# BIOS 755: Foundational concepts

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# Outline

# Introduction

**Lecture goals:**

- Give an overview of the objectives of longitudinal analysis and discuss features in the data.
- Longitudinal analysis estimates how individuals change throughout the study.
- Examine the factors related to individual differences over time.
- Review features of longitudinal study designs.
- Introduce notation.

# Treatment of Lead-Exposed Chidren (TLC) Trial

Recall the TLC study (a balanced design)

- Exposure to lead during infancy is associated with substantial deficits in tests of cognitive ability
- Chelation treatment of children with high lead levels usually requires injections and hospitalization
- A new agent, Succimer, can be given orally
- Randomized trial examining changes in blood lead level during the course of treatment
- 100 children randomized to placebo or succimer
- Measures of blood lead level at baseline, 1, 4, and 6 weeks

# Objectives of Longitudinal Analysis

- Defining feature of longitudinal study: two or more observations taken on (at least) some subjects.
- Multiple measurements over time allow assessment of within-individual changes in the response variable.
- Thus, some main goals are to:
  - characterize (a loaded word) the change in the response over time.
  - determine whether changes are related to exposures of interest

# Longitudinal Analysis

- One way to achieve this is to look at *"change scores"* or *"difference scores,"* between pre- and post-treatment.
- There are different ways to form such a question
  1. are the *change scores* related to group.
  2. is the average difference in the change scores related to covariates.
  3. is the final score related to covariates (path analysis).
- 1 could be answered using a paired t-test.
- 2 could be answered using standard linear regression techniques (possibly adjusting for the pre-score and differences in time).
- 3 also could use linear regression (adjusting for the pre-score and differences in time).

# Longitudinal Analysis

- The usefulness of change score analysis is limited to situations with two measurements; you will have multiple change scores with more than two measurements.
- Analyses with change scores should be used with caution as they
  - have been shown to lead to bias in observational (non-randomized) studies (reference), and
  - require complete data or multiple imputation.

# Number of measurements

- The number of measurements can vary greatly from study to study and can be equally or unequally separated in time.
  - The amount of vigorous physical activity per hour for 14 days.
  - BMI measured in spring, fall, and summer for two years.
  - Height measured every 3 months until 3 years old, then every year thereafter.
- All of the above are considered to be **balanced**.

# Number of measurements

- **Unbalanced** data are very common in the health sciences.
  - individuals will miss scheduled visits,
  - visits are not made exactly at the scheduled date,
  - timings are relative to a benchmark event (e.g., relative to seroconversion) or
  - visits are themselves random (common in retrospective data).
- Missing data are the rule, not the exception, so unbalanced data are the rule.

# Data Notation

- Consider the following

$$Y_{ij} = \text{the } j\text{th measurement taken on unit } i.$$

  where $i = 1, 2, \ldots, N$ and $j = 1, 2, \ldots, n$
- In the TLC data, each child had four measurements at baseline, 1, 4, and 6 weeks.
- $Y_{ij}$ represents the **random** response of the $i$th child at measurement $j$, for $j = 1, 2, 3, 4$.
- $t_{ij}$ is the time of the observation of the $i$th child at measurement $j$, for all $i$

$$t_{i1} = 0, \quad t_{i2} = 1, \quad t_{i3} = 4, \quad t_4 = 6$$

# Random Vectors

- It is convenient to represent all observations for a specific unit as a **random vector**.
- For the TLC data each child has,

$$\boldsymbol{Y}_i = \begin{pmatrix} Y_{i1} \\ Y_{i2} \\ Y_{i3} \\ Y_{i4} \end{pmatrix}$$

  the random vector for child $i$.
- Also use $\boldsymbol{Y}_i = (Y_{i1}, Y_{i2}, Y_{i3}, Y_{i4})'$.
- In general, we have $\boldsymbol{Y}_i = (Y_{i1}, Y_{i2}, \ldots, Y_{in})'$.

# Expectations and mean

- The mean, average, or "expectation" of each response is

$$E(Y_{ij}) = \mu_{ij}$$

$\mu_{ij}$ is the *conditional* mean at the $j$th occasion (i.e., conditional on covariate values).

# Dependence and Correlation Introduction

- Two variables are said to be independent if the behavior of one variable does not depend on the value of another variable.
- For example, LDL cholesterol, and sex are independent if the distribution of LDL cholesterol is the same for males and females.
- Longitudinal data methods do not assume that the observations are independent.
- For example, if I tell you my LDL cholesterol at baseline was 80, what is a plausible range for this value at 4 weeks?
- What if it was 165 at baseline?

# Variance and Covariance

- Along with the expectation, we'll use variance

$$\text{var}(Y_{ij}) = E(Y_{ij} - \mu_{ij})^2 = \sigma_j^2$$

- The standard deviation is $\sqrt{\sigma_j^2} = \sigma_j$.
- **Covariance:** a measure of how two random variables vary together.
- Mathematically, this is expressed as,

$$\text{cov}(Y_{ij}, Y_{ik}) = E\{(Y_{ij} - \mu_{ij})(Y_{ik} - \mu_{ik})\} = \sigma_{jk}$$

# Covariance Matix

- The covariance matrix of $\boldsymbol{Y}_i = (Y_{i1}, Y_{i2}, \ldots, Y_{in})'$

$$\mathrm{Cov}(\boldsymbol{Y}_i) = \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \ldots & \sigma_{1n} \\ \sigma_{21} & \sigma_2^2 & \ldots & \sigma_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{n1} & \sigma_{n2} & \ldots & \sigma_n^2 \end{pmatrix} = \Sigma$$

- You will sometimes see $\sigma_j^2 = \mathrm{var}(Y_{ij}) = \mathrm{cov}(Y_{ij}, Y_{ij}) = \sigma_{jj}$.

