

# **Session 9: Repeated Measures and Longitudinal Analysis I**

Levi Waldron

CUNY SPH Biostatistics 2

# Learning objectives and outline

# Learning objectives

## Learning objectives:

- 1 Identify and define hierarchical and longitudinal data
- 2 Analyze correlated data using Analysis of Variance
- 3 Define and calculate Intraclass Correlation
- 4 Identify and define random and fixed effects

## Textbook sections:

- Vittinghoff sections 7.1 (7.2-7.3 next class)

# Outline

- 1 Introduction to hierarchical and longitudinal data
- 2 Fecal Fat example
- 3 Correlations within subjects (ICC)
- 4 Random and fixed effects

# **Intro: hierarchical and longitudinal data**

# What are hierarchical and longitudinal data?

- Knee radiographs are taken yearly in order to understand the onset of osteoarthritis
- An indicator of heart damage is measured at 1, 3, and 6 days following a brain hemorrhage.
- Groups of patients in a urinary incontinence trial are assembled from different treatment centers
- Susceptibility to tuberculosis is measured in family members
- A study of the choice of type of surgery to treat a brain aneurysm either by clipping the base of the aneurysm or implanting a small coil. The study is conducted by measuring the type of surgery a patient receives from a number of surgeons at a number of different institutions.

# What is the distinction between hierarchical and longitudinal data?

- Longitudinal data are repeated measures over time
- Longitudinal data are a type of hierarchical data
  - repeated measures are correlated, and nested within the observational unit (individual)
- Other non-longitudinal data can also be hierarchical

*Definition:* Hierarchical data are data (responses or predictors) collected from or specific to different levels within a study.

# Important features of this type of data

- 1 The outcomes are correlated across observations
- 2 The predictor variables can be associated with different levels of a hierarchy. e.g. we might be interested in:
  - the volume of operations at the hospital,
  - whether it is a for-profit or not-for-profit hospital,
  - years of experience of the surgeon or where surgeons were trained,
  - how the choice of surgery type depends on the age and gender of the patient.



# Fecal Fat example

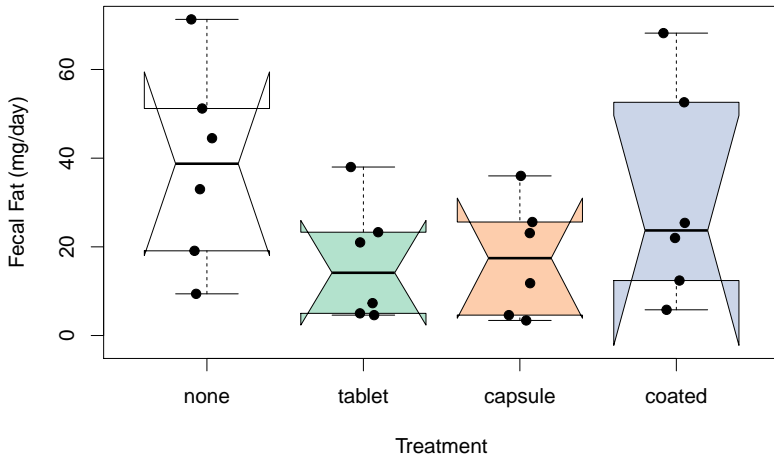
# A Repeated Measures Example

- 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 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

# Option 1: non-hierarchical analysis (wrong)



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```
fit1way <- lm(fecfat ~ pilltype, data=fecfat)
```

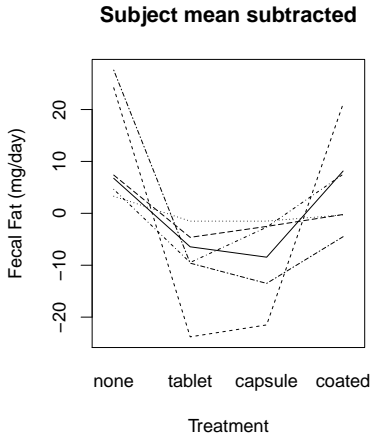
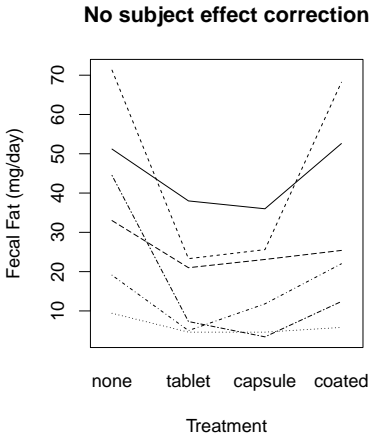
	Df	Sum Sq	Mean Sq	F value	Pr(>F)
pilltype	3	2008.60	669.53	1.86	0.1687
Residuals	20	7193.36	359.67		

**Table 1:** One-way analysis of variance table for fecal fat dataset

- Does not account for similarity of measurements within individual
- Would be correct if each treatment were given to a different individual

# Option 2: two-way analysis of variance (getting closer)

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



## Option 2: 2-way analysis of variance (getting closer)

