Randomized Controlled Studies

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Statistics in Health and Medicine

- Clinical Trials: Evaluate safety and effectiveness of new drug or therapy
- Epidemiology: Investigate distribution and determinants of health and disease
- Biostatistics: Development and application of data-analytic techniques to health related research
3 types of studies:

1. Randomized studies
   - starts with a sample of subjects, who are then randomly assigned into comparison groups (e.g. drug/placebo).

2. Observational studies (nonrandomized comparison)
   - group membership is observed, rather than randomly assigned (e.g. smoker/nonsmoker, male/female)

3. Anecdotal studies (no comparison)

Questions:

1. Why do we need comparison groups?

2. What is the advantage of randomized comparisons over nonrandomized comparisons?
**Grade School Study**

“In a large study of children in grades 1-3, it was found that children who weighed less than 40 pounds knew 50% fewer words than children who weighed over 40 pounds.”

Possible Scenarios for Grade School Study:

A. Weight $\rightarrow$ Vocabulary

B. Vocabulary $\rightarrow$ Weight

C. Age $\leftrightarrow$ Weight

D. More . . .

“Age” is a lurking variable here.
The effects of “Age” and “Weight” are con**founded**.
Expert Conclusion:
   Age is *the* variable which “drives” the relationship between Vocabulary and Weight (or Height, Shoe Size)

Problem:
   Statistical techniques cannot tell cause-and effect. On paper, the following plots all look the same

   (i) Vocabulary vs Weight
   (ii) Vocabulary vs Height
   (iii) Vocabulary vs Age

Moral:
   Data Analysis = Numerical Methods + Subject Matter
Does Antibiotic Exposure During Infancy Lead to Development of Asthma?

Marra F. et al., J. of the ACCP, March 2006, pp. 610-618

Objective:
To determine the association between antibiotic exposure in the first year of life and the development of childhood asthma.

Conclusion:
Exposure to at least one course of antibiotics in the first year of life appears to be a risk factor for the development of childhood asthma.
Possible Scenarios?

A. Antibiotic $\rightarrow$ Asthma

B. Asthma $\rightarrow$ Antibiotic

C. Infection, Allergies $\leftrightarrow$ Antibiotic $\leftrightarrow$ Asthma

Caution:
In cause-and-effect studies, beware of direction and lurking variables.
Leg Injury in Motor Vehicle Collisions


‘In a study of trauma-center population in Maryland, it was found that:
(a) there was a higher incidence of lower extremity injury in frontal collisions,
(b) seatbelt use was not effective in preventing lower extremity fractures, and
(c) there was a higher incidence of lower extremity fracture among women.’
Leg Injury in Motor Vehicle Collisions


‘For both men and women, results indicate an association between driver height and the incidence of lower extremity fractures. The incidence of injuries increased among shorter drivers, most of whom were women.’

Lurking Variable: Height  Gender  Leg injury
Removing kidney stones

<table>
<thead>
<tr>
<th>Success</th>
<th>&lt; 2 cm</th>
<th>≥ 2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open surgery</td>
<td>78%</td>
<td>93%</td>
</tr>
<tr>
<td>PCNL</td>
<td>83%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Percent of Sample

<table>
<thead>
<tr>
<th></th>
<th>Open Surgery</th>
<th>PCNL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Simpson’s Paradox:
Beware of comparing combined scores
Simpson’s Paradox: (Comparing aggregate scores)

**Basketball**

<table>
<thead>
<tr>
<th></th>
<th>Shot %</th>
<th>FT</th>
<th>3-pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>0.540</td>
<td>0.600</td>
<td>0.300</td>
</tr>
<tr>
<td>You</td>
<td>0.460</td>
<td>0.700</td>
<td>0.400</td>
</tr>
</tbody>
</table>

Percentage of population

<table>
<thead>
<tr>
<th></th>
<th>80%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>You</td>
<td>20%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Q: Are there situations where we can (safely) jump to conclusions?
A: Yes.

Soundbite:

The Treatment and Control groups should be the same in all aspects except for the treatment.

Silver Bullet: *Randomization*
Ex. Clinical study: “Lipitor lowers cholesterol.”

Design: Take 1000 patients, randomize into Treatment and Control groups.

Toss coin

.5 ↙ ↘ .5

| Treatment | Control |

Age profile of the two groups? Balanced!
Diet?
Exercise?
Attitudes?
Q: Why not do this for all studies?
A: Not always possible.

Ex. ”Smokers average higher medical claims”

| Smokers | Nonsmokers |

Cannot randomize. Group membership is *observed* rather than *assigned*.

*Observational* studies

versus

*Randomized Controlled* studies
Observational studies have a problem

 довольные оранжевым

 Apples and Oranges

The smokers group is different from nonsmokers in other ways besides smoking! (e.g. Smokers drink more coffee, stand out in the cold more, etc.)

If average claims for the two groups are different, is this due to smoking or diet or lifestyle?

