

Repeated Measures and Longitudinal Data Analysis II

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Welcome and outline - session 10

- ▶ Learning objectives
 - ▶ identify hierarchical data
 - ▶ define mixed effects models and population average models
 - ▶ perform model diagnostics for random effects models
 - ▶ interpret random intercepts and random slopes
- ▶ Vittinghoff sections 8.2, 8.3, 8.5

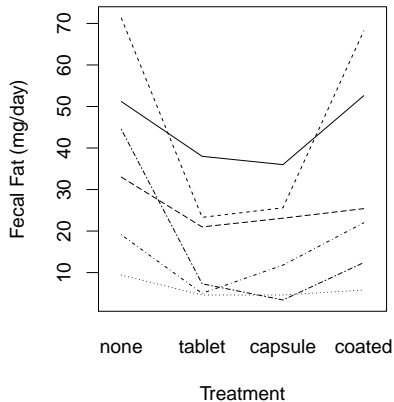
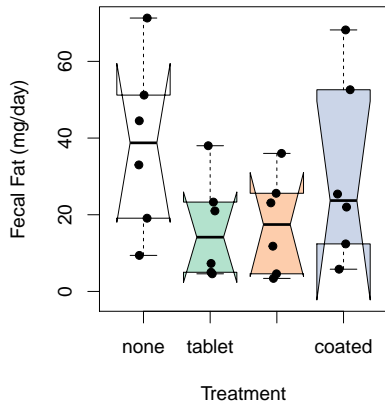
Recall the simple repeated measures example: fecal fat

- ▶ 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 alleviate the problem.
 - ▶ fecfat.csv: a study of fecal fat quantity (g/day) for individuals given each of a placebo and 3 types of pills

Table 7.1 Fecal fat (g/day) for six subjects

Subject number	Pill type				Subject Average
	None	Tablet	Capsule	Coated	
1	44.5	7.3	3.4	12.4	16.9
2	33.0	21.0	23.1	25.4	25.6
3	19.1	5.0	11.8	22.0	14.5
4	9.4	4.6	4.6	5.8	6.1
5	71.3	23.3	25.6	68.2	47.1
6	51.2	38.0	36.0	52.6	44.5
Pill type average	38.1	16.5	17.4	31.1	25.8

Fecal fat dataset



Analysis strategies for hierarchical data

- ▶ Analyses for each subgroup
 - ▶ e.g., look at each patient independently
 - ▶ doesn't work at all in this example, and in general is not an integrated analysis of the whole data
 - ▶ could sort of work for an example with many patients per doctor, a few doctors
- ▶ Analysis at the highest level in the hierarchy
 - ▶ first summarize data to highest level
 - ▶ doesn't work at all in this example
 - ▶ could sort of work for an example with many patients per doctor, a few doctors
- ▶ Analysis on “Derived Variables”
 - ▶ consider each treatment type separately, take differences in fat levels between treatment/control for each patient and use paired t-tests
 - ▶ can work, but not work for unbalanced groups (e.g. incomplete data for some participants)

Better analysis strategies for hierarchical data

- ▶ Fixed effects models
- ▶ Random / mixed effects models
 - ▶ model certain regression coefficients (intercept, slopes) as random variables
- ▶ Population average models
 - ▶ using Generalized Estimating Equations (GEE)

When is hierarchical analysis needed?

- ▶ Hierarchical analysis strategies are needed:
 1. when the correlation structure is of primary interest, e.g. familial aggregation of disease, or consistency of treatment within centers,
 2. when we wish to “borrow strength” across the levels of a hierarchy in order to improve estimates, and
 3. when dealing with unbalanced, correlated data.

