

Introduction to Causal Inference

CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Ezra Morrison, Ph.D.

Assistant Professor of Biostatistics

UC Davis School of Medicine

Learning Objectives

- 1. Define causes and effects
- 2. Understand how causal inference is used in medical research
- 3. Define confounding and understand how it makes causal inference difficult
- Understand how to select study design and analysis methods to answer causal questions

Potential outcomes

- A potential outcome is the outcome that an individual would experience if we intervene to give them a particular treatment or exposure.
- Denoted Y(x); may or may not be the outcome that actually occurs, Y

Example: phototherapy for neonatal jaundice

- Example: treating neonatal jaundice (excess bilirubin) with light exposure ("phototherapy")
 - Outcome (Y): 1 = condition worsens within 48 hours; 0 = not.
 - Treatment (X): 1 = phototherapy; 0 = watchful waiting
 - Y(1): if we choose phototherapy, will the jaundice worsen?
 - Y(0): if we choose watchful waiting, will the jaundice worsen?
- Data set: 20,731 newborns at 12 NorCal Kaiser hospitals between 1995-2004, with bilirubin levels within 3mg/dL of the guideline threshold for phototherapy
 - (Newman et al, Pediatrics 2009; https://doi.org/10.1542/peds.2008-1635)
- Analysis: Vittinghoff et al, Regression Methods in Biostatistics 2e, 2012, Springer
 - https://link.springer.com/book/10.1007/978-1-4614-1353-0

Defining causes

- "x causes y" if:
 - -y would occur if we did x, and
 - y would not occur if we did some alternative to x
- If a given infant would recover with phototherapy and not with watchful waiting, then phototherapy causes recovery for that infant.
- Y(x) = y and $Y(x') \neq y$ for some $x' \neq x$
- Necessary cause: y would not occur for any alternative to x.
- Sufficient cause: y would occur if we did x, no matter what else we also did.

Defining effects

- The effect of an intervention on an individual is a comparison between the potential outcomes for that intervention and some alternative: Y(1) versus Y(0).
 - Difference in potential outcomes: Y(1) Y(0)
 - Potential outcomes ratio: $\frac{Y(1)}{Y(0)}$
 - Relative difference in potential outcomes: $\frac{Y(1)-Y(0)}{Y(0)}$

Average effects

- E[Y(x)]: Average potential outcome of treatment x for a population of individuals
- E[Y(x) Y(x')]: Average Treatment Effect (ATE) or Average Causal Effect (ACE)
- E[Y(x)|Z=z]: Average potential outcome of treatment x in subpopulation Z=z
- E[Y(1) Y(0)|X = 1]: "Average Treatment effect among the Treated" (ATT)
- For binary outcomes with Y = 1 denoting the adverse event:
 - Potential risk: P(Y(x) = 1) = E[Y(x)]
 - Causal risk difference: $P(Y(x) = 1) P(Y(x') = 1) = \mathbb{E}[Y(x) Y(x')]$
 - Causal risk ratio: $P(Y(x) = 1) / P(Y(x^*) = 1)$
 - Causal odds ratio:

$$\frac{P(Y(x) = 1)/P(Y(x) = 0)}{P(Y(x') = 1)/P(Y(x') = 0)}$$

Calculating effects

- Suppose we have data on 10 individuals (e.g., newborns with jaundice)
- We would like to estimate the average potential outcomes and average causal effect:

$$-\hat{E}[Y(1)] = \frac{1}{n} (Y_1(1) + Y_2(1) + \dots + Y_{10}(1))$$

$$- \hat{E}[Y(1) - Y(0)] = \hat{E}[Y(1)] - \hat{E}[Y(0)]$$

• What do we know about Y(1) and Y(0)?

| X | Y | Y (1) | <i>Y</i> (0) |
|---|---|--------------|--------------|
| 0 | 1 | ? | ? |
| 0 | 1 | ? | ? |
| 0 | 0 | ? | ? |
| 0 | 1 | ? | ? |
| 0 | 1 | ? | ? |
| 1 | 0 | ? | ? |
| 1 | 1 | ? | ? |
| 1 | 1 | ? | ? |
| 1 | 0 | ? | ? |
| 1 | 1 | ? | ? |