```
fit1way <- lm(fecfat ~ pilltype, data=fecfat)
```

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
pilltype	3	2008.60	669.53	1.86	0.1687
Residuals	20	7193.36	359.67		

**Table 2:** One-way analysis of variance table for fecal fat dataset

```
fit2way <- lm(fecfat ~ subject + pilltype, data=fecfat)
```

	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 3:** Two-way analysis of variance table. Note the similarity of the pilltype row.

# What happened??

- 1-way ANOVA correctly estimates the effect of pill type
- However, 1-way ANOVA fails to accommodate the correlation within subjects
- 1-way ANOVA over-estimates the residual variance
  - under-estimates the significance of pill type

# Regression models for 1 and 2-way ANOVA

- Recall for ordinary multiple linear regression:

$$E[y|x] = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p$$

- $x_p$  are the predictors or independent variables
- $y$  is the outcome, response, or dependent variable
- $E[y|x]$  is the expected value of  $y$  given  $x$
- $\beta_p$  are the regression coefficients



# Regression models for 1 and 2-way ANOVA

- One-way ANOVA (person  $i$  with pill type  $j$ ):

$$\begin{aligned} FECFAT_{ij} &= \text{fecal fat measurement for person } i \text{ with pill type } j \\ &= \mu + PILLTYPE_j + \epsilon_{ij} \end{aligned}$$

- Two-way ANOVA:

$$FECFAT_{ij} = \mu + SUBJECT_i + PILLTYPE_j + \epsilon_{ij}$$

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

# Correlations within subjects

- One-way ANOVA fails because it does not account for the correlation of measurements within-person
- How highly correlated are measurements on the same person? Consider subject  $i$ , pill types  $j$  and  $k$ :

$$\text{corr}(FECFAT_{ij}, FECFAT_{ik}) = \frac{\text{cov}(FECFAT_{ij}, FECFAT_{ik})}{sd(FECFAT_{ij})sd(FECFAT_{ik})}$$

\* This is a measure of how large the subject effect is, in relation to the error term

# Correlation within subjects

$$\begin{aligned} cov(FECFAT_{ij}, FECFAT_{ik}) &= cov(SUBJECT_i, SUBJECT_i) \\ &= var(SUBJECT_i) \\ &= \sigma_{subject}^2 \cdot (\text{definition}) \end{aligned}$$

- Equality 1:
  - $\mu$  and *pilltype* terms are assumed to be constant, so do not enter into covariance calculation
  - residuals  $\epsilon$  are assumed to be independent
- Equality 2:
  - covariance with self is variance

Recall  $SUBJECT_i$  is the term for individual in 2-way AOV. Now  $\beta_i * subjectID$ , will later be treated as a **random variable**

# Correlation within subjects

Previous slide calculated *covariance*. Also need *variance*.

$$\begin{aligned} \text{var}(FECFAT_{ij}) &= \text{var}(SUBJECT_i, SUBJECT_i) + \text{var}(\epsilon_{ij}) \\ &= \sigma_{subject}^2 + \sigma_{\epsilon}^2. (\text{definition}) \end{aligned}$$

- Difference is that the independent residuals do contribute to  $\text{var}(FECFAT_{ij})$
- Variance is broken into components due to *subject* and *residual* variance

# Correlations within subjects (ICC)

# Intraclass Correlation

The correlation between two treatments  $j$  and  $k$  across subjects  $i$  is:

$$\begin{aligned} \text{corr}(FECFAT_{ij}, FECFAT_{ik}) &= \frac{\text{cov}(FECFAT_{ij}, FECFAT_{ik})}{\text{sd}(FECFAT_{ij})\text{sd}(FECFAT_{ik})} \\ &= \frac{\sigma_{\text{subj}}^2}{\sigma_{\text{subj}}^2 + \sigma_{\epsilon}^2} \\ ICC &= \frac{\tau_{00}^2}{\tau_{00}^2 + \sigma_{\epsilon}^2} \end{aligned}$$

# Intuition behind correlations within subjects

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

Subject number	Pill type				Subject Average
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**Figure 2:** Fecal Fat dataset

Variance of the subject averages (279.4) is increased by correlation of measurements within individual.

# Calculation of correlations within subjects (ICC)

What is your estimate of the variability due to subjects, from the 2-way ANOVA?