Fixed effects: two-way analysis of variance

- ▶ Two-way ANOVA (person i with pill type j):

$$FECFAT_{ij} = \beta_0 + \beta_{subjecti} SUBJECT_i + \beta_{pilltypej} PILLTYPE_j + \epsilon_{ij}$$

Assumption: $\epsilon_i \stackrel{iid}{\sim} N(0, \sigma_\epsilon^2)$

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
subject	5	5588.38	1117.68	10.45	0.0002
pilltype	3	2008.60	669.53	6.26	0.0057
Residuals	15	1604.98	107.00		

Table 1: Two-way analysis of variance table. Equivalent to subtracting the mean fecal fat content for each individual.

* Accounts for individual differences in mean fecal fat * Fits a coefficient for mean fecal fat per individual

Mixed effects model

- ▶ Model looks like two-way ANOVA:

$$FECFAT_{ij} = \beta_0 + \beta_{subject_i} SUBJECT_i + \beta_{pilltype_j} PILLTYPE_j + \epsilon_{ij}$$

- ▶ Assumption: $\epsilon_i \stackrel{iid}{\sim} N(0, \sigma_\epsilon^2)$
- ▶ But instead of fitting a β to each individual, we assume that the subject effects are selected from a distribution of possible subject effects:

$$FECFAT_{ij} = \beta_0 + SUBJECT_i + \beta_{pilltype_j} PILLTYPE_j + \epsilon_{ij}$$

Where we assume: $SUBJECT_i \stackrel{iid}{\sim} N(0, \tau_{00}^2)$

- ▶ This is a *mixed effects* model because:
 - ▶ the “true” intercept varies randomly from patient to patient
 - ▶ the “true” (population) coefficient of treatment is fixed (the same for everyone)

Mixed effects model coefficients, variances, ICC

```
## Linear mixed-effects model fit by REML
## Data: fecfat
## Log-restricted-likelihood: -84.55594
## Fixed: fecfat ~ pilltype
## (Intercept) pilltypetablet pilltypecapsule pilltypecoated
## 38.083334 -21.550001 -20.666667 -7.016668
##
## Random effects:
## Formula: ~1 | subject
## (Intercept) Residual
## StdDev: 15.89557 10.34403
##
## Number of Observations: 24
## Number of Groups: 6
```

$$ICC = 15.9^2 / (15.9^2 + 10.34^2) = 0.7 = 0.7.$$

- ▶ Recall ICC is a measure of how large the subject effect is, in relation to the error term
- ▶ Variances were estimated directly by the model!

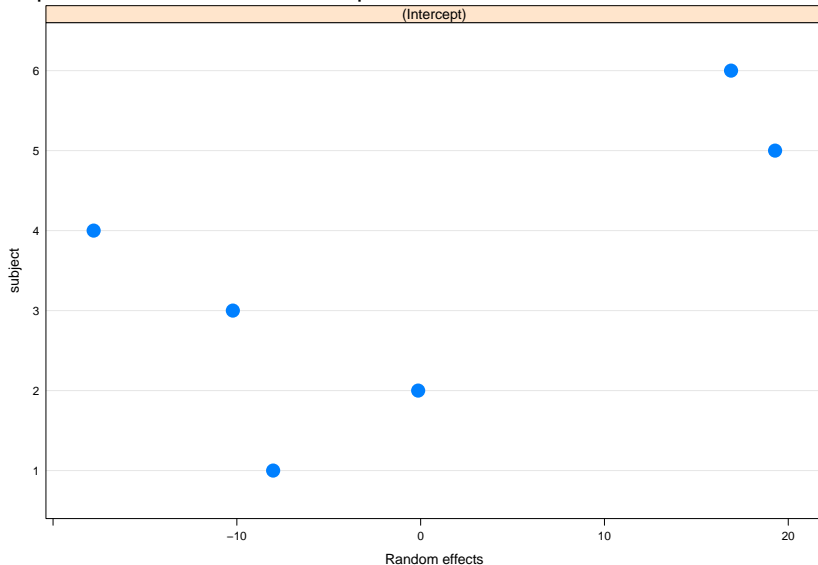
Assumptions of the mixed model

$$FECFAT_{ij} = \beta_0 + SUBJECT_i + \beta_{pilltypej} PILLTYPE_j + \epsilon_{ij}$$