- Q1: Are the observed treatments the same as the potential interventions we are interested in?
 - How long is phototherapy applied?
 - How bright is the light?
 - "Consistency assumption": If X = x, then Y(x) = Y
- Q2: does treating one individual affect any other individuals?
 - Vaccinating one individual can protect others
 - Educating one individual can affect others
 - "Non-interference assumption"
- Consistency + Non-interference = "Stable Treatment Value Assumption" (SUTVA)

• If we assume consistency and noninterference, we can fill in half of the potential outcomes:

| X | Y | Y (1) | Y (0) |
|---|---|--------------|-----------------------|
| 0 | 1 | ? | ? |
| 0 | 1 | ? | ? |
| 0 | 0 | ? | ? |
| 0 | 1 | ? | ? |
| 0 | 1 | ? | ? |
| 1 | 0 | ? | ? |
| 1 | 1 | ? | ? |
| 1 | 1 | ? | ? |
| 1 | 0 | ? | ? |
| 1 | 1 | ? | ? |

• If we assume consistency and noninterference, we can fill in half of the potential outcomes:

• For
$$X = 0$$
, $Y(0) = Y$

| X | Y | <i>Y</i> (1) | Y (0) |
|---|---|--------------|-----------------------|
| 0 | 1 | ? | 1 |
| 0 | 1 | ? | 1 |
| 0 | 0 | ? | 0 |
| 0 | 1 | ? | 1 |
| 0 | 1 | ? | 1 |
| 1 | 0 | ? | ? |
| 1 | 1 | ? | ? |
| 1 | 1 | ? | ? |
| 1 | 0 | ? | ? |
| 1 | 1 | ? | ? |

• If we assume consistency and noninterference, we can fill in half of the potential outcomes:

• For
$$X = 0$$
, $Y(0) = Y$

• For
$$X = 1$$
, $Y(1) = Y$

| X | Y | Y (1) | Y (0) |
|---|---|--------------|-----------------------|
| 0 | 1 | ? | 1 |
| 0 | 1 | ? | 1 |
| 0 | 0 | ? | 0 |
| 0 | 1 | ? | 1 |
| 0 | 1 | ? | 1 |
| 1 | 0 | 0 | ? |
| 1 | 1 | 1 | ? |
| 1 | 1 | 1 | ? |
| 1 | 0 | 0 | ? |
| 1 | 1 | 1 | ? |

The Fundamental Problem of Causal Inference

- Even assuming consistency and noninterference:
 - We are still missing half of the potential outcomes
 - No rows are complete
- If we want to estimate average potential outcomes and risk differences, we need to decide what to do about the missing potential outcomes.

| X | Y | Y (1) | <i>Y</i> (0) |
|---|---|--------------|--------------|
| 0 | 1 | ? | 1 |
| 0 | 1 | ? | 1 |
| 0 | 0 | ? | 0 |
| 0 | 1 | ? | 1 |
| 0 | 1 | ? | 1 |
| 1 | 0 | 0 | ? |
| 1 | 1 | 1 | ? |
| 1 | 1 | 1 | ? |
| 1 | 0 | 0 | ? |
| 1 | 1 | 1 | ? |

Analysis 1: Assume treatment is randomized

• We could assume observed treatments are completely random, or at least, assume that the observed treatments are **independent** of the potential outcomes (i.e., $Y(x) \perp \!\!\! \perp X$) (an independence assumption). Then:

•
$$E[Y(1)|X = 0] = E[Y(1)] = E[Y(1)|X = 1] = E[Y|X = 1]$$

•
$$\hat{E}[Y|X=1] = \frac{1}{5}(0+1+0+1+1) = \frac{3}{5}$$

•
$$\hat{E}[Y(1)] = \frac{1}{10} \left[\left(5 \times \frac{3}{5} \right) + 3 \right] = \frac{3}{5} = 60\%$$

| X | Y | Y (1) | Y (0) |
|---|---|--------------|--------------|
| 0 | 1 | 3/5 | 1 |
| 0 | 1 | 3/5 | 1 |
| 0 | 0 | 3/5 | 0 |
| 0 | 1 | 3/5 | 1 |
| 0 | 1 | 3/5 | 1 |
| 1 | 0 | 0 | ? |
| 1 | 1 | 1 | ? |
| 1 | 1 | 1 | ? |
| 1 | 0 | 0 | ? |
| 1 | 1 | 1 | ? |

