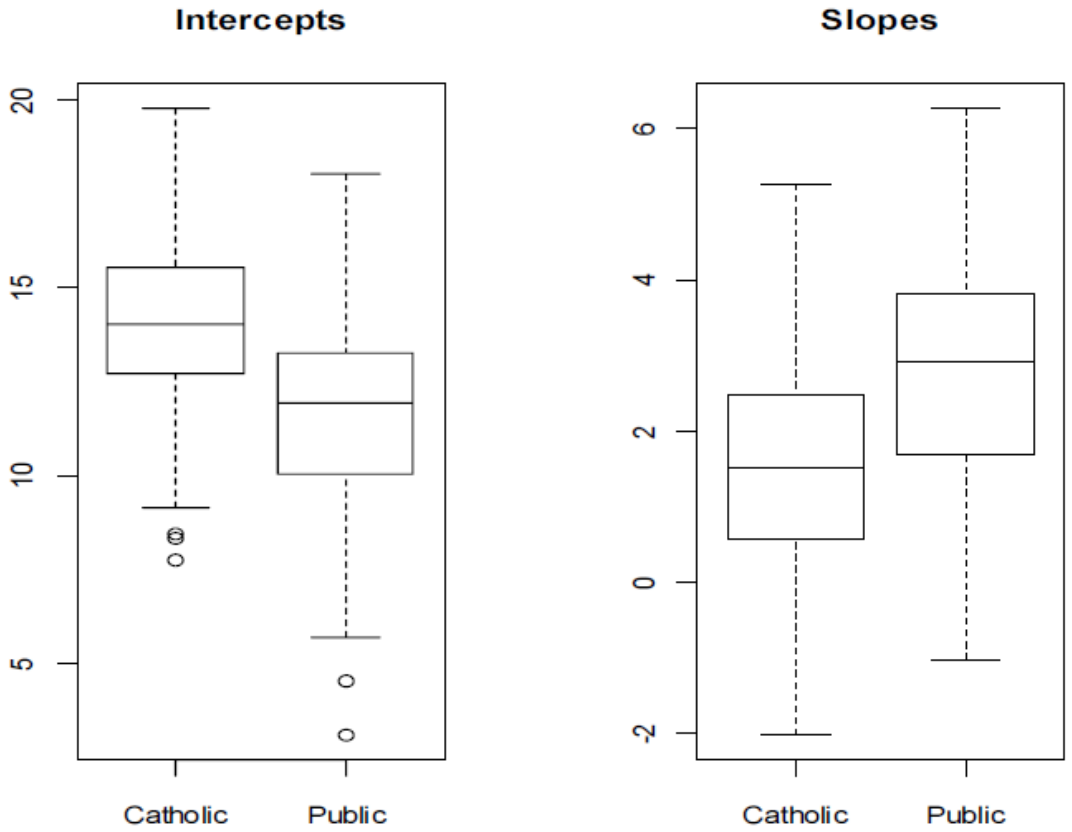
Math achievement example: from John Fox's appendix to *An R and S-PLUS Companion to Applied Regression*



Trellis display of math achievement by socio-economic status for 20 randomly selected Public schools. The broken lines give linear least-squares fits, the solid lines local-regression fits.

Examining Random Intercepts and Slopes

Math achievement example: from John Fox's appendix to *An R and S-PLUS Companion to Applied Regression*



Boxplots of intercepts and slopes for the SEPARATE regressions of math achievement on SES in Catholic and public schools. It appears SECTOR explains some variability in the intercepts and in the slopes, in what way?

Examining Random Intercepts and Slopes

Math achievement example: Results including both SECTOR and MEANSES as level 2 covariates

Solution for Fixed Effects

Parameter	Estimate	Std Error	DDF	T	PR > |T|
INTERCEPT	12.11358496	0.19880323	157	60.93	0.0001
CSES	2.93876223	0.15509265	7022	18.95	0.0001
MEANSES	5.33911631	0.36929107	157	14.46	0.0001
SECTOR	1.21667252	0.30637896	157	3.97	0.0001
CSES*MEANSES	1.03887054	0.29890063	7022	3.48	0.0005
CSES*SECTOR	-1.64258263	0.23979107	7022	-6.85	0.0001

Public: MATHACH = 12.11 + 5.34 MEANSES + 2.94 CSES
+ 1.03 MEANSES*CSES

Catholic: MATHACH = 13.33 + 5.34 MEANSES + 1.30 CSES
+ 1.03 MEANSES*CSES

Testing Whether Random Coefficients Are Needed

- Testing whether a random coefficient should be included in a multilevel model involves the test of whether the variance of that random coefficient is equal to 0. This is problematic because the null hypothesis lies on the boundary of the parameter space.
- A Wald test and the likelihood ratio statistics can be considered but the problem is technically they don't have nominal Type 1 errors.
- There is a substantial literature about approximate tests for the variance components, e.g. using a mixture of a chi-square as a reference distribution with k and k+1 degrees of freedom (where k is the number of variance components being tested). These methods do not appear to implemented yet in existing software.
- Recommendation is to use the AIC or BIC criteria to decide by comparing models with and without the random coefficients.

