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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
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

<table>
<thead>
<tr>
<th>Clofibrate Group (p &lt; .01)</th>
<th>Five Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliers</td>
<td>.15</td>
</tr>
<tr>
<td>Non-compliers</td>
<td>.25</td>
</tr>
</tbody>
</table>
Coronary heart disease

Results from group randomized to take Clofibrate

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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

<table>
<thead>
<tr>
<th>Placebo Group (p &lt; .01)</th>
<th>Five Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliers</td>
<td>.15</td>
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</tbody>
</table>
The Dangers of Self-Selection

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

<table>
<thead>
<tr>
<th></th>
<th>Five Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofibrate</td>
<td>n = 1,103</td>
</tr>
<tr>
<td></td>
<td>.0.20 (20%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>n = 2,789</td>
</tr>
<tr>
<td></td>
<td>0.21 (21%)</td>
</tr>
</tbody>
</table>
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

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
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

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio</td>
<td>82</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>No Polio</td>
<td>200,663</td>
<td>201,067</td>
<td></td>
</tr>
</tbody>
</table>
How to test for an association between vaccine and polio? (Flashback to 611!)
- \( H_0: \ p_{\text{vaccine}} = p_{\text{placebo}} \)
- \( H_A: \ p_{\text{vaccine}} \neq p_{\text{placebo}} \)

Where \( p_{\text{vaccine}} \) is the percentage of children with polio in vaccine group, \( p_{\text{placebo}} \) 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
Randomized Study Design

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