Analysis 1: Assume treatment is randomized

• Similarly: E[Y(0)|X = 1] = E[Y(0)] = E[Y(0)|X = 0] = E[Y|X = 0]

$$\hat{\mathbf{E}}[Y|X=0] = \frac{1}{5}(1+1+0+1+1) = \frac{4}{5}$$

•
$$\hat{E}[Y(0)] = \frac{1}{10} \left[4 + \left(5 \times \frac{4}{5} \right) \right] = \frac{4}{5} = 80\%$$

$$\hat{\mathbf{E}}[Y(1) - Y(0)] = \hat{\mathbf{E}}[Y(1)] - \hat{\mathbf{E}}[Y(0)]$$
$$= \frac{3}{5} - \frac{4}{5} = -\frac{1}{5} = -20\%$$

 Given our assumptions, we would estimate that treatment 1 (phototherapy) reduces the risk of worsening jaundice by 20 percentage points.

| X | Y | Y (1) | Y (0) |
|---|---|--------------|-----------------------|
| 0 | 1 | 3/5 | 1 |
| 0 | 1 | 3/5 | 1 |
| 0 | 0 | 3/5 | 0 |
| 0 | 1 | 3/5 | 1 |
| 0 | 1 | 3/5 | 1 |
| 1 | 0 | 0 | 4/5 |
| 1 | 1 | 1 | 4/5 |
| 1 | 1 | 1 | 4/5 |
| 1 | 0 | 0 | 4/5 |
| 1 | 1 | 1 | 4/5 |

Analyzing the phototherapy data, assuming observed treatment is completely random

| | Condition Worsened $(Y = 1)$ | Condition Stabilized or Improving $(Y = 0)$ | All |
|----------------------------|------------------------------|---|-----------------|
| Phototherapy $(X = 1)$ | 15 (0.3%) | 4569 (99.7%) | 4584 (22%) |
| Watchful Waiting $(X = 0)$ | 113 (0.7%) | 16,034 (99.3%) | 16,147 (78%) |
| All | 128 (0.6%) | 20,603 (99.4%) | 20,731 |

Under our assumptions (consistency, no interference, observed treatment is independent of the potential outcomes):

- Estimated Causal Risk (of jaundice worsening if we choose phototherapy) = $\hat{P}[Y(1) = 1] = 0.3\%$
- Estimated Causal Risk (of jaundice worsening if we choose waiting) = $\widehat{P}[Y(0) = 1] = 0.7\%$
- Estimated Causal Risk Difference = 0.3% 0.7% = -0.4%

That is, we estimate that giving phototherapy to all cases would reduce the event rate by 0.4%

Not-completely-random treatment assignment

- Maybe, the pattern of observed treatments is not completely random
- Maybe, the infants who received phototherapy have different characteristics than those who were treated with watchful waiting

Gestational Age and Phototherapy

| | Watchful Waiting $(X = 0)$ | Phototherapy $(X = 1)$ | All |
|---|----------------------------|------------------------|-----------------|
| Gestational Age \leq 37 weeks $(Z = 0)$ | 4240 (69%) | 1900 (31%) | 6140 (30%) |
| Gestational Age > 37 weeks $(Z = 1)$ | 11,907 (82%) | 2684 (18%) | 14,591 (70%) |
| All | 16,147 (78%) | 4584 (22%) | 20,731 |



Non-random treatment assignment

- We know X is not independent of Z
- We're not sure if $Y(x) \perp \!\!\! \perp X$
- Suppose Z indicates the gestational age of the infant, categorized:
 - -Z = 0 if gest. age ≤ 37 weeks
 - -Z = 1 if gest. age > 37 weeks
- 2 of 5 infants who received phototherapy had gest. age > 37 weeks, versus 3 of 5 of infants who did not receive phototherapy
- Does it still make sense to just average the observed outcomes from all the phototherapy infants together?

