Observational Studies: Identifying Causal Effects

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Non-small cell lung cancer

- Surgical resection is the current treatment of choice

- There are a number of surgical options:
  - wedge resection
  - segmentectomy
  - lobectomy

- Differ in terms of how much lung tissue is removed

- Decision between procedures is based, in part at least, on an attempt to balance between post-operative lung function and risk of recurrence

- First step might be to establish if there is a difference in the risk of recurrence
  - let $Y=0/1$ denote recurrence within some frame (e.g. 1 year)
• For simplicity, we can consider a binary surgical ‘treatment’, denoted $A$
  ✴ $A = 0$ for wedge resection
  ✴ $A = 1$ for anatomic resection
    ✴ segmentectomy/lobectomy

Q What is the causal association between $A$ and $Y$?

• To answer this question we need to
  (i) explicitly define what we mean by ‘causal association’
  (ii) come up with a method for estimating it given data from either
    ✴ a randomized study
    ✴ an observational study
Counterfactual outcomes

Q: What is the difference in risk of recurrence be if a patient undergoes anatomic resection versus wedge resection?

• Question is framed in terms of the application of two treatments to the same person
  ★ natural framing that aligns with how we think and make decisions

• Towards a formal treatment of this question, we introduce the notion of a counterfactual outcome
  ★ denoted by $Y(a)$
  ★ value of $Y$ had, possibly contrary to fact, the individual been exposed to $A = a$
  ★ also called a potential outcome
For the lung surgery setting, each individual has two counterfactuals:

- \( Y_{(0)} \): the value of response had they undergone wedge resection
- \( Y_{(1)} \): the value of response had they undergone anatomic resection

In more general settings, an individual has a counterfactual outcome for each possible treatment scenario:

- continuous treatments
  - \( A \) takes on an infinite number of possible values
  - e.g. dose for some drug therapy
  - e.g. amount of time exercising

- a course of treatment
  - \( A \) is a vector describing treatment at a series of time points
  - e.g. surgery followed by chemotherapy for 3 or 6 months
  - e.g. 200mg every other day or 100mg every day

- define \( Y_{(a)} \) for all possible treatment regimens
**Individual causal effects**

- Focusing on binary treatments, \( A \) has a **causal effect** if

\[
Y_{(0)} \neq Y_{(1)}
\]

- \( A \) has **no causal effect** if

\[
Y_{(0)} = Y_{(1)}
\]

★ say that the *sharp causal null hypothesis* holds if this is true for all subjects in the population.

- While these align with how we make decisions, in the *factual* world, at most one counterfactual outcome can be observed for any given individual

★ i.e. the counterfactual corresponding to the treatment actually experienced
• Hence we are faced with a missing data problem
  ⭐ one that can never be resolved with data

• Individual causal effects, therefore, cannot be determined
  ⭐ on the basis of either a randomized study or an observational study
  ⭐ not without extrapolating beyond the observable world

• Need another definition of ‘causal effects’
  ⭐ one that can, in principle, be determined with data
  ⭐ one that requires weaker assumptions
Average causal effects

- One way forward is to define ‘causation’ in terms of a comparison between the distributions of the counterfactuals across the population of interest or some summary feature of the distribution.

- For a binary outcome, it would be natural to examine

  \[ P(Y(a) = 1) \]

  * proportion of individuals who experience the outcome for a scenario where everyone receives treatment \( A = a \)

- A comparison between \( P(Y(1) = 1) \) and \( P(Y(0) = 1) \) therefore describes a comparison between two (possibly hypothetical) treatment scenarios for an entire population:

  - \( A=0 \): everyone underwent wedge resection
  - \( A=1 \): everyone underwent anatomic resection
- Causal risk difference:

\[
\text{RD} = P(Y_{(1)} = 1) - P(Y_{(0)} = 1)
\]

- Causal risk ratio:

\[
\text{RR} = \frac{P(Y_{(1)} = 1)}{P(Y_{(0)} = 1)}
\]

- Causal odds ratio:

\[
\text{OR} = \frac{P(Y_{(1)} = 1)/(1 - P(Y_{(1)} = 1))}{P(Y_{(0)} = 1)/(1 - P(Y_{(0)} = 1))}
\]

- When \(P(Y_{(1)} = 1) = P(Y_{(0)} = 1)\) then there is no causal effect
  * regardless of the choice of effect measure

- If we could estimate \(P(Y_{(a)} = 1)\) then we could report any (or all) of the above effect measures
Estimating causal effects: a randomized study

- Suppose we recruit 100 subjects in a study of surgical treatment for lung cancer
  - randomize half to $A = 0$ and half to $A = 1$
  - record their outcomes:

<table>
<thead>
<tr>
<th>$A = 0$</th>
<th>$A = 1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Y_{0,1}$</td>
<td>$Y_{1,1}$</td>
</tr>
<tr>
<td>$\vdots$</td>
<td>$\vdots$</td>
</tr>
<tr>
<td>$Y_{0,50}$</td>
<td>$Y_{1,50}$</td>
</tr>
<tr>
<td>$\bar{Y}_0$</td>
<td>$\bar{Y}_1$</td>
</tr>
</tbody>
</table>

- Estimate $P(Y_{(a)} = 1)$ by the empirical mean, $\bar{Y}_a$
  - the mean of $Y$ among the 50 individuals who actually received $A = a$
Plug-in the values of $\overline{Y}_a$ to estimate the causal risk difference:

$$\hat{RD} = \overline{Y}_1 - \overline{Y}_0,$$

or the causal risk ratio:

$$\hat{RR} = \frac{\overline{Y}_1}{\overline{Y}_0},$$

or the causal odds ratio:

$$\hat{OR} = \frac{\overline{Y}_1/(1 - \overline{Y}_1)}{\overline{Y}_0/(1 - \overline{Y}_0)}.$$

Q: Why is it that can we interpret these estimates in terms of causation?

Intuitively, we appeal to randomization but what is the formal justification?
We first need to outline two assumptions:

(i) **Consistency**

\[
\text{if } A = a \text{ then } Y_{(a)} = Y
\]

★ in principle, the (two) counterfactual outcomes exist regardless of which treatment is actually given

★ guarantees that what we observe when we do give a specific treatment is the corresponding counterfactual

(ii) **Exchangeability**

\[
A \perp \perp Y_{(a)}, \forall a
\]

★ treatment allocation is independent of the counterfactual outcomes

★ that is, treatment decisions are not based on what the outcomes might be under various scenarios for treatment
• Given consistency and exchangeability we have that

\[ P(Y(a) = 1) = P(Y(a) = 1 | A) \]
\[ = P(Y(a) = 1 | A = a) \]
\[ = P(Y = 1 | A = a) \]

• That is, the probability of experiencing the outcome had, possibly contrary to fact, everyone been exposed to \( a \) is the same as the probability of experiencing the outcome among individuals who did get exposed to \( a \)
  * the first is generally hypothetical, unobservable
  * the second is observable

• The core reason why randomized studies are viewed as superior to observational studies is that exchangeability is (in theory) guaranteed

Q: Why?
Estimating causal effects: an observational study

- In practice, it isn’t always possible to conduct a randomized study
  - most often because of ethical considerations
  - sometimes for logistical reasons

- In the absence of a randomized study, we must appeal to observational data to answer questions of interest
  - data collected as part of a specific research study
  - data collected for some other (primary) purpose
    - e.g. an administrative claims data or EHR data

- For example, to learn about differences in surgical treatment options for NSCLC we could use data on patients who underwent surgery at BWH
  - data collected during the course of usual clinical care at BWH
Q: Are there any issues associated with using observational data to establish causation?

- Key issue: surgical procedure was not randomized at BWH

Q: How were the decisions among possible procedures made?

- Choice of procedure was likely driven by a number of factors
  - age
  - lung function e.g. FEV$_1$, COPD
  - smoking history
  - other co-morbidities e.g. BMI
  - expertise of the surgeon

- Each of these factors may also be related to the risk of recurrence

Q: What impact does this ‘structure’ have on our ability to establish causality?
• For simplicity, let's consider smoking history

\[ L = \begin{cases} 
0 & \text{never smoker} \\
1 & \text{former/current smoker} 
\end{cases} \]

• Reasonable to suppose that smokers are more likely to
  - have diminished lung function
  - experience a recurrence

• Summarize these relationships with a directed acyclic graph (DAG):

\[ \text{Diagram}\]
Consider those who actually underwent wedge resection

- loss of lung function is likely a concern
- more likely to be former/current smokers

Consider those who actually underwent anatomic resection

- loss of lung function is of less concern
- more likely to be never smokers

**Q:** What would have happened to the wedge resection patients had they undergone anatomic resection?

<table>
<thead>
<tr>
<th>Actual treatment</th>
<th>Smoking distribution</th>
<th>Counterfactuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A = 0$</td>
<td>more former/current smokers</td>
<td>$Y_{(0)}, Y_{(1)}$</td>
</tr>
<tr>
<td>$A = 1$</td>
<td>more never smokers</td>
<td>$Y_{(0)}, Y_{(1)}$</td>
</tr>
</tbody>
</table>
• The distribution of their counterfactual outcomes would likely not be the same as the distribution of the counterfactual outcomes among the patients who did undergo anatomic resection
  ✧ \([A = 0]\) is ‘enriched’ with smokers who tend to have worse outcomes

• So, the distributions of the counterfactual outcomes are not independent of treatment allocation

\[ Y(a) \not\perp\!\!\!\perp A \]

✧ the exchangeability assumption does not hold
Confounding

Q: What if we ignore this absence of exchangeability?