- ▶ Normally distributed residuals as in fixed effects model:
 - ▶ $\epsilon_i \stackrel{iid}{\sim} N(0, \sigma_\epsilon^2)$
- ▶ Normally distributed **latent variable**:
 - ▶ $SUBJECT_i \stackrel{iid}{\sim} N(0, \tau_{00}^2)$

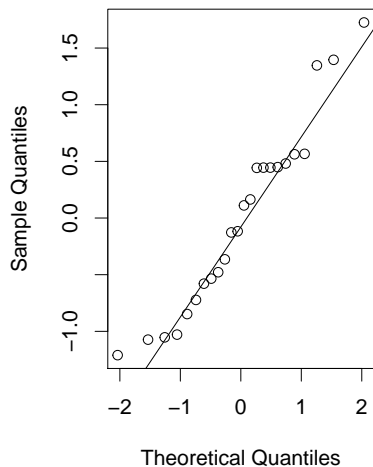
Mixed effects model results (cont'd)

A plot of the random intercept:

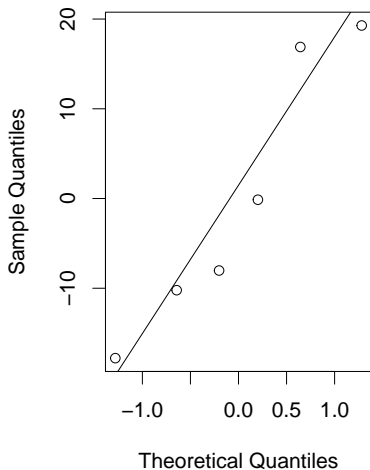


Mixed effects model diagnostics

QQ plot residuals



QQ plot random intercepts



Mixed effects model results

```
## Linear mixed-effects model fit by REML
## Data: fecfat
##      AIC      BIC    logLik
##  181.1119 187.0863 -84.55594
##
## Random effects:
## Formula: ~1 | subject
##      (Intercept) Residual
## StdDev:      15.89557 10.34403
##
## Fixed effects: fecfat ~ pilltype
##              Value Std.Error DF   t-value p-value
## (Intercept)   38.08333  7.742396 15   4.918805  0.0002
## pilltypetablet -21.55000  5.972127 15  -3.608430  0.0026
## pilltypecapsule -20.66667  5.972127 15  -3.460521  0.0035
## pilltypecoated  -7.01667  5.972127 15  -1.174903  0.2583
## Correlation:
##              (Intr) plltypt plltypcp
## pilltypetablet -0.386
## pilltypecapsule -0.386  0.500
## pilltypecoated -0.386  0.500  0.500
##
## Standardized Within-Group Residuals:
##              Min          Q1          Med          Q3          Max
## -1.210052934 -0.615068039 -0.002727166  0.457105344  1.725618643
##
## Number of Observations: 24
## Number of Groups: 6
```

- Note: correlation of the estimator of the fixed effects
 - high correlations may (but not necessarily) be due to collinearity

Mixed effects model results (cont'd)

Inference for variance terms (and fixed effects):

```
## Approximate 95% confidence intervals
##
## Fixed effects:
##           lower      est.      upper
## (Intercept)  21.58081  38.083334  54.585860
## pilltypetablet -34.27929 -21.550001 -8.820714
## pilltypecapsule -33.39595 -20.666667 -7.937381
## pilltypecoated -19.74595  -7.016668  5.712618
## attr("label")
## [1] "Fixed effects:"
##
## Random Effects:
## Level: subject
##           lower      est.      upper
## sd((Intercept)) 8.001171 15.89557 31.57904
##
## Within-group standard error:
##           lower      est.      upper
## 7.232404 10.344027 14.794374
```

- ▶ Would conclude that variation of the intercept between subjects is non-zero
 - ▶ not attributable to within-subject variation