Random Intercept and Slope and Covariates at Both Levels

$$Y_{ij} = \beta_{0i} + \beta_{1i}X_{ij} + e_{ij}$$
$$\beta_{0i} = \alpha_{00} + \alpha_{01}W_i + \delta_{0i}$$
$$\beta_{1i} = \alpha_{10} + \alpha_{11}W_i + \delta_{1i}$$

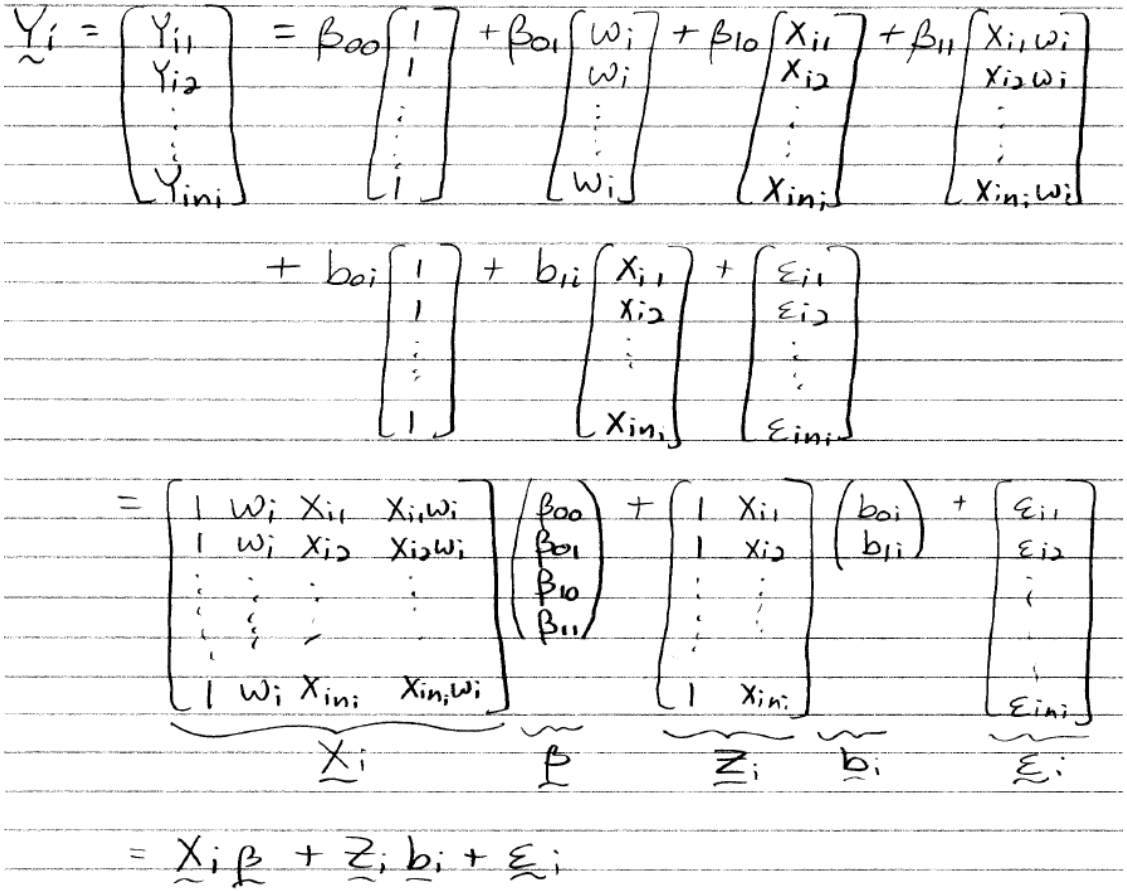
where $e_{ij} \sim N(0, \sigma^2)$ and $\begin{pmatrix} \delta_{0i} \\ \delta_{1i} \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_{00} & \tau_{10} \\ \tau_{10} & \tau_{11} \end{pmatrix}\right]$

Specifically for the example we've seen, Y_{ij} represents Math Achievement, where *i* subscripts schools and *j* subscripts kids within schools. X_{ij} would be kid level SES, W_i could be an indicator of whether the school is catholic or public.

In general X_{ij} could by p-dimensional, and so β_{1i} would also be p-dimensional with potential for random variation associated with each covariate. Furthermore W_i could be q-dimensional.

General Formulation for the Mixed Effects Model

Let $\mathbf{Y}_i$ be the response vector for each level 2 unit i (e.g. either each school in Math Achievment example or family in weight-ses example or individual in fat enzyme example) which will have length n_i (e.g. where n_i is the number of kids in school i or the number of persons in family or 4 treatments in enzyme example). Then we can write in general matrix notation...



General Formulation for the Mixed Effects Model

$$\mathbf{Y}_i = \underbrace{\mathbf{X}_i\beta}_{\text{fixed}} + \underbrace{\mathbf{Z}_i\mathbf{b}_i + \mathbf{e}_i}_{\text{random}}$$

Note that across *i* the vectors of observations $\mathbf{Y}_i$ are i.i.d. (e.g. schools are independent or mice are independent from one another), implicitly this is because we assume b_i are e_i are i.i.d. across *i*. Further, since we assume a linear link between $\mathbf{Y}_i$ and the predictors, then the normality assumption on b_i are e_i imply that

$$\boldsymbol{Y}_i \sim i.i.d\ N(\boldsymbol{X}_i\beta, \boldsymbol{Z}_i\boldsymbol{G}\boldsymbol{Z}_i' + \boldsymbol{R}_i)$$

where $\mathbf{G}$ = Var(b_i) and $\mathbf{R}_i$ is a matrix specifying the covariance of the e_i which will typically be a function of a few parameters e.g. σ^2 and ρ.

