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

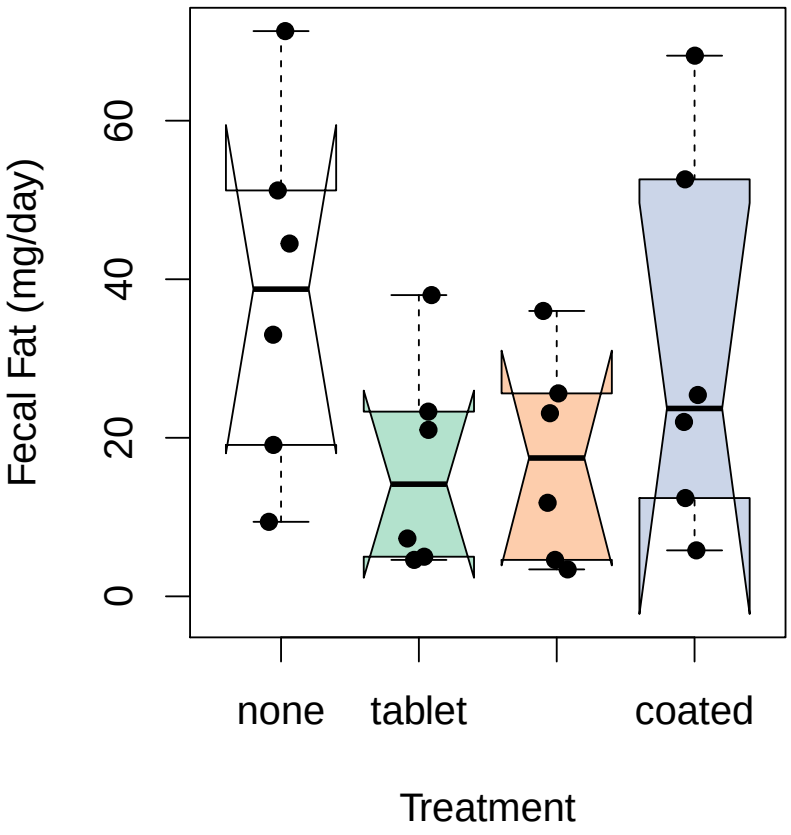
Recall the simple repeated measures example: fecal fat

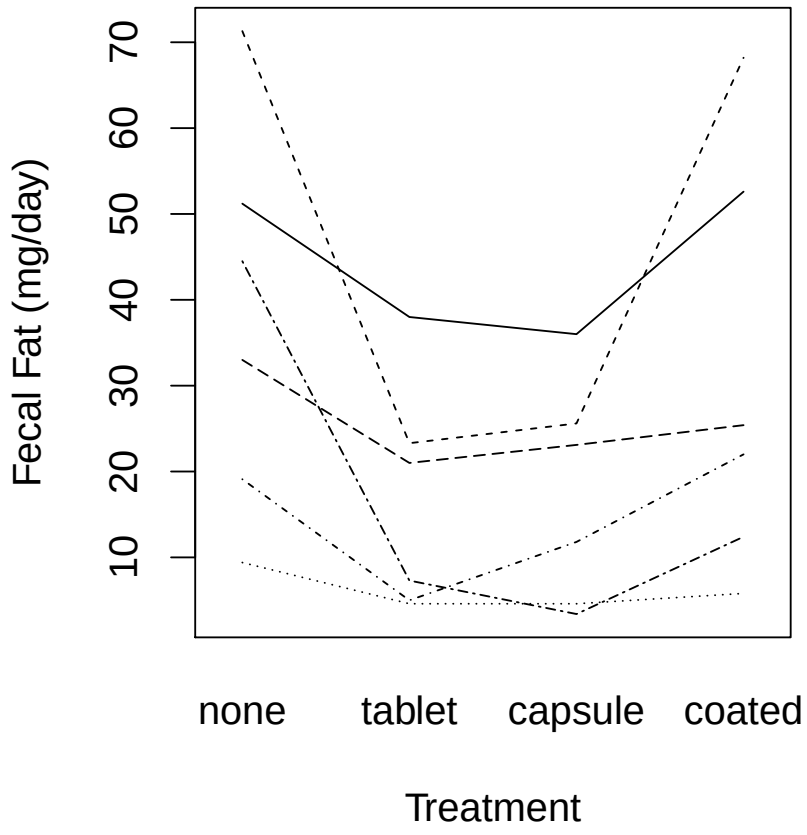
- Lack of digestive enzymes in the intestine can cause bowel absorption problems.
  - This will be indicated by excess fat in the feces.
  - Pancreatic enzyme supplements can alleviate the problem.
  - fecfat.csv: a study of fecal fat quantity (g/day) for individuals given each of a placebo and 3 types 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: $\epsilon_i \overset{iid}{\sim} N(0, \sigma^2_\epsilon)$