Longitudinal data

- ▶ Interested in the change in the value of a variable within a “subject”
- ▶ Collect data repeatedly through time.
- ▶ For hierarchical longitudinal analysis to be effective, before/after measurements need to be positively correlated

Longitudinal data

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Longitudinal data examples

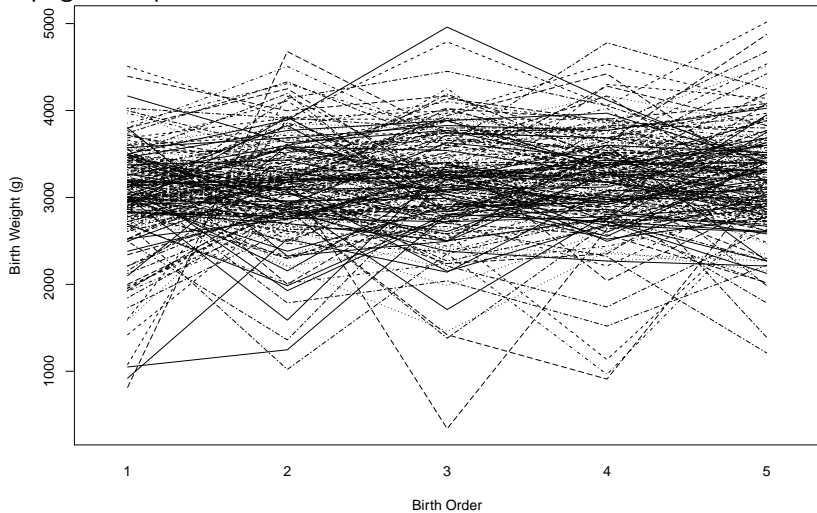
- ▶ Example 1: a measure of sleepiness before and after administration of treatment or placebo
- ▶ Example 2: Study of Osteoporotic Fractures (SOF dataset)
 - ▶ 9,704 women tracked with clinical visits every two years
 - ▶ Bone Mineral Density (BMD), Body Mass Index (BMI), many other variables
- ▶ Questions for Example 2:
 1. Is change in BMD related to age at menopause? This is a time-invariant predictor, age at menopause, with time-dependent changes in the outcome, BMD.
 2. Is change in BMD related to change in BMI? This is an analysis relating a time-varying predictor, BMI, with changes in the outcome, BMD. BMI varies quite a lot between women, but also varies within a woman over time.

Longitudinal data examples (cont'd)

- ▶ birthweight and birth order
- ▶ provides birthweights and order of infants from mothers who had 5 children in Georgia
 - ▶ interested in whether birthweight of babies changes with order
 - ▶ whether this difference depends on the *mother's age at first childbirth* or on the *weight of initial baby*.

Georgia Birthweights dataset

“Spaghetti” plot:



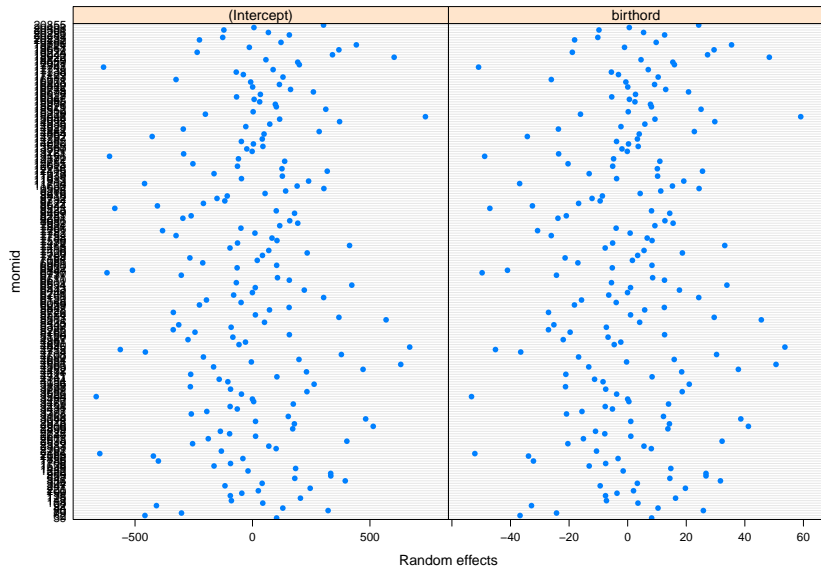
Georgia Birthweights dataset

- ▶ Do birth weights or the effect of birth order vary by mother?
 - ▶ random intercept, random slope

```
gafit1 <- nlme::lme(bweight ~ birthord, data=ga,  
  random=~birthord|momid,  
  na.action=na.omit,  
  control=list(msMaxIter=600, msMaxEval=600,  
    sing.tol=1e-20, msVerbose=FALSE))
```

Note: the control argument increases the max # iterations to allow convergence. If `msVerbose=TRUE`, it produces verbose output.

Georgia Birthweights dataset (cont'd)



Georgia Birthweights dataset (cont'd)

```
summary(gafit1)
```

```
## Linear mixed-effects model fit by REML
## Data: ga
##      AIC      BIC    logLik
## 15321.23 15350.67 -7654.616
##
## Random effects:
## Formula: ~birthord | momid
## Structure: General positive-definite, Log-Cholesky parametrization
##           StdDev   Corr
## (Intercept) 296.36304 (Intr)
## birthord    23.82664 0.996
## Residual    443.43313
##
## Fixed effects: bweight ~ birthord
##           Value Std.Error DF t-value p-value
## (Intercept) 2995.640  38.99534 799 76.82046      0
## birthord    46.608  10.05758 799 4.63411      0
## Correlation:
##           (Intr)
## birthord -0.662
##
## Standardized Within-Group Residuals:
##           Min      Q1      Med      Q3      Max
## -5.32850276 -0.42195082  0.04103012  0.53113344  3.25512201
##
## Number of Observations: 1000
## Number of Groups: 200
```

Georgia Birthweights dataset (cont'd)

```
intervals(gafit1)
```

```
## Approximate 95% confidence intervals
##
## Fixed effects:
##           lower      est.      upper
## (Intercept) 2919.09459 2995.640 3072.18541
## birthord    26.86559   46.608   66.35041
## attr(,"label")
## [1] "Fixed effects:"
##
## Random Effects:
## Level: momid
##           lower      est.      upper
## sd((Intercept))    227.421283 296.3630360 386.20418
## sd(birthord)        9.351472  23.8266383  60.70795
## cor((Intercept),birthord) -1.000000  0.9964047  1.00000
##
## Within-group standard error:
##           lower      est.      upper
## 422.2138 443.4331 465.7189
```

- ▶ Do birth weights or the effect of birth order vary by mother?
 - ▶ yes: both standard deviations are non-zero

Population Average Models

- ▶ An alternative to random / mixed-effects models that is more robust to assumptions of:
 - ▶ distribution of random effects
 - ▶ correlation structure
- ▶ Estimates correlation structure from the data rather than assuming normality
 - ▶ Requires a fair bit more clusters than observations per cluster
- ▶ Estimates regression coefficients and robust standard errors
 - ▶ commonly by Generalized Estimating Equations (GEE)

Population Average Models

- ▶ Compare mixed model multiple linear regression:

$$E[Y_{ij}|X_{ij}] = \beta_0 + \alpha_{0j} + \beta_1 X_{ij}, \alpha_{0j} \sim N(0, \sigma)$$

for subject i in group j .

- ▶ to a population average model:

$$E[Y_{ij}|X_{ij}] = \beta_0^* + \beta_1^* X_{ij}$$

- ▶ Interpretations of β^* and β are equivalent
- ▶ Numerically equivalent for linear and log-linear models (if specification of mixed model is correct), but not for logistic link.