Estimation by Maximum Likelihood

Let $Var(\boldsymbol{Y}_i) = \boldsymbol{V}_i = \boldsymbol{Z}_i \boldsymbol{G} \boldsymbol{Z}_i' + \boldsymbol{R}_i$. Let **Y** be the vector which stacks all the $\sum_{i=1}^{N} n_i$ observations, similarly let **X** be the matrix which stacks all the covariates $\mathbf{X}_i$ and finally let **V** be the block diagonal matrix with matrices $\mathbf{V}_i$ on the diagonal, similarly **R** is the block diagonal matrix of $\mathbf{R}_i$. Then the log-likelihood is a function of the multivariate normal distribution, i.e.

$$\ell(\beta, \mathbf{G}, \mathbf{R}|\mathbf{Y}) = -\frac{n}{2} log 2\pi - \frac{1}{2} log|\mathbf{V}| - \frac{1}{2}(\mathbf{Y} - \mathbf{X}\beta)'\mathbf{V}^{-1}(\mathbf{Y} - \mathbf{X}\beta)$$

which can be optimized to find the MLE's of β, **G**, and **R**.

This looks similar to the log likelihood for the general linear model except here **V** is more complicated and has several parameters within it that need to be estimated.

Note, in the general linear model from before, we did NOT have **G** or $\mathbf{Z}_i$ at all and $\mathbf{R} = \sigma^2 \mathbf{I}$.

Estimation by Maximum Likelihood

OLS (ordinary least squares) can be shown to be the same as maximum likelihood for normally distributed data for the general linear model. Here notice the form $(Y - X\beta)'V^{-1}(Y - X\beta)$ in the likelihood. This has the form of Generalized Least Squares (GLS) and represents the quantity we want to minimize. However, to do this requires **V** to be known and therefore **G** and **R** to be known. One approach is to use an estimated $\hat{V}$ and plug this in, hence the task is to obtain reasonable estimates for **G** and **R**.

In principle the likelihood is straightforward to maximize the likelihood but problems arise in estimating the variance parameters **G** and **R**. There are different numerical algorithms which can be used to find the optimal G and R, in smaller samples they may give different results.

It can happen that ML finds the "best fitting" variance parameters to be negative. Since a negative variance is not a possible value, the reported estimate is taken to be zero.

Also, since it is well known that ML variance estimates are biased (since they use n rather than n-1 as denominators), a commonly preferred technique (and the default in SAS/R, but not STATA) is to use REML which stands for restricted (or residual) maximum likelihood. Essentially REML uses an unbiased method for estimating the variance components.

Mixed Effect Models for Non-normal Responses

A generalized linear model which incorporates random effects is called a "generalized linear mixed model".

As long as the link is linear, it is feasible to obtain estimates for the mixed effect model $\boldsymbol{Y}_i = \boldsymbol{X}_i\beta + \boldsymbol{Z}_i b_i + e_i$. When our outcome data is not modeled well with a linear link to the mean structure, e.g. binary data with a logit link, or Poisson data with a log link, then estimation becomes much more difficult using Maximum likelihood.

The reason is that the corresponding likelihood

$$L(\boldsymbol{\beta}, \mathbf{G}, \mathbf{R}|\mathbf{Y}) = \prod_{i=1}^{n} \int f(\mathbf{Y}_i|\mathbf{b}_i, \boldsymbol{\beta}, \mathbf{R}) g(\mathbf{b}_i|\mathbf{G}) d\mathbf{b}_i$$

has an integral in it that does not lend itself to straightforward maximization.

Estimation for Generalized Linear Mixed Models

A variety of approaches are available (still an active area of research) to approximate this likelihood using theoretical and numerical methods.

- In SAS, PROC NLMIXED/ In STATA: xtmelogit; xtmepoisson; gllamm (user-written package) in STATA / In R the nlme() function can be used to maximize the likelihood for a generalized linear mixed model, also Bayesian methods are commonly implemented for this model. Though theoretically maximizing the likelihood is the best approach, it is common to run into computational problems with these numerical methods.
- Another approach, which may be referred to as Pseudo-likelihood (Wolfinger, R. and O'Connell, M. (1993) Generalized linear mixed models: a pseudo-likelihood approach. *Journal of Statistical Computation and Simulation* 48, 233-243) which is implemented by Proc GLIMMIX (formerly the GLIMMIX macro in SAS) and approximates the nonlinear likelihood with a linear form and iteratively improves the estimates for **G** and **R**. It can also be implemented in R using glmmPQL().
- Completely avoid the likelihood and instead focus on Generalized Estimating Equations (GEE).

Generalized Estimating Equations

Consider again $\boldsymbol{Y}_i$ which represents the vector of observations in the i^{th} cluster. Let $E(\boldsymbol{Y}_i) = \mu_i$ which is linked to the linear predictor such that $g(\mu_i) = \boldsymbol{X}_i\beta$. Let $Var(\boldsymbol{Y}_i) \equiv Var(\boldsymbol{Y}_i; \beta, \alpha)$ where α represents parameters that model the correlation structure within individuals.

Parameters β are then estimated by solving the following score equation

$$\sum_{i=1}^{N} \left(\frac{\partial \mu_i}{\partial \beta}\right)' Var(Y_i)^{-1}(Y_i - \mu_i) = 0$$

- The key point which makes this method feasible and robust is that we don't need to know $Var(\boldsymbol{Y}_i)$, the estimates for β are consistent even if $Var(\boldsymbol{Y}_i)$ is misspecified.
- In GEE we use what is called the "working correlation matrix" as the best guess to the structure of $Var(\boldsymbol{Y}_i)$.
- This lack of focus on the $Var(\boldsymbol{Y}_i)$ is the key difference between random effects modeling and using GEE. With GEE, the focus is entirely on getting good estimates of β and their standard errors. We will not obtain estimates of person level variability or be able to say that some covariate explained X% of the between person variability.