| Z | X | Y | Y (1) | Y (0) |
|---|---|---|--------------|-----------------------|
| 0 | 0 | 1 | ? | 1 |
| 0 | 0 | 1 | ? | 1 |
| 1 | 0 | 0 | ? | 0 |
| 1 | 0 | 1 | ? | 1 |
| 1 | 0 | 1 | ? | 1 |
| 0 | 1 | 0 | 0 | ? |
| 0 | 1 | 1 | 1 | ? |
| 0 | 1 | 1 | 1 | ? |
| 1 | 1 | 0 | 0 | ? |
| 1 | 1 | 1 | 1 | ? |

- Maybe we are willing to assume that the observed treatment is being randomly chosen, conditional on gestational age Z; (mathematically: Y(x) ⊥ X|Z). This is called a "conditional independence" assumption (or "conditional exchangeability" or "ignorability")
- Then:

$$E[Y(1)|Z = 0, X = 0] = E[Y(1)|Z = 0, X = 1]$$

= $E[Y|Z = 0, X = 1]$

| Z | X | Y | Y (1) | Y (0) |
|---|---|---|--------------|-----------------------|
| 0 | 0 | 1 | 2/3 | 1 |
| 0 | 0 | 1 | 2/3 | 1 |
| 1 | 0 | 0 | ? | 0 |
| 1 | 0 | 1 | ? | 1 |
| 1 | 0 | 1 | ? | 1 |
| 0 | 1 | 0 | 0 | ? |
| 0 | 1 | 1 | 1 | ? |
| 0 | 1 | 1 | 1 | ? |
| 1 | 1 | 0 | 0 | ? |
| 1 | 1 | 1 | 1 | ? |

- Maybe we are willing to assume that the observed treatment is being randomly chosen, conditional on gestational age Z; (mathematically: Y(x) ⊥ X|Z). This is called a "conditional independence" assumption (or "conditional exchangeability" or "ignorability")
- Then:

$$E[Y(1)|Z = 1, X = 0] = E[Y(1)|Z = 1, X = 1]$$

= $E[Y|Z = 1, X = 1]$

| Z | X | Y | <i>Y</i> (1) | <i>Y</i> (0) |
|---|---|---|--------------|--------------|
| 0 | 0 | 1 | 2/3 | 1 |
| 0 | 0 | 1 | 2/3 | 1 |
| 1 | 0 | 0 | 1/2 | 0 |
| 1 | 0 | 1 | 1/2 | 1 |
| 1 | 0 | 1 | 1/2 | 1 |
| 0 | 1 | 0 | 0 | ? |
| 0 | 1 | 1 | 1 | ? |
| 0 | 1 | 1 | 1 | ? |
| 1 | 1 | 0 | 0 | ? |
| 1 | 1 | 1 | 1 | ? |

- Maybe we are willing to assume that the observed treatment is being randomly chosen, conditional on gestational age Z; (mathematically: Y(x) ⊥ X|Z). This is called a "conditional independence" assumption (or "conditional exchangeability" or "ignorability")
- Then:

$$E[Y(0)|X = 1, Z = 0] = E[Y(0)|X = 0, Z = 0]$$

= $E[Y|X = 0, Z = 0]$

| Z | X | Y | Y (1) | <i>Y</i> (0) |
|---|---|---|--------------|--------------|
| 0 | 0 | 1 | 2/3 | 1 |
| 0 | 0 | 1 | 2/3 | 1 |
| 1 | 0 | 0 | 1/2 | 0 |
| 1 | 0 | 1 | 1/2 | 1 |
| 1 | 0 | 1 | 1/2 | 1 |
| 0 | 1 | 0 | 0 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 1 | 1 | 0 | 0 | ? |
| 1 | 1 | 1 | 1 | ? |