Fit a population average model

```
gafit.gee <- gee::gee(bweight ~ birthord, corstr="exchangeable",  
                     id=momid, data=ga)
```

```
summary(gafit.gee)
```

```
##  
## GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA  
## gee S-function, version 4.13 modified 98/01/27 (1998)  
##  
## Model:  
## Link: Identity  
## Variance to Mean Relation: Gaussian  
## Correlation Structure: Exchangeable  
##  
## Call:  
## gee::gee(formula = bweight ~ birthord, id = momid, data = ga,  
## corstr = "exchangeable")  
##  
## Summary of Residuals:  
##      Min      1Q    Median      3Q      Max  
## -2795.464 -299.126   48.840   341.144  1824.536  
##  
##  
## Coefficients:  
##      Estimate Naive S.E.   Naive z Robust S.E.  Robust z  
## (Intercept) 2995.640  41.973695 71.369462   38.808066  77.191170  
## birthord      46.608   9.958128  4.680398    9.996256   4.662546  
##  
## Estimated Scale Parameter: 332525.3  
## Number of Iterations: 1  
##  
## Working Correlation  
##      [,1]      [,2]      [,3]      [,4]      [,5]  
## [1,] 1.0000000 0.4035684 0.4035684 0.4035684 0.4035684
```

GEE working correlation types

- ▶ Must make some assumption about form correlation among observations from the same subject, same hospital, etc
- ▶ Independence
 - ▶ no correlation between measurements within group
- ▶ Exchangeable
 - ▶ all correlations (except those variables with themselves) are a common value
 - ▶ nothing to distinguish one member of a cluster from another
 - ▶ appropriate in the absence of other data structures such as measurements taken through time or space
- ▶ Auto-regressive
 - ▶ observations taken more closely in time are more highly correlated

GEE working correlation types

- ▶ Unstructured
 - ▶ estimates a separate correlation between observations taken on each pair of “times”
- ▶ Non-stationary
 - ▶ similar to unstructured, but assumes all correlations for pairs separated far enough in time are zero
- ▶ Stationary
 - ▶ e.g. stationary of order 2: observations taken at time points 1 and 3 have the same correlation as time points 2 and 4
 - ▶ but this might be different from the correlation between observations taken at times 2 and 3
 - ▶ correlations for observations 3 or more time periods apart assumed to be zero

Fewer assumptions requires more data, and good assumptions improve results

Help in choosing a method

Characteristic	Marginal	Fixed-effect	Mixed-effect
Distinguishes observations belonging to the same or different subjects	Yes ^a	Yes	Yes
Reliant on distribution of subject-specific effects	No	No	Yes
Subjects considered a sample from a population larger than the sample itself	Yes ^a	No	Yes
Computation handles few subjects well	No	Yes	No
Computation handles a very large number of subjects well	Yes	No	Yes
Noisy for few observations per subject	No	Yes	No
Computation handles a large number of observations per subject	Depends ^b	Yes	Yes
Accommodates variable observations per subject	Yes	Yes	Yes

Note: ^aOnly for calculation of standard errors.

^bProblems can arise under some specifications of the working covariance structure and depending on the estimation method used.

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Figure 2: decision table

Conclusions

- ▶ Ignoring within-subject correlations can produce very wrong results, and is not always “conservative”
- ▶ Hierarchical analysis strategies are needed for any of:
 1. When the correlation structure is of primary interest, e.g. familial aggregation of disease, or consistency of treatment within centers,
 2. When we wish to “borrow strength” across the levels of a hierarchy in order to improve estimates, and
 3. When dealing with unbalanced correlated data. E.g., no requirement that each Georgia mother have exactly 5 children.
- ▶ Population average models provide a robust alternative to mixed models
 - ▶ for one level of hierarchy

Lab exercise

- ▶ Continue the MLM_R.pdf lab from session 9
- ▶ Fit population average models using several different working correlation structures, and compare the results to each other and to the mixed model