Standard Errors for GEE

There are two types of standard errors available for GEE:

1. Model Based taken from the $\text{Co}v\left(\hat{\beta}\right) = I_0^{-1}$ where

   $I_0 = \sum_{i=1}^{N} \left(\frac{\partial \mu_i}{\partial \beta}\right)' V_i^{-1} \left(\frac{\partial \mu_i}{\partial \beta}\right)$

2. Empirical or robust or "sandwich formula" which uses $\text{Co}v\left(\hat{\beta}\right) = I_0^{-1} I_1 I_0^{-1}$

   where $I_1 = \sum_{i=1}^{N} \left(\frac{\partial \mu_i}{\partial \beta}\right)' V_i^{-1} Cov(Y_i) V_i^{-1} \left(\frac{\partial \mu_i}{\partial \beta}\right)$ where $Cov(Y_i)$ is replaced by the sum of squared residuals, i.e. $\left(Y_i - \mu_i\left(\hat{\beta}\right)\right)\left(Y_i - \mu_i\left(\hat{\beta}\right)\right)'$

The Model Based standard errors will only be correct when the correlation structure for $\mathbf{V}_i$ is specified correctly. But, the robust "sandwich" estimator can perform poorly in data with small samples. The "sandwich" estimator is consistent for the standard errors even when the correlations are specified incorrectly, but this property doesn't kick-in unless the N is large especially compared to the n_i (i.e. more clusters not more measurements within cluster) Both SAS and R use the robust standard errors by default. Stata uses the model based by default.

Implementing GEE in SAS, R, and Stata

In SAS: use Proc GENMOD with a Repeated statement.

In R: use function gee()

In STATA: use xtgee or xtreg with the pa “population average” option

Need to specify the “working correlation matrix”, that is, a covariance structure that mimics the likely covariance structure in the data. Common structures are: Compound symmetry or Exchangeable, Autoregressive, Unstructured, and Independent.

Pros and Cons of GEE compared to Generalized linear Mixed effect modeling (GLMM)

- GEE: Only one level of clustering, GLMM: multiple levels
- GEE: Not designed for inference about the covariance of random part, GLMM: Can do inference on covariance of error structure (random part)
- GEE: Does not give predicted values for each cluster, GLMM: can obtain a predicted value separate for each cluster.
- GEE: Computationally straightforward and fast, GLMM: Computationally hard and slow
- GEE: Consistent estimates of fixed effect parameters, GLMM: Consistent estimates of fixed effects parameters and most efficient if random effects covariance structure is correct.
- GEE: Assumes missing data is MCAR, GLMM: Assumes missing data is MAR
- GEE: fits marginal model, GLMM: fits conditional model

Marginal versus Conditional Models

There are two main ways to build in correlation in a statistical model:

- Marginal: Assume a model, e.g. logistic, that holds averaged over all the clusters (sometimes called population averaged). Coefficients have the interpretation as the average change in the response (over the entire population) for a unit change in the predictor.
- Conditional: Assume a model specific to each cluster (sometimes called subject specific). If you want to know about the population, average it over all the clusters. Coefficients have the interpretation as the change in the response for each cluster in the population.

NOTE: when the outcome-predictor relationship is linear, these are equivalent. That is, the average of the individual's coefficients is the same as the overall population (or marginal) coefficient. When the relationship is non-linear, e.g. logit, they are NOT the same. See example taken from VGSM text Section 8.5.

Marginal versus Conditional Models

Hypothetical example from VGSM text Section 8.5...

Suppose we are modeling the chance that a patient will be able to withstand a course of chemotherapy without serious adverse reactions. Patients have very different tolerances for chemotherapy, so the subject specific curves are quite different (See plots on next pages)...

For further reading of the differences between marginal (GEE) and conditional models (GLMM) see:

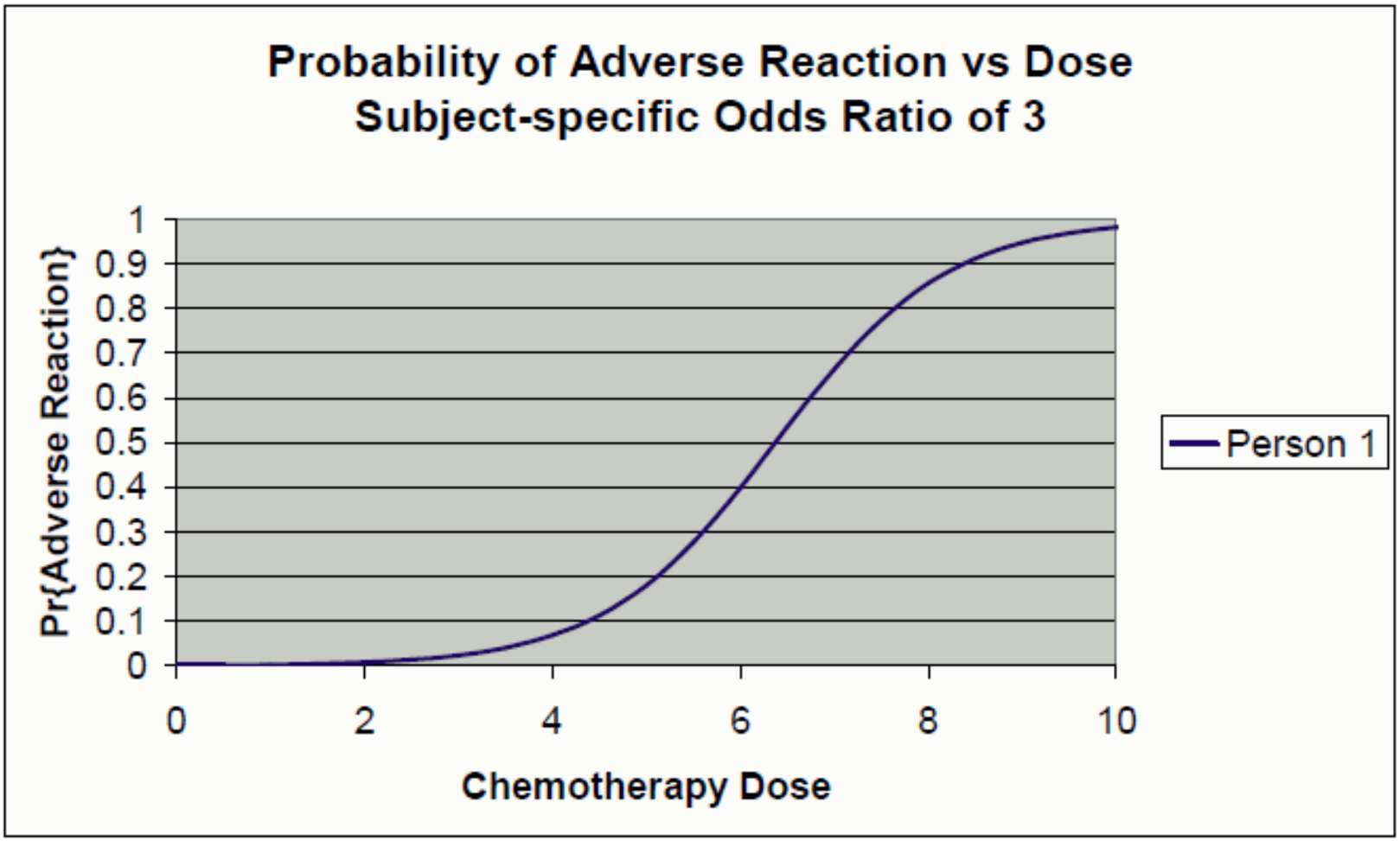
Carriere I and Bouyer J (2002) Choosing marginal or random-effects models for longitudinal binary responses: application to self-reported disability among older persons, BMC Medical research Methodology, 2:15.

Burton, P., Gurrin, L., Sly, P. Tutorial in Biostatistics: Extending the Simple Linear Regression Model to Account for Correlated Responses: An Introduction to Generalized Estimating Equations and Multi-Level Modelling" Statistics in Medicine 17, 1261-1291 (1998).

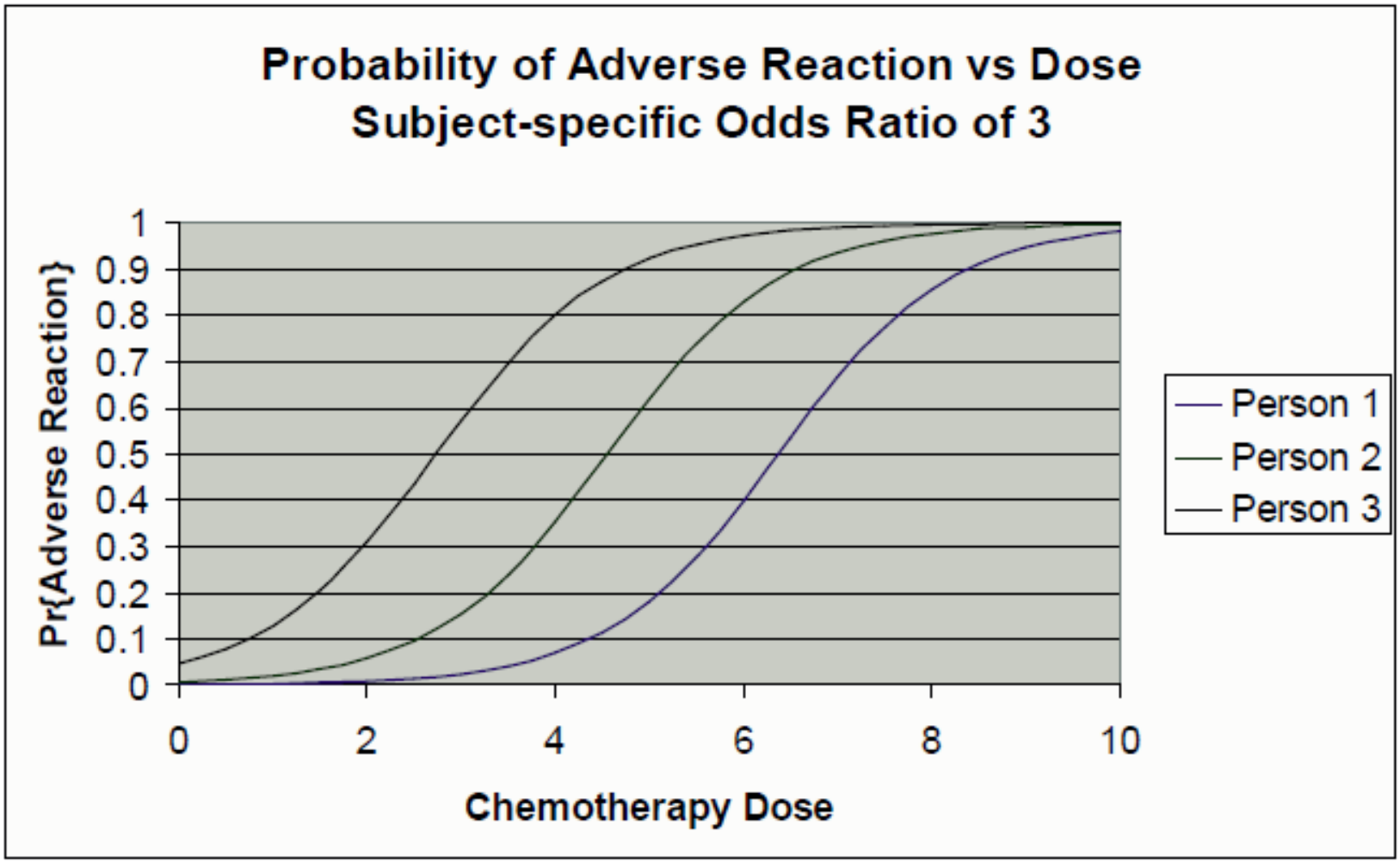
Anath CV, Platt RW, Savitz DA (2005) Regression Models for clustered binary responses: implications of ignoring the intracluster correlation in an analysis of perinatal mortality in twin gestations. Annals of Epidemiology, 15(4), 293-301.