# Covariance to correlation

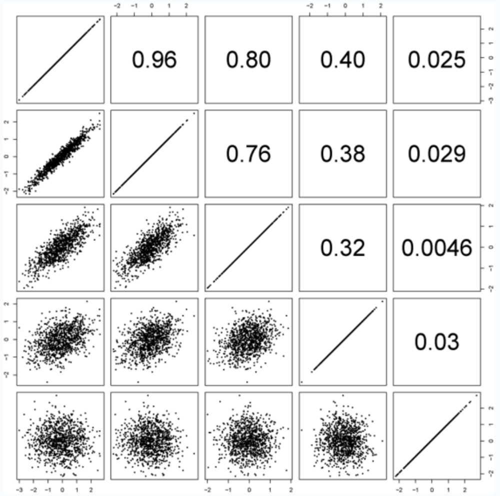
- The covariance values are hard to interpret since their magnitude depends on the variables' variance.
- Covariance is commonly standardized to correlation.
- The population correlation of two elements is

$$\rho_{jk} = \frac{\sigma_{jk}}{\sqrt{\sigma_j^2 \sigma_k^2}}$$

- Which gives the correlation matrix

$$\text{Corr}(\boldsymbol{Y}_i) = \begin{pmatrix} 1 & \rho_{12} & \dots & \rho_{1n} \\ \rho_{21} & 1 & \dots & \rho_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{n1} & \rho_{n2} & \dots & 1 \end{pmatrix}$$

# Correlation Matix Example



# Objectives of TLC Trial

- Goal: determine whether the new treatment reduces blood lead levels over time relative to placebo.
- Let $\mu_{jS}$ and $\mu_{jP}$ are the mean levels at occasion $j$ for succimer and placebo groups, respectively.
- Different ways to answer this question:
  1. $H_0 : \mu_{jS} = \mu_{jP}$ for all $j = 1, \ldots, 4$.
  2. $H_0 : \mu_{jS} - \mu_{1S} = \mu_{jP} - \mu_{1P}$ for $j = 2, 3, 4$.

# Correlation in TLC

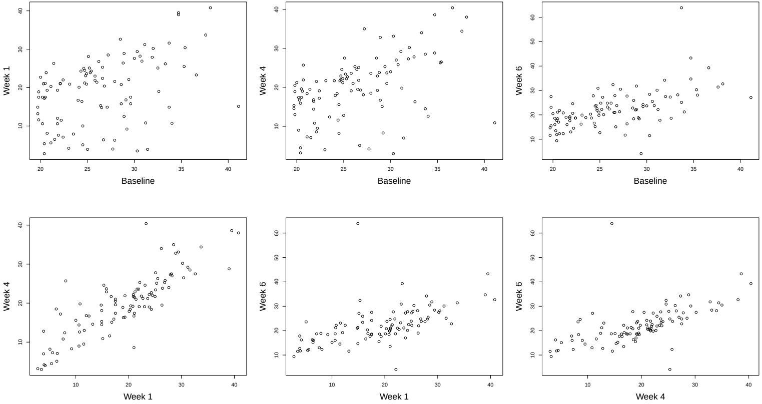



Figure: Correlation for 50 children in the placebo group

# Estimated covariance & correlation matrices

- The estimated covariance matrix for the TLC

$$\mathrm{Cov}(\boldsymbol{Y}_i) = \begin{pmatrix} 25.2 & 22.8 & 24.3 & 21.4 \\ 22.8 & 29.8 & 27.0 & 23.4 \\ 24.3 & 27.0 & 33.1 & 28.2 \\ 21.4 & 23.4 & 28.2 & 31.8 \end{pmatrix}$$

- The estimated correlation matrix for the TLC

$$\mathrm{Corr}(\boldsymbol{Y}_i) = \begin{pmatrix} 1 & 0.83 & 0.84 & 0.76 \\ 0.83 & 1 & 0.86 & 0.76 \\ 0.84 & 0.86 & 1 & 0.87 \\ 0.76 & 0.76 & 0.87 & 1 \end{pmatrix}$$

# Time plot for TLC

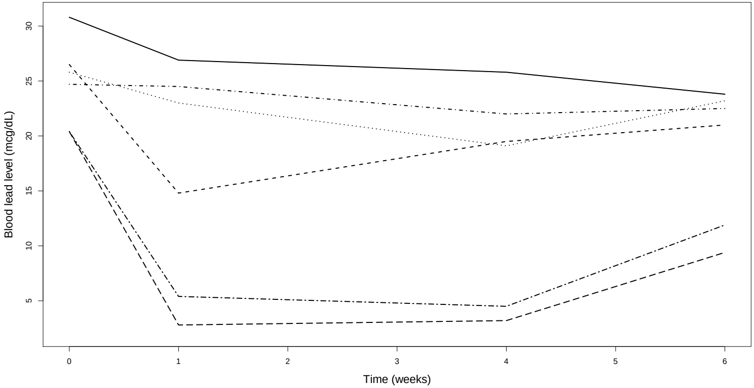



Figure: Time plot for six subjects

# Correlation "truths"

1. the correlations are positive
2. the correlations often decrease with increasing time separation
3. the correlations between repeated measures rarely ever approach zero
4. the correlation between a pair of repeated measures taken very closely rarely approaches one.

# Sources of variability

Three potential sources of variability

- between-individual heterogeneity
- within-individual biological variation
- measurement error