	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 indivudual

Mixed effects model

- Model looks like two-way ANOVA:

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

  - Assumption: $\epsilon_i \overset{iid}{\sim} N(0, \sigma^2_\epsilon)$

- But instead of fitting a β to each individual, we assume that the subject effects are selected from a distribution of possible subject effects:

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

Where we assume: $SUBJECT_i \overset{iid}{\sim} N(0, \tau^2_{00})$

- 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 coeffients, 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!

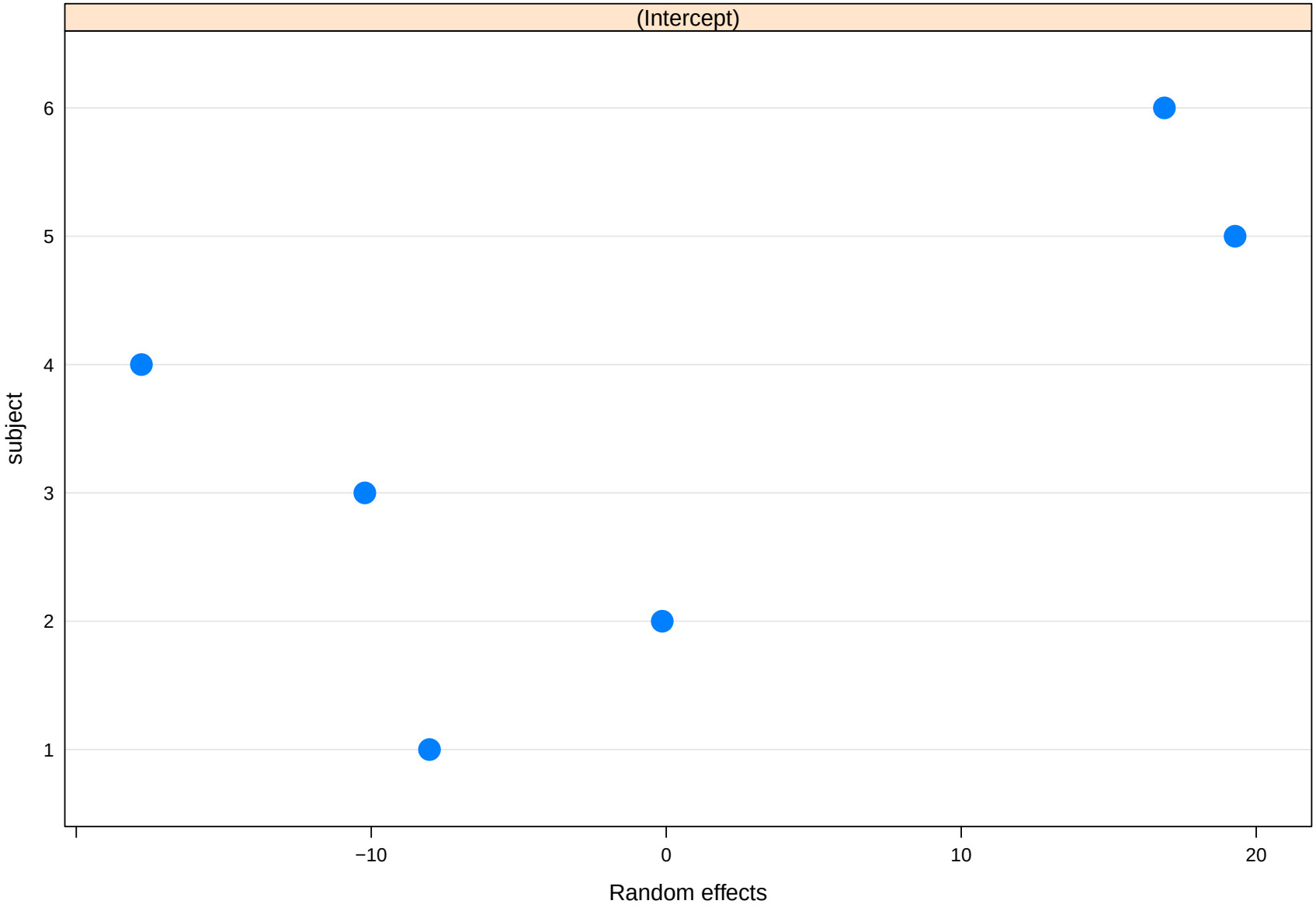
Assumptions of the mixed model

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

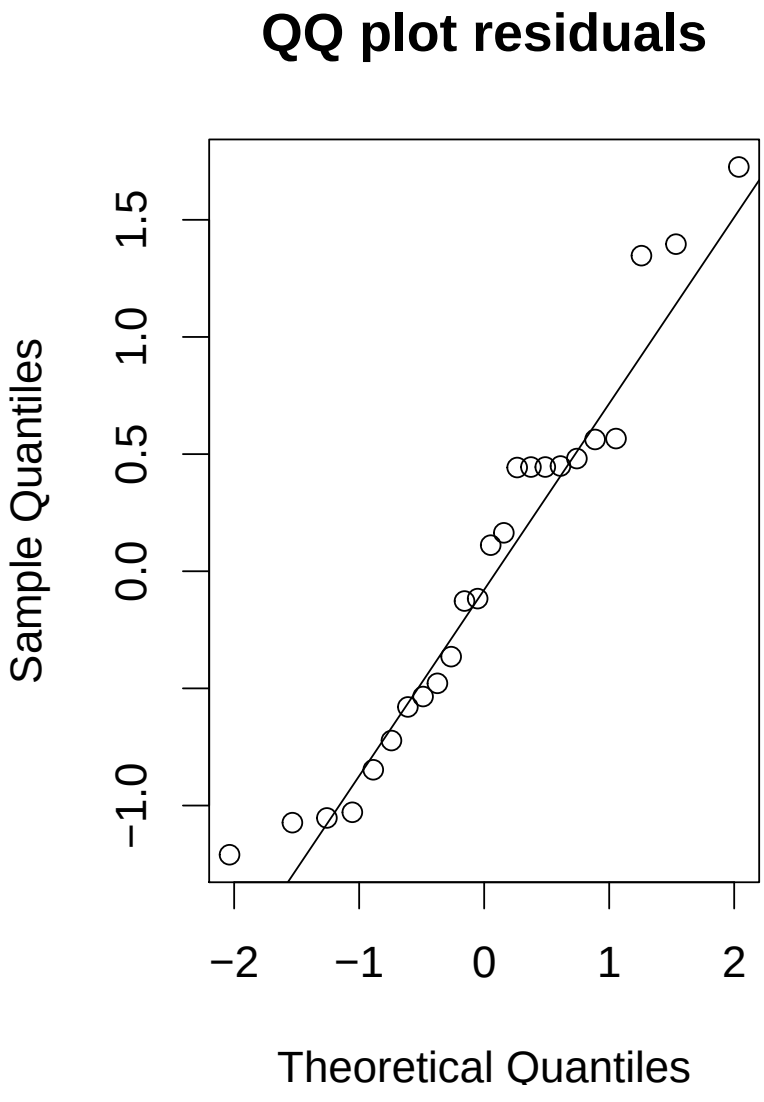
- Normally distributed residuals as in fixed effects model:
  - $\epsilon_i \overset{iid}{\sim} N(0, \sigma^2_\epsilon)$
- Normally distributed **latent variable**:
  - $SUBJECT_i \overset{iid}{\sim} N(0, \tau^2_{00})$