- Maybe we are willing to assume that the observed treatment is being randomly chosen, conditional on gestational age Z; (mathematically: Y(x) ⊥ X|Z). This is called a "conditional independence" assumption (or "conditional exchangeability" or "ignorability")
- Then:

$$E[Y(0)|X = 1, Z = 1] = E[Y(0)|X = 0, Z = 1]$$

= $E[Y|X = 0, Z = 1]$

| Z | X | Y | <i>Y</i> (1) | <i>Y</i> (0) |
|---|---|---|--------------|--------------|
| 0 | 0 | 1 | 2/3 | 1 |
| 0 | 0 | 1 | 2/3 | 1 |
| 1 | 0 | 0 | 1/2 | 0 |
| 1 | 0 | 1 | 1/2 | 1 |
| 1 | 0 | 1 | 1/2 | 1 |
| 0 | 1 | 0 | 0 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 1 | 1 | 0 | 0 | 2/3 |
| 1 | 1 | 1 | 1 | 2/3 |

• Once we have imputed all of the Y(1)s and Y(0)s, we can estimate $\hat{E}[Y(0)]$ and $\hat{E}[Y(1)]$:

•
$$\widehat{E}[Y(1)] = \frac{1}{10} \left[\left(\frac{2}{3} \times 2 \right) + \left(\frac{1}{2} \times 3 \right) + 2 + 1 \right] = .58$$

| Z | X | Y | Y (1) | Y(0) |
|---|---|---|--------------|-------------|
| 0 | 0 | 1 | 2/3 | 1 |
| 0 | 0 | 1 | 2/3 | 1 |
| 1 | 0 | 0 | 1/2 | 0 |
| 1 | 0 | 1 | 1/2 | 1 |
| 1 | 0 | 1 | 1/2 | 1 |
| 0 | 1 | 0 | 0 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 1 | 1 | 0 | 0 | 2/3 |
| 1 | 1 | 1 | 1 | 2/3 |

• Once we have imputed all of the Y(1)s and Y(0)s, we can estimate $\hat{E}[Y(0)]$ and $\hat{E}[Y(1)]$:

•
$$\widehat{E}[Y(1)] = \frac{1}{10} \left[\left(\frac{2}{3} \times 2 \right) + \left(\frac{1}{2} \times 3 \right) + 2 + 1 \right] = .58$$

•
$$\widehat{E}[Y(0)] = \frac{1}{10} \left[2 + 2 + \left(\frac{2}{2} \times 3 \right) + \left(\frac{2}{3} \times 2 \right) \right] = .83$$

•
$$\hat{E}[Y(1) - Y(0)] = .58 - .83 = -.25$$

 Compare with what we got from the unstratified analysis:

$$\hat{E}[Y(1) - Y(0)] = .6 - .8 = -.20$$

| Z | X | Y | Y (1) | Y (0) |
|---|---|---|--------------|-----------------------|
| 0 | 0 | 1 | 2/3 | 1 |
| 0 | 0 | 1 | 2/3 | 1 |
| 1 | 0 | 0 | 1/2 | 0 |
| 1 | 0 | 1 | 1/2 | 1 |
| 1 | 0 | 1 | 1/2 | 1 |
| 0 | 1 | 0 | 0 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 0 | 1 | 1 | 1 | 2/2 |
| 1 | 1 | 0 | 0 | 2/3 |
| 1 | 1 | 1 | 1 | 2/3 |

Gestational Age, Phototherapy, and Worsened Jaundice

| | | Condition Stabilized or Improving $(Y = 0)$ | Condition Worsened $(Y = 1)$ | All | All |
|---|----------------------------|---|------------------------------|-----------------|--------|
| $\begin{aligned} \text{Gestational Age} & \leq 37 \\ \text{weeks} \\ (Z = 0) \end{aligned}$ | Watchful Waiting $(X = 0)$ | 4154 (98.0%) | 86 (2.0%) | 4240 (69%) | 6140 |
| | Phototherapy $(X = 1)$ | 1890 (99.5%) | 10 (0.5%) | 1900 (31%) | (30%) |
| Gestational Age > 37 weeks (Z = 1) | Watchful Waiting $(X = 0)$ | 11,880 (99.8%) | 27 (0.2%) | 11,907 (82%) | 14,591 |
| | Phototherapy $(X = 1)$ | 2679 (99.8%) | 5 (0.2%) | 2684 (18%) | (70%) |
| All | | 20,603 (99.4%) | 128 (0.6%) | | 20,731 |

