INTRODUCTION TO CAUSAL INFERENCE IN CLINICAL RESEARCH

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Outline

1. Platonic model: science as the search for "truth"
2. "Cause" – a counter-factual perspective
3. Comparing like to like
   i. Randomization
   ii. Stratification
   iii. Statistical adjustment

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What is Science

- Search for truth
- Scientific method
  - Competing hypotheses: H0, H1, H2, …
  - Design an experiment to generate data
  - Data support / falsify some hypotheses more than others

What Is Biostatistics?

The science of learning from biomedical data involving appreciable variability or uncertainty

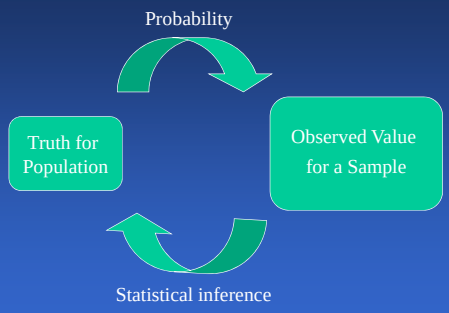
A thought example

- H1: Vitamin D supplementation delays the onset of frailty among pre-frail women
- H0: Vitamin D supplementation does not delay the onset of frailty among pre-frail women
- Experiment
  - Select a sample of pre-frail women
  - Randomize half to Vitamin D, half to placebo
  - Follow up to observe frailty onset

Thought example: Sources of uncertainty

- How the randomization turns out
- Selection of the initial sample
- Measurement of frailty
- Who stays in the study
- …

Search for Truth



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Clinical Investigations to Determine "Cause"

- Definition of Cause (OED):

"That which produces an effect; that which gives rise to any action, phenomenon, or condition."

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Whether a "cause" produces the "effect"

- Three queries (*Pearl, 2000*)
  - Predictions
    - "Probabilistic causality" (*von Suppes, 1970*)
    - Is frailty delay probable among the treated?
  - Interventions / Experiments (*Bollen, 1989*)
    - Association, temporality, isolation
    - Does an attenuation in frailty onset follow treatment?
  - Counterfactual
    - Does one's frailty onset differ if treated vs. not?
    - *Neyman, 1923; Stalnaker, 1968; Lewis, 1973; Rubin, 1974; Robins 1986; Holland 1988*

Counterfactual Definition of "Causal Effect" of Treatment

The difference between a population characteristic having given the treatment to everyone and the same characteristic absent the treatment

"Counterfactual" because we can not observe the response for a person both with and without the treatment (at one time). Each patient is either treated or not

Can be a useful way to organize ones thinking about "truth" in some circumstances

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Counterfactual Data Table

Person	Vit D	Y(0)	Y(1)	Y(1)-Y(0)
1	0	22	16	-6
2	0	18	17	-1
3	0	20	15	-5
4	1	20	18	-2
5	1	18	16	-2
6	1	22	14	-8
Average		20	16	-4

Here: Y = frailty "score" (higher=worse)

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Actual Data Table

Person	Vit D	Y(0)	Y(1)	Y(1)-Y(0)
1	0	22	?	?
2	0	18	?	?
3	0	20	?	?
4	1	?	18	?
5	1	?	16	?
6	1	?	14	?
Average		20	16	-4

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Goal of Statistical "Causal" Inference

- "Fill-in" missing information in the counterfactual data table
- Use data for persons receiving the other treatment to fill-in a persons missing outcome
- Inherent assumption that the other persons are similar except for the treatment
- Data as evidence: *Compare like-to-like*

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Comparing Like-to-Like

Randomize treatment to persons

Stratify person into groups that are similar; make causal inference within groups and then pool results

Use a statistical adjustment to attain same end

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Randomization

- We can *expect* the groups to be exchangeable with respect to measured and unmeasured variables
- Groups not necessarily similar in small studies
- Randomization is "successful" if you use a proper procedure, not if the data are apparently balanced on measured variables

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Stratification

- Used in randomization and/or analysis
- In analysis:
  - Divide sample into subsets of "similar" people
    - only similar for observed variables
  - Estimate treatment effects separately within each stratum
  - If treatment effect similar across strata ("no effect modification"), pool results

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A few practical considerations

- Validity of findings on effectiveness depends on
  - Correspondence of data to population "truth"
    - Proactive determination of population
    - Sample selection
    - Validity of measurements
    - Bias avoidance: blinding, etc.
    - Measure characteristics largely determining uncertainty beforehand
    - Study design to minimize uncertainty

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A few practical considerations

- Validity of findings on effectiveness depends on
  - Approximation to the causal comparison
    - Always out-source the randomization
    - Measure characteristics inducing unlikeness
    - Partner with a statistician to compare like-to-like

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Main Points Once Again

A clinical investigation is a search for truth – how a treatment affects population, not only your sample.

"Cause" – a comparison of response with and without treatment for each person; inference involves filling in the missing boxes in the counterfactual data table

Compare like to like: randomization rules; stratification; statistical adjustment if necessary

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