Hubbard AE, Ahern J, Fleischer NL et al. (2010) To GEE or Not to GEE Comparing Population Average and Mixed Models for Estimating the Associations Between Neighborhood Risk Factors and Health. Epidemiology, Volume 21, Number 4, July 2010

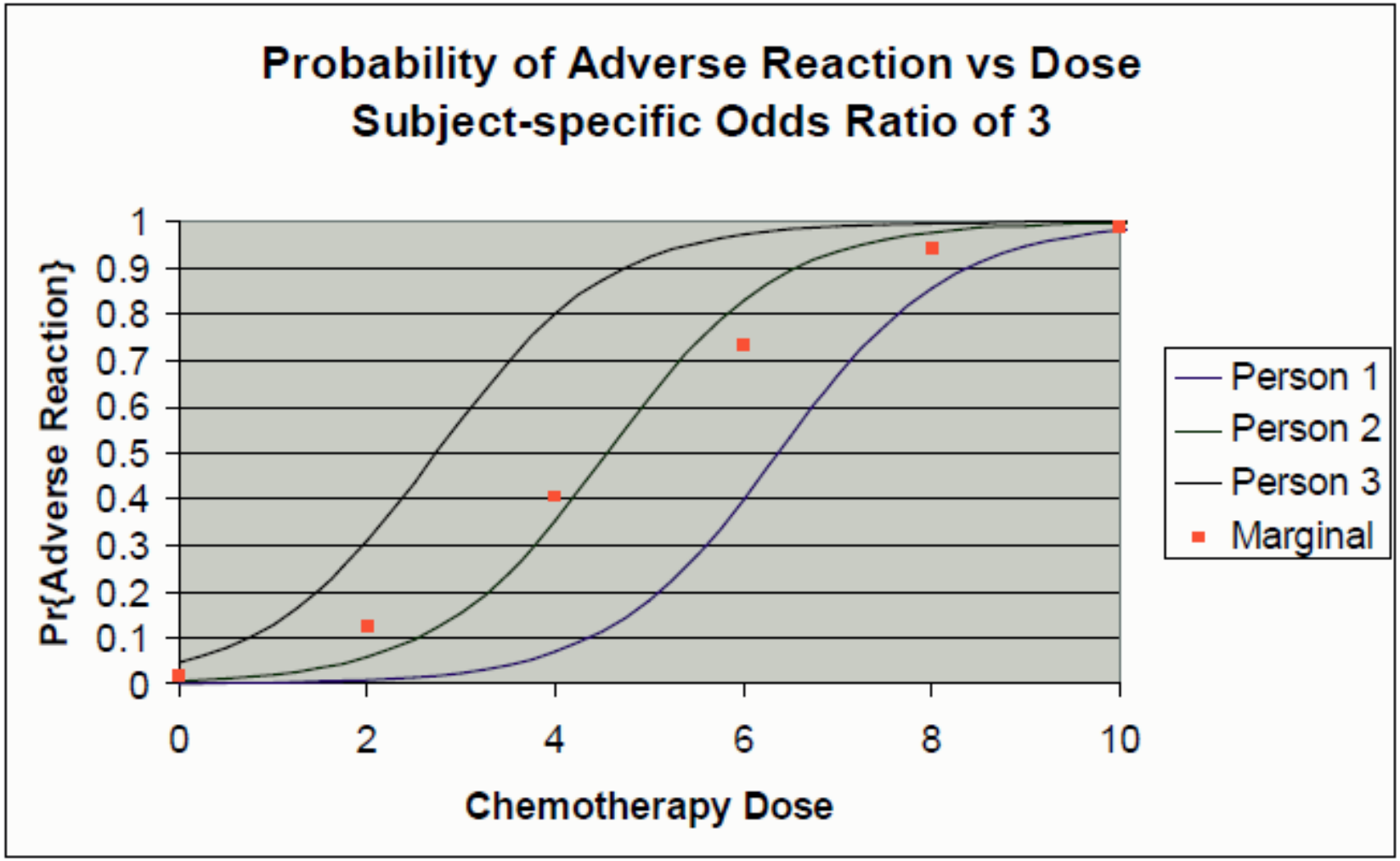
One person:


Probability of Adverse Reaction vs Dose
Subject-specific Odds Ratio of 3
Pr{Adverse Reaction}
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
Chemotherapy Dose
Person 1