Estimated causal risk of phototherapy = 0.3%Estimated causal risk of waiting = 0.8% Estimated Causal Risk Difference from Stratified Analysis = -.5% (Estimated Causal Risk Difference from Unstratified Analysis = -.4%)



Analysis 3: Regression

- What if Z is a numeric variable, e.g., gestational age measured in weeks?
- Stratification likely won't work: there aren't any rows with Z = 37 and X = 0 that we can use to estimate E[Y|Z = 37, X = 0].
- We could categorize Z as we did before, but maybe we need Z in its continuous form to justify $Y \perp \!\!\! \perp X(x)|Z$.
- However, we can still estimate E[Y|Z=37, X=0] by fitting a regression model!

| Z | X | Y | Y (1) | Y (0) |
|----|---|---|--------------|-----------------------|
| 36 | 0 | 1 | ? | 1 |
| 35 | 0 | 1 | ? | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Assumptions for Causal Regression Modeling

Still need conditional independence:
V(x) | V|Z

$$Y(x) \perp \!\!\! \perp X|Z$$

- Still need consistency and non-interference
- Need all treatment options to be possible for every possible value of Z:

$$0 < P(X = 1|Z = z) < 1$$

- Called "positivity assumption"; more of a practical requirement: if there some observations with X=1 and Z=33 but none with X=0 and $Z\approx33$, then how can we reliably predict $\mathrm{E}[Y|X=0,Z=33]$?
- Will end up extrapolating, with extreme uncertainty (low precision).

| Z | X | Y | Y (1) | Y (0) |
|----|---|---|--------------|-----------------------|
| 36 | 0 | 1 | ? | 1 |
| 35 | 0 | 1 | ? | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Estimating Causal Effects with Regression Modeling

- If our assumptions hold, then: E[Y(1)|X=0,Z=z] = E[Y|X=0,Z=z]
- We can impute the missing potential outcomes:

| Z | X | Y | Y (1) | Y (0) |
|----|---|---|---------------------------|-----------------------|
| 36 | 0 | 1 | $\widehat{E}[Y X=1,Z=36]$ | 1 |
| 35 | 0 | 1 | ? | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Estimating Causal Effects with Regression Modeling

- If our assumptions hold, then: E[Y(1)|X=0,Z=z] = E[Y|X=0,Z=z]
- We can impute the missing potential outcomes:

| Z | X | Y | Y (1) | <i>Y</i> (0) |
|----|---|---|---------------------------|--------------|
| 36 | 0 | 1 | $\widehat{E}[Y X=1,Z=36]$ | 1 |
| 35 | 0 | 1 | $\widehat{E}[Y X=1,Z=35]$ | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Estimating Causal Effects with Regression Modeling

- If our assumptions hold, then: E[Y(1)|X=0,Z=z] = E[Y|X=0,Z=z]
- We can impute the missing potential outcomes
- Can also regress on more than one Z variable, to better justify $Y(x) \perp\!\!\!\perp X|Z_1, \dots, Z_p$

| Z | X | Y | Y (1) | Y (0) |
|----|---|---|------------------------------------|-----------------------|
| 36 | 0 | 1 | $\widehat{\mathbf{E}}[Y X=1,Z=36]$ | 1 |
| 35 | 0 | 1 | $\widehat{E}[Y X=1,Z=35]$ | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Causal regression modeling of phototherapy and jaundice

- Vittinghoff et al (2012) performed logistic regression modeling on the jaundice data using the following predictor covariates: treatment (phototherapy vs. watchful waiting), chromosomal sex, gestational age (discretized into 6 categories), birth weight (numeric, linear term), interaction between gestational age and birth weight, bilirubin level at time of treatment assignment (relative to a guideline threshold for phototherapy treatment), age at time of treatment assignment (discretized into days), and hospital (treated as a clustering variable)
- Results:
 - $-\widehat{P}[Y(1) = 1] = 0.16\%;$
 - $-\widehat{P}[Y(1) = 0] = 0.96\%;$
 - Estimated risk difference = -0.79%
- Compare: unadjusted analysis risk difference: -0.4%; risk difference stratifying on gestational age ≤ 37 weeks: -0.5%