```
sum(residuals(fit2way)^2) / 15 / 4 #df=15, divided by 4 pilltypes
```

```
## [1] 26.74972
```

```
279.419 - 26.75 #var(SUBJECT_i)
```

```
## [1] 252.669
```

Residual variance is:

```
sum(residuals(fit2way)^2) / 15 #df=15
```

```
## [1] 106.9989
```



## Calculation of correlations within subjects (ICC)

Finally calculate ICC:

$$\begin{aligned} ICC &= \frac{\sigma_{subj}^2}{\sigma_{subj}^2 + \sigma_{\epsilon}^2} \\ &= \frac{253}{253 + 107} = 0.70 \end{aligned}$$

This calculation will become easier when we learn to estimate *random coefficients* in directly in the regression model.

# Random and fixed effects

# The next step: a mixed effects model

- Two-way ANOVA is a fixed effects model:

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

- Assumption:  $\epsilon_i \stackrel{iid}{\sim} N(0, \sigma_\epsilon^2)$
- Instead of fitting a  $\beta_{subjecti}$  to each individual, assume that subject effects are selected from a distribution of possible subject effects:

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

where  $SUBJECT_i \stackrel{iid}{\sim} N(0, \sigma_{subj}^2)$

- Here subject is a *random* effect, and pill type is a *fixed* effect.
- This is also a random intercept model

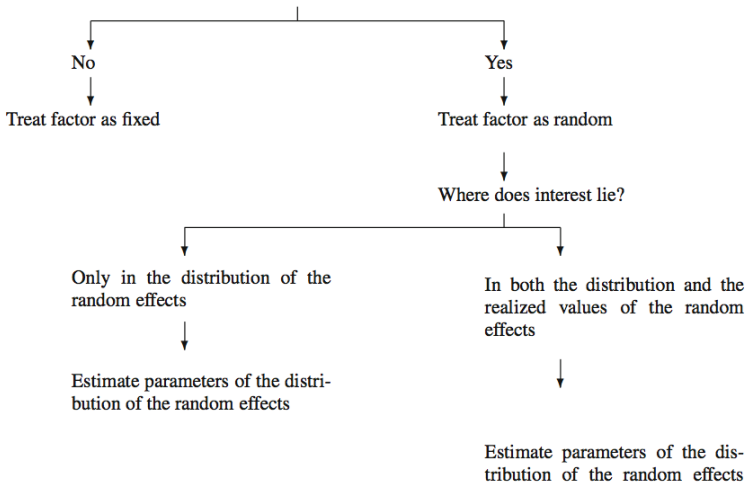
# Random and fixed effects

## 7.6 Re-Analysis of the Georgia Babies Data Set

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**Table 7.14** Decision tree for deciding between fixed and random

Is it reasonable to assume levels of the factor come from a probability distribution?



# Summary: correlations within subjects

- Subject-to-subject variability simultaneously raises or lowers all the observations on a subject
  - induces correlation of within-subject measurements
- Variability of individual measurements can be separated into that due to subjects and that left to residual variance.
  - $var(FECFAT_{ij}) = \sigma_{subj}^2 + \sigma_{\epsilon}^2$
- 2-way ANOVA does not directly estimate variability due to subjects
  - variance of coefficients for individual is not too far off

# Summary: hierarchical data

- Estimates of coefficients (or “effect sizes”) are unchanged by hierarchical modeling
- Ignoring within-subject correlations results in incorrect estimates of variance, F statistics, p-values
  - not always “conservative”
- Intraclass Correlation (ICC) provides a measure of correlation induced by grouping
- Should be able to recognize fixed and random effects