Smoking effects are "confounded" with Diet effects, Lifestyle effects, etc. (a lot of lurking 3rd variables here).
Looking back: observational studies

**Antibiotic/Asthma Study:**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No Antibiotic</th>
</tr>
</thead>
</table>

Health history, etc.: Not Balanced

**Driver Leg Injury Study**

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
</table>

-Height: Not Balanced

**Kidney Stones Study**

<table>
<thead>
<tr>
<th>Open Surgery</th>
<th>PCNL</th>
</tr>
</thead>
</table>

-Size of stones, etc.: Not Balanced
An Exercise:

**Clofibrate Study**

Clofibrate is a cholesterol lowering drug. The study looked at mortality rates of patients with heart disease over a period of 5 years.

<table>
<thead>
<tr>
<th></th>
<th>Clofibrate</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Deaths</td>
<td>Number</td>
<td>Deaths</td>
</tr>
<tr>
<td>Total</td>
<td>1103</td>
<td>20%</td>
<td>2789</td>
<td>21%</td>
</tr>
<tr>
<td>Adherers</td>
<td>708</td>
<td>15%</td>
<td>1813</td>
<td>15%</td>
</tr>
<tr>
<td>Non-adherers</td>
<td>357</td>
<td>25%</td>
<td>882</td>
<td>28%</td>
</tr>
</tbody>
</table>

Conclusions?

1. Clofibrate is not effective
2. Adherers are different from non-adherers
Anecdotal Studies

Silicone Breast Implants Controversy

1960s
The first silicone breast implants

1977
First lawsuit: Cleveland woman claims ruptured implants and subsequent operations had caused pain and suffering. Dow Corning settles, $170,000. Case receives little publicity.

1984
San Francisco woman’s systemic autoimmune disease is found by a jury to be caused by her silicone implants. Jury awards $211,000 in compensatory damages, $1.5 million in punitive damages.

June 1988
FDA classifies the implants into Class III. Requires manufacturers to prove their safety in order to keep them on the market.

December 1990
Dangers of silicone implants airs on "Face to Face with Connie Chung."
December 1990
Congressional hearing on safety of silicone implants.

July 1991
Dow Corning releases 329 studies to FDA.

September 1991
FDA concludes that the silicone implant manufacturers' data does not prove the devices are safe—or harmful. Manufacturers are told to submit further data.

December 1991
A San Francisco woman wins $7.3 million from Dow Corning. Jury concludes her mixed connective-tissue disease is linked to her ruptured silicone implants.

December 1991
137 lawsuits have been filed against Dow Corning.

January 1992
FDA Commissioner David Kessler calls for a voluntary moratorium on the use of silicone implants until the FDA and the advisory panel have an opportunity to consider newly available information. The manufacturers agree.

February 1992
Class action lawsuit is filed in Cincinnati.

December 1993
12,359 lawsuits have been filed against Dow Corning.

June 1994
Mayo Clinic epidemiologic study is published in NEJM. Finds no increased risk of connective-tissue disease and other disorders.

December 1994
19,092 lawsuits have been filed against Dow Corning.

May 1995
Dow Corning files for Chapter 11 bankruptcy.

June 1995
Harvard Nurses Epidemiologic Study published in NEJM. Finds no increased risk of connective-tissue disease.

December 1995
By now more than 20 studies in the U.S. and internationally fail to support a causal relationship between implants and auto-immune illnesses.

November 1998
Dow Corning files for bankruptcy reorganization. Offers claimants several payout options. Those who
want to cash-out immediately and not file a disease claim will be paid $2,000. This figure can be combined with $5,000 for implant removal surgery and $20,000 for a ruptured implant.

Today
Silicone implants remain off the market. Available only to women who will have breast surgery for a medical condition, and only if they agree to be part of a scientific study.
The Harvard Nurses Study

New England Journal of Medicine, June 22, 1995

Data: 87,501 nurses followed for other research purposes from 1976 through May 31, 1990. None of the women had connective tissue disease at the start of the study.

During the time frame of the study, 3 women with breast implants developed connective tissue diseases.

Number of women with breast implants, who then developed disease:

3

Projected nationwide, the data suggests that we may find 3000 women with breast implants who developed connective tissue diseases.
Data is missing!

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No Implant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The rest of the story!

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant</td>
<td>3</td>
<td>1,180</td>
</tr>
<tr>
<td>No Implant</td>
<td>513</td>
<td>85,805</td>
</tr>
</tbody>
</table>

Disease rates:
- Implant: .25% had connective tissue diseases
- No implant: .59% had connective tissue diseases

Soundbite:

Don’t ask whether $B$ occurs after $A$. Instead ask whether $B$ occurs after $A$ more frequently than after $A^c$. 
In the news (Causation or Coincidence)?
- Breast implants and autoimmune diseases
- MMR vaccination and autism
- Gulf War Syndrome
- Power lines and cancer
- Cell Phones and cancer
- Radar guns and cancer
- Microwaves and cancer

- Infomercials
  - Golf club and increased distance or accuracy
  - Exercise gadget and better fitness
Summary:

Show me the study!

Randomized Controlled Studies

≥

Observational Studies

≥

Anecdotal Studies

Questions:

1. Why do we need comparison groups?
   A: We cannot determine the magnitude of treatment effect without comparing to nontreatment.

2. What is the advantage of randomized comparisons over nonrandomized comparisons?
   A: Randomization minimizes differences between comparison groups that may be falsely attributed to treatment effect.