JOHNS HOPKINS
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Study Design

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Lecture Topics

- Randomized/controlled study design

- Methods of randomization

- Natural experiments

- Observational studies

- Case/control studies

Section A

Making the Case for Randomized Controlled Studies

Clofibrate Trial

- A study was performed to look at the effect of a drug, Clofibrate, on mortality rates for individuals with heart disease
  - Individuals were followed for five years after administration of the drug

Results: Clofibrate Group

- Coronary heart disease
  - Results from group randomized to take Clofibrate

	Five Year Mortality	
Clofibrate Group (p < .01)	Compliers	.15
	Non-compliers	.25

Results: Clofibrate Group

- Coronary heart disease
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	Five Year Mortality	
Clofibrate Group (p < .01)	Compliers	.15
	Non-compliers	.25

  - Question: Do these results strongly demonstrate the efficacy of Clofibrate in reducing the mortality in subjects with CHD?

Results: Placebo Group

- Coronary heart disease
  - Results from group randomized to take placebo

	Five Year Mortality	
Placebo Group (p <.01)	Compliers	.15
	Non-compliers	.25

The Dangers of Self-Selection

- Overall mortality in each of the groups in this randomized trial

	Five Year Mortality	
Clofibrate	n = 1,103	.0.20 (20%)
Placebo	n = 2,789	0.21 (21%)

The Dangers of Self-Selection

- Randomized trial
    - No significant difference (p > .20) between the treatment and placebo groups!

- No difference between TX groups
    - The compilers and non-compilers were similar with respect to other variables (age, etc.)
    - There were no apparent harsh side effects of Clofibrate relative to placebo that may have resulted in differential compliance between the Clofibrate and placebo groups

Source: Coronary drug research group (1980). *NEJM*, 1038–1041.

A Randomized Control Group

- Important for accounting for many kinds of biases

- Randomization, done correctly on a large number of subjects nearly ensures that the only systematic difference in the groups being compared is the exposure(s) of interest

Note

- A very famous randomized trial (once again)
  - 200,745 vaccinated for polio
  - ≈ 400,000 school children randomized
  - 201,229 given a placebo

1954 Salk Polio Vaccine Trial

- At the end of the follow-up period there were 82 cases in the vaccine group and 162 in the placebo group

- Subsequently analyses report slightly different numbers because some false positives were discovered in each of the two groups

1954 Salk Polio Vaccine Trial

- Results

	Vaccine	Placebo	Total
Polio	82	162	
No Polio	200,663	201,067	

Results in 2x2 Table Format

- How to test for an association between vaccine and polio? (Flashback to 611!)
  - H_o: $p_{vaccine} = p_{placebo}$
  - H_A: $p_{vaccine} \neq p_{placebo}$

- Where $p_{vaccine}$ is the percentage of children with polio in vaccine group, $p_{placebo}$ is the percentage in the placebo group

- How to test for an association between vaccine and polio? (Flashback to 611!)
  - You can use either Fisher's Exact test or Chi-Squared test (Why?)

- With FET, p < .001

Randomized Study Design

- Prospective cohort studies
  - Choose a fixed number with and without exposure
  - Follow subjects for set time period and determine who has disease/outcome of interest

- Measures of association
  - Difference in proportions
  - Relative risk (ratio of proportions)
  - Odds ratio

Benefits of Randomization

- Randomization helps protect against self selection biases
  - Examples:
    - ▶ Males are more likely to volunteer for placebo than females
    - ▶ Smokers are less likely to be in the exposed group
    - ▶ Healthier persons sign up for the intervention

- The goal of randomization is to eliminate any systematic differences in characteristics of subjects in each of the exposure groups under study, save for the exposure itself

Randomized Study Design

- Many epidemiological studies are concerned with estimating an association between two dichotomous (binary) variables
  - Example: exposure-disease association

- Randomized study design with control group is a type of **prospective cohort study**

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