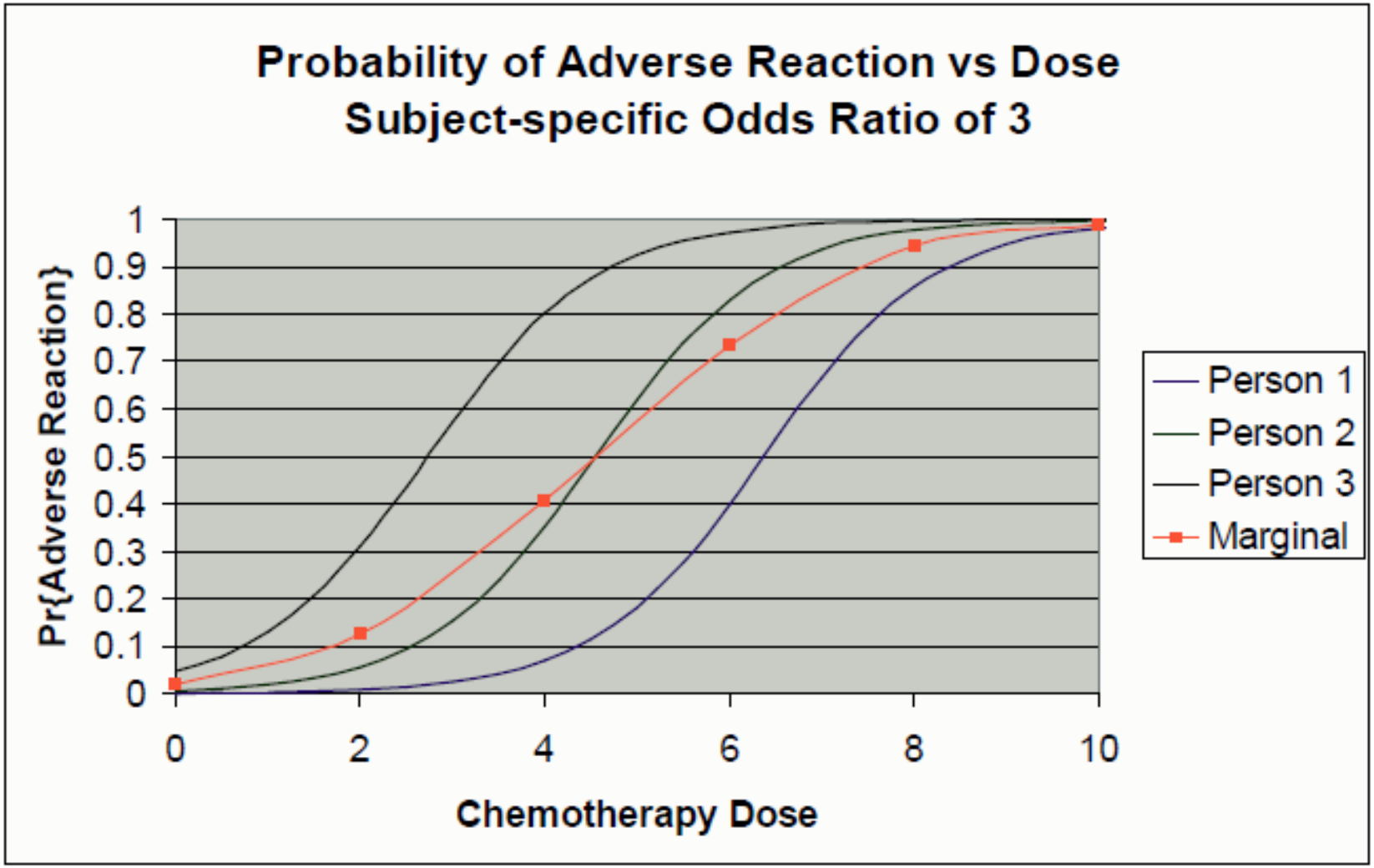
Multiple people:



Averages at specific doses



Marginal regression:



Non-Linear Link: Georgia Birthweight Example

Georgia Birthweight data: birthweights of first-born and last-born infants from mothers (each of whom had five children) from vital statistics in Georgia. (VGSM Chapter 8.3.2)

Research question: How the low birthweight status (<3,000g) of babies changes by birth order (first to fifth) and whether this difference depends on the age of the woman when she had her first-born.

Georgia Birthweight Example: independent correlation

```
. xtgee lowbrth birthord initage, i(momid) corr(ind) family(binomial) link(logit) ef
GEE population-averaged model                   Number of obs      =      1000
Group variable:                         momid   Number of groups   =       200
Link:                                   logit   Obs per group: min =         5
Family:                              binomial                  avg =       5.0
Correlation:                      independent                  max =         5
                                                Wald chi2(2)       =     18.13
Scale parameter:                            1   Prob > chi2        =    0.0001

Pearson chi2(1000):                   1003.09   Deviance           =   1299.35
Dispersion (Pearson):                1.003089   Dispersion         =  1.299354
------------------------------------------------------------------------------
     lowbrth | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |   .9204561   .0430753    -1.77   0.077     .8397861    1.008875
     initage |   .9155828   .0207316    -3.89   0.000      .875838    .9571313
       _cons |   3.505028   1.477288     2.98   0.003     1.534368    8.006694
------------------------------------------------------------------------------
```

This is equivalent to:

```
. glm lowbrth birthord initage, family(binomial) link(logit) ef
```