Analysis 4: Matching (briefly)

If a given observation has no exact counterparts (with opposite treatment), maybe we can use an approximate counterpart instead:

| Z | X | Y | <i>Y</i> (1) | <i>Y</i> (0) |
|----|---|---|--------------|--------------|
| 36 | 0 | 1 | ? | 1 |
| 35 | 0 | 1 | ? | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Analysis 4: Matching (briefly)

- If a given observation has no exact counterparts (with opposite treatment), maybe we can use an approximate counterpart instead.
- Maybe we just pick one of the closest matches and call it close enough?

| Z | X | Y | Y (1) | Y (0) |
|----|---|---|--------------|-----------------------|
| 36 | 0 | 1 | ? | 1 |
| 35 | 0 | 1 | ? | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | ? |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Analysis 4: Matching (briefly)

- If a given observation has no exact counterparts (with opposite treatment), maybe we can use an approximate counterpart instead.
- Maybe we just pick one of the closest matches and call it close enough?
- Maybe we pick one "matching" counterpart for every observation?
- We might need to discard some observations without any close matches.
- There are many different methods for matching.

| Z | X | Y | Y (1) | Y (0) |
|----|---|---|--------------|-----------------------|
| 36 | 0 | 1 | ? | 1 |
| 35 | 0 | 1 | ? | 1 |
| 38 | 0 | 0 | ? | 0 |
| 40 | 0 | 1 | ? | 1 |
| 39 | 0 | 1 | ? | 1 |
| 35 | 1 | 0 | 0 | ? |
| 37 | 1 | 1 | 1 | 0 |
| 36 | 1 | 1 | 1 | ? |
| 40 | 1 | 0 | 0 | ? |
| 38 | 1 | 1 | 1 | ? |

Analysis 5: Propensity scores (also briefly)

- If we need several Zs to justify the conditional independence assumption, stratification, regression, and matching can become very complicated.
- Maybe we can combine those Zs into a single variable that summarizes them and still provides conditional independence.
- If X is binary and the conditional independence assumption holds for Z_1, \ldots, Z_p , then it also holds for $\pi(z_1, \ldots, z_p) = P(X = 1 | Z_1 = z_1, \ldots, Z_p = z_p)$; that is, $Y(x) \perp \!\!\! \perp X \mid \pi(Z)$
- We can estimate $\hat{\pi}(z_1, ..., z_p) = \hat{P}(X = 1 | Z_1 = z_1, ..., Z_p = z_p)$ and use it with univariate stratification, regression, or matching.
- More on this topic in the third seminar in this series!



How do we know if we have the right covariates?

- The conditional independence assumption is crucial for all the methods we discussed today. How can we tell if it is plausible? Hard to even think about.
- Maybe we can make smaller, easier-to-understand, possibly even testable, assumptions, from which we could mathematically deduce whether a given set of covariates provides conditional independence.
- Next session: we draw flow-chart diagrams (called directed acyclic graphs, "DAGs") to represent our assumptions about the data-generating process, and analyze these diagrams to determine which sets of covariates would produce conditional independence, given our assumptions.

Other causal inference topics to explore

- We haven't discussed how to compute standard errors or confidence intervals for our causal effect estimates.
 - There are various methods, but when in doubt, try the bootstrap: often conceptually simple, although computationally time-consuming.
- There are other common causal inference methods:
 - inverse-probability weighting (IPW)
 - g-estimation
 - Instrumental variables

Help is available

- My email: demorrison@ucdavis.edu
- CTSC and Cancer Center Biostatistics Office Hours
 - Every Tuesday from 12 2:00 currently via WebEx
 - 1st & 3rd Wednesday from 1:00 2:00 currently via WebEx
 - Sign-up through the CTSC Biostatistics Website
- EHS Biostatistics Office Hours
 - Upon request
- Request Biostatistics Consultations
 - CTSC
 - MIND IDDRC
 - Cancer Center Shared Resource
 - EHS Center



Thanks for attending!