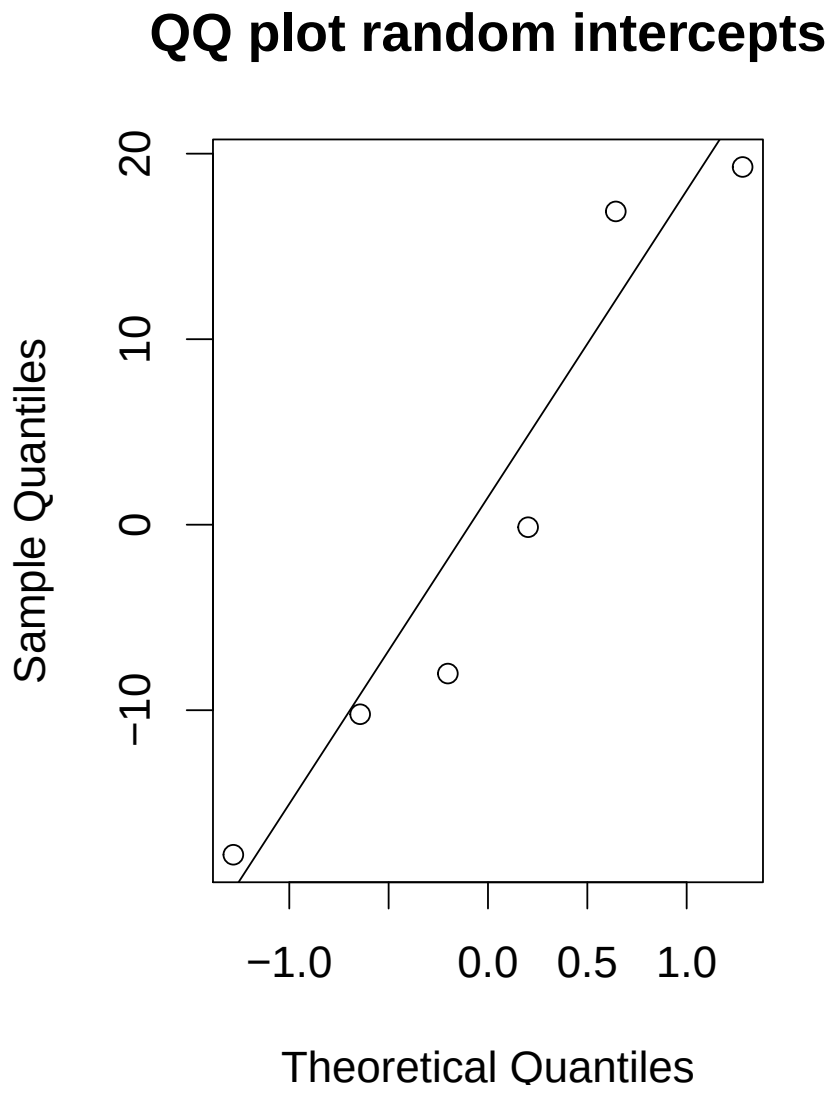
Mixed effects model results (cont'd)

A plot of the random intercept:



Mixed effects model diagnostics





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

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Longitudinal data examples

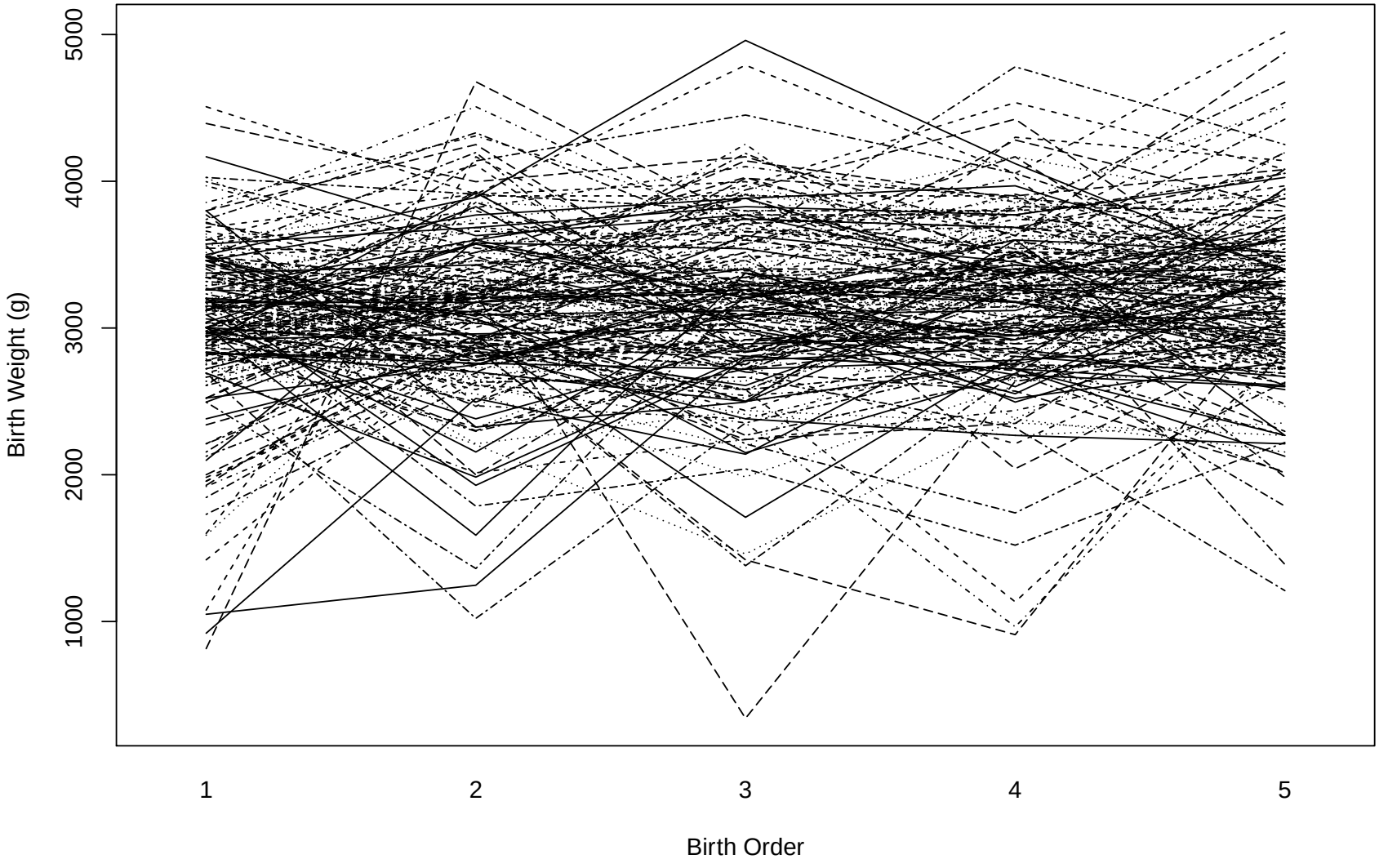
- Example 1: a measure of sleepiness before and after administration of treatment or placebo
- Example 2: Study of Osteoporotic Fractores (SOF dataset)
  - 9,704 women tracked with clinical visits every two years
  - Bone Mineral Density (BMD), Body Mass Index (BMI), many other variables
- Questions 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:



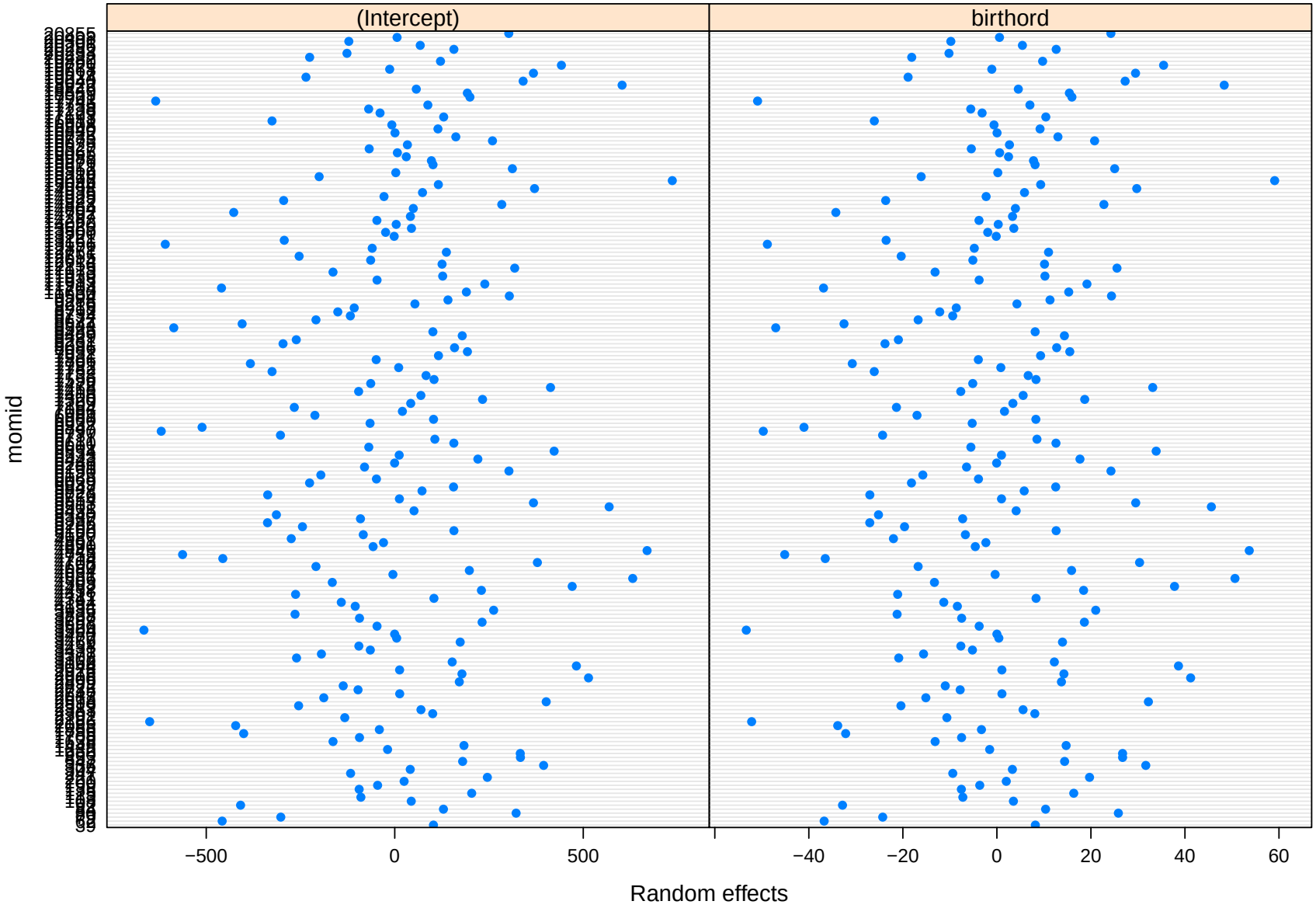
Georgia Birthweights dataset

- 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: [a]Only for calculation of standard errors.

[b]Problems 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