Georgia Birthweight Example: exchangeable correlation

```
. xtgee lowbrth birthord initage, i(momid) corr(exch) family(binomial) link(logit) ef
GEE population-averaged model                   Number of obs      =      1000
Group variable:                        momid    Number of groups   =       200
Link:                                  logit    Obs per group: min =         5
Family:                             binomial                   avg =       5.0
Correlation:                   exchangeable                   max =         5
                                                Wald chi2(2)       =     11.30
Scale parameter:                           1    Prob > chi2        =    0.0035
------------------------------------------------------------------------------
     lowbrth | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |   .9204098   .0359157    -2.13   0.034     .8526408    .9935651
     initage |   .9148199   .0308985    -2.64   0.008      .856221    .9774293
       _cons |   3.553325   2.144814     2.10   0.036     1.088537    11.59917
------------------------------------------------------------------------------
```

Robust standard errors:

```
. xtgee lowbrth birthord initage, … vce(robust)
------------------------------------------------------------------------------
             |             Semirobust
     lowbrth | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |   .9204098     .03542    -2.16   0.031     .8535413    .9925168
     initage |   .9148199   .0312663    -2.60   0.009     .8555464    .9781999
       _cons |   3.553325   2.167263     2.08   0.038     1.075142    11.74368
------------------------------------------------------------------------------
```

Georgia Birthweight Example: exchangeable correlation

```
proc genmod data=bwt descending;
           class momid;
           model lowbrth=birthord initage / dist = binomial link = logit type3;
           repeated subject = momid /type = cs modelse;
           estimate "OR(birthord)" birthord 1/exp;
           estimate "OR(initage)" initage 1/exp;
run;
   Exchangeable Working
        Correlation
Correlation    0.3049933764     ← In Stata, use ╥estat wcor- after ╥xtgee- to obtain this estimate

  GEE Fit Criteria
QIC          1309.6471           ← similar to AIC/BIC in LMM. In stata, download ╥qic- package
QICu         1305.3556

             Analysis Of GEE Parameter Estimates
              Empirical Standard Error Estimates
                   Standard   95% Confidence
Parameter Estimate    Error       Limits            Z Pr > |Z|
Intercept   1.2679   0.6084   0.0754   2.4603    2.08   0.0372
birthord   -0.0829   0.0384  -0.1582  -0.0077   -2.16   0.0307
initage    -0.0890   0.0341  -0.1558  -0.0222   -2.61   0.0090

             Analysis Of GEE Parameter Estimates
             Model-Based Standard Error Estimates
                   Standard   95% Confidence
Parameter Estimate    Error       Limits            Z Pr > |Z|
Intercept   1.2679   0.6034   0.0853   2.4504    2.10   0.0356
birthord   -0.0829   0.0390  -0.1594  -0.0064   -2.12   0.0336
initage    -0.0890   0.0338  -0.1552  -0.0229   -2.64   0.0084
```

Georgia Birthweight Example: GLMM

```
proc glimmix data=bwt;
           class momid;
           model lowbrth(descending)=birthord initage / dist = binomial link = logit solution;
           random intercept / subject = momid;
           estimate "OR(birthord)" birthord 1/exp;
           estimate "OR(initage)" initage 1/exp;
run;

The GLIMMIX Procedure
       Covariance Parameter Estimates
                                    Standard
Cov Parm     Subject    Estimate       Error
Intercept    momid        1.5042      0.2755

                  Solutions for Fixed Effects
                        Standard
Effect       Estimate       Error       DF    t Value    Pr > |t|
Intercept      1.4250      0.6700      198       2.13      0.0347
birthord     -0.09961     0.05132      799      -1.94      0.0526
initage       -0.1002     0.03684      799      -2.72      0.0067

                                    Estimates
                          Standard                                    Exponentiated
Label           Estimate       Error       DF    t Value    Pr > |t|         Estimate
OR(birthord)    -0.09961     0.05132      799      -1.94      0.0526           0.9052
OR(initage)      -0.1002     0.03684      799      -2.72      0.0067           0.9047
```

Georgia Birthweight Example: GLMM

```
. xtmelogit lowbrth birthord initage || momid:, or var
Mixed-effects logistic regression               Number of obs      =      1000
Group variable: momid                           Number of groups   =       200
                                                Obs per group: min =         5
                                                               avg =       5.0
                                                               max =         5
Integration points =   7                        Wald chi2(2)       =     11.85
Log likelihood = -588.07113                     Prob > chi2        =    0.0027
------------------------------------------------------------------------------
     lowbrth | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    birthord |   .8872745   .0500702    -2.12   0.034     .7943711    .9910432
     initage |   .8808974   .0406081    -2.75   0.006     .8047967    .9641941
       _cons |   6.009049   4.991562     2.16   0.031       1.1796    30.61095
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
momid: Identity              |
                  var(_cons) |    2.58756   .5393782      1.719718    3.893354
------------------------------------------------------------------------------
LR test vs. logistic regression: chibar2(01) =   123.21 Prob>=chibar2 = 0.0000
```

Note: Stata and SAS use different methods (MLE vs Pseudo-likelihood) to estimate the parameters, so the results are slightly different.

GEE vs GLMM: Interpretation for ORs

GEE: Odds of having a low birthweight baby decrease by 8% with each increase in birth order. It represents the Odds of having a low birthweight baby for a randomly chosen mom compared to odds of having a low birthweight baby for another randomly chosen mom at lower birth order.

GLMM: Odd of having a low birthweight baby decrease by 11% with each increase in birth order, *for a specific mom*.

Note: It is very common to see the OR from the random effect model being larger (farther from 1) in magnitude than the Population average (i.e. averaging over different rates of abstaining at different clinics) estimate.