* we can, of course, continue to estimate $P(Y = 1 \mid A = a)$ by $\bar{Y}_a$

* and compute contrasts such as

$$\hat{RD} = \bar{Y}_1 - \bar{Y}_0$$

• The problem is that $P(Y = 1 \mid A = a) \neq P(Y_{(a)} = 1)$

• Consequently, in the absence of exchangeability, effect measures based on $P(Y = 1 \mid A = a)$ (i.e. quantities that are estimable) will not have a causal interpretation

Q: So what are we estimating?
• If we don’t control for $L$, we are estimating some mixture of two components:

![Diagram](image)

(i) the ‘direct’ causal association from $A \rightarrow Y$

(ii) an ‘indirect’ association, through $L$

* sometimes referred to as a *backdoor* path

• The result is a *spurious* or *distorted* association

• Formally, the difference between what we are estimating and the causal association is referred to as *confounding bias*
• Covariates that contribute to confounding bias are *confounders*

• The extent of confounding bias will depend on many aspects of the problem
  - number and type of confounders that have not been included in the analysis
  - i.e. unmeasured confounders, $U$
  - strength of the associations between $U$ and both $A$ and $Y$
  - strength of association between $A$ and $Y$

• In practice, the interrelationships between $A$, $Y$ and all potential confounders will likely be complex
  - use the DAG framework to identify sufficient sets of covariates that permit the control of confounding
  - domain knowledge will be critical as statistical criteria are generally inadequate
  - Hernan and Robins (2017; Chapter 7)
• Within the counterfactual framework, to estimate causal associations from observational data we need to extend our assumptions:

(i) **Consistency**

if $A = a$ then $Y(a) = Y$

(ii) **Conditional exchangeability**

$A \perp Y(a) \mid L = l, \forall a, l$

(iii) **Positivity**

if $f_L(l) > 0$ then $f_{A\mid L}(a\mid l) > 0, \forall a$
• Conditional exchangeability states that exchangeability holds *within* strata defined by $L$

<table>
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<tr>
<th>Smoking status, $L$</th>
<th>Actual treatment</th>
<th>Counterfactuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>never smokers</td>
<td>$A = 0$</td>
<td>$Y_{(0)}$, $Y_{(1)}$</td>
</tr>
<tr>
<td>never smokers</td>
<td>$A = 1$</td>
<td>$Y_{(0)}$, $Y_{(1)}$</td>
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**Q:** Is treatment allocation independent of $Y_{(a)}$ among never smokers?

**Q:** Is treatment allocation independent of $Y_{(a)}$ among former/current smokers?

• Referred to as the ‘no unmeasured confounding’ assumption
• Positivity states that all treatment choices are available to all sub-populations defined by $L$

• Would not hold, for example, if never smokers were never treated with wedge resection
  ✧ i.e. don’t worry as much about lung function and always go for the anatomic resection which minimizes future risk

• The practical implications are that if one is comparing $A = 0$ vs. $A = 1$, one shouldn’t include sub-populations that would never receive one of the treatment choices
  ✧ if one does, estimation will rely on extrapolation
  ✧ interpretation of the estimated causal effects is unclear
Interpreting causal effects

- Although in some settings we have to use observational data/methods, thinking about the randomized study we would have conducted is a useful thought experiment

**Q:** If we could perform a randomized study, what would it look like?

- use this to drive decisions in our analysis of the observational data

- A key aspect of a randomized study is a well-defined intervention
  - patients are randomized to a finite number of treatment regimens
  - study protocols specify regimens in great detail

- For the lung surgery example, we would randomize patients to receive one of two treatment/intervention options:
  - wedge resection
  - anatomic resection
• In some instances, it may be difficulty to conceptualize a hypothetical randomized study

• Consider a study published by Rosenman et al (JAMA 233:872-877, 1975)
  - Western Collaborative Group Study
  - prospective study of coronary heart disease
  - participants were categorized into one of two behavior pattern groups:

  **Type A**: characterized by *enhanced aggressiveness, ambitiousness, competitive drive, and chronic sense of urgency*

  **Type B**: characterized by *more relaxed and non-competitive*

Q: For the WCGS data, what would this intervention look like?

Q: Can we conceive of an intervention that directly corresponds to this ‘exposure’?
• We could conceive of an intervention that seeks to make Type A individuals more relaxed
  ✫ herbal tea, yoga, a holiday?!?!?

• But this is not what the paper was reporting on

• If we cannot conceive of an intervention that directly corresponds to behavior type

  Q: What does ‘causation’ mean in this context?

  Q: What are we estimating when we ‘adjust for confounding’?

  Q: Can we call it a ‘causal effect’?

• These issues arise in a broad range of public health settings:
  ✫ age, gender, race, weight, blood pressure, . . .

• The key is to be precise in our interpretation of the results
The control of confounding bias

- **Study design:**
  - *randomization*
    - known and unknown confounders
  - *matching and/or restriction*
    - known confounders only

- **Analysis:**
  - *inverse-probability weighting/standardization*
    - known confounders only
  - *stratification-based methods (stratified analyses, restriction, regression)*
    - known confounders only
Reading

• Rothman K, Greenland S, and Lash T. Modern Epidemiology (2008)
  ★ Chapter 4, Measures of effect and measures of association

• Hernan M and Robins J. Causal Inference (2017)
  ★ Chapter 7, Confounding
  ★ available in pdf form through Miguel Hernan’s website

• Krieger N and Davey Smith G. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. International Journal of Epidemiology (2016)