Assessing the impact of unmeasured confounding: confounding functions for causal inference

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1. What is causal inference?
2. How can the impact of unmeasured confounding be assessed?
3. An example: abciximab and death in percutaneous coronary intervention patients.
There are many situations in which randomised trials cannot be conducted:

- Often difficult or unethical to randomise patients to treatments.
- But there may exist observational data containing treatments/exposures and outcomes of interest!

**Causal inference permits causal interpretations of associations.**

- Strict assumptions required:
  - The one I care about here is no unmeasured confounding.
  - Assume the others are satisfied.
- Use the potential outcomes framework.
Potential outcomes: abciximab and death

Each patient has two potential outcomes:

\[ Y^1 = \text{death if received abciximab} \]

\[ Y^0 = \text{death if no abciximab} \]
Potential outcomes: abciximab and death

Each patient has two potential outcomes:

\[ Y^1 = \text{death if received abciximab} \]

\[ Y^0 = \text{death if no abciximab} \]

Of which only one is observed:

\[ Y = Y^1 = \text{death if abciximab} \]

\[ Y^0 = \text{death if no abciximab} \]
Potential outcomes and the causal odds ratio

$A = 0$ if patient did not receive treatment; $A = 1$ if received treatment.

- Causal odds ratio:

$$OR^c = \frac{P(Y^1 = 1)}{1 - P(Y^1 = 1)} \div \frac{P(Y^0 = 1)}{1 - P(Y^0 = 1)}$$
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- Conditional odds ratio:
  \[ OR = \frac{P(Y = 1 | A = 1)}{1 - P(Y = 1 | A = 1)} \div \frac{P(Y = 1 | A = 0)}{1 - P(Y = 1 | A = 0)} \]
Potential outcomes and the causal odds ratio

\[ A = 0 \text{ if patient did not receive treatment; } A = 1 \text{ if received treatment.} \]

- Causal odds ratio:

\[ OR_c = \frac{P(Y^1 = 1)}{1 - P(Y^1 = 1)} \div \frac{P(Y^0 = 1)}{1 - P(Y^0 = 1)} \]

- Conditional odds ratio:

\[ OR = \frac{P(Y = 1|A = 1)}{1 - P(Y = 1|A = 1)} \div \frac{P(Y = 1|A = 0)}{1 - P(Y = 1|A = 0)} \]

If causal inference assumptions are satisfied, \( OR_c = OR \).
Differences between treatment groups

- If data are observational, likely to be differences between treatment groups.
  - **Measured confounders:**
    - e.g. treated subjects tend to be older & older patients more likely to experience the outcome.
  - **Unmeasured confounders:**
    - e.g. cognitive function; social connectedness; some measure of overall health.
- Adjusting for measured confounders:
  - Assume an inverse probability of treatment weighting approach used to estimate a marginal odds ratio.
  - Skip the details!
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How can we adjust for the unmeasured differences that we suspect are present?
Correcting for unmeasured confounding

- **Instrumental variables**: a variable related to treatment and only related to outcome through treatment.
  - Able to adjust for the entire impact of unmeasured confounding.
  - Problem: IVs may not be available if there is a limited set of recorded variables.

- **External adjustment**: assume the existence of one or more unmeasured (binary) confounders.
  - Useful if you have good expert knowledge on particular unmeasured confounders.
  - Problems:
    - difficult to assess the entire impact of unmeasured confounding;
    - assumptions may be as untenable as original assumption of no unmeasured confounding.
Confounding function approach

Adjust estimates using a confounding function that describes the degree of unmeasured confounding

\[
c(a) = \frac{P(Y^a = 1|A = 1)}{P(Y^a = 1|A = 0)}, \quad a = 0, 1
\]

1Following Brumback et al (Stat Med 2004), Robins (Synthese 1999)
Confounding function approach

Adjust estimates using a confounding function that describes the degree of unmeasured confounding

\[ c(0) = \frac{P(Y^0 = 1|A = 1)}{P(Y^0 = 1|A = 0)}, \quad c(1) = \frac{P(Y^1 = 1|A = 1)}{P(Y^1 = 1|A = 0)} \]

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Confounding function approach

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- \( c(0), c(1) \) are counterfactual quantities: values selected by investigators.
- Requires contextual knowledge to quantify the impact of unmeasured confounding, in terms of counterfactual outcomes.

What differences in the outcomes are due to unaccounted-for differences in the treatment groups, rather than due to the effect of treatment on the outcome?

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Confounding function approach

\[ A = 0 \Rightarrow \text{no treatment, } A = 1 \Rightarrow \text{received treatment:} \]

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\[ c(0) = c(1) = 1 \Rightarrow \text{No unmeasured confounding is present.} \]

\[ c(0) > 1, \quad c(1) > 1, \quad c(0) = c(1) \Rightarrow \text{• Risk of (both) potential outcomes higher among those actually treated.} \]

\[ \text{• Some of the observed risk of the outcome for treated subjects is due to some unmeasured 'ill health';} \]

\[ \text{• Effect of treatment the same in treated and untreated groups.} \]
Confounding function approach

\[ A = 0 \implies \text{no treatment}, \ A = 1 \implies \text{received treatment}: \]

\[ c(0) = \frac{P(Y^0 = 1 \mid A = 1)}{P(Y^0 = 1 \mid A = 0)}, \quad c(1) = \frac{P(Y^1 = 1 \mid A = 1)}{P(Y^1 = 1 \mid A = 0)} \]

\[ c(0) = c(1) = 1 \implies \]

- No unmeasured confounding is present.
Confounding function approach

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- No unmeasured confounding is present.

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- Risk of (both) potential outcomes higher among those actually treated.
- Some of the observed risk of the outcome for treated subjects is due to some unmeasured ‘ill health’;
- Effect of treatment the same in treated and untreated groups.
Adjusting for unmeasured confounding

\[
OR^c = \frac{P(Y^1 = 1)}{1 - P(Y^1 = 1)} \div \frac{P(Y^0 = 1)}{1 - P(Y^0 = 1)}
\]

\[
c(a) = \frac{P(Y^a = 1 | A = 1)}{P(Y^a = 1 | A = 0)}, \quad h(a) = P(A = 0) + c(a)P(A = 1)
\]

The causal odds ratio can be written as:

\[
OR^c = \frac{h(1)P(Y = 1 | A = 1)/c(1)}{1 - h(1)P(Y = 1 | A = 1)/c(1)} \div \frac{h(0)P(Y = 1 | A = 0)}{1 - h(0)P(Y = 1 | A = 0)}
\]

- Consider sensitivity of \(OR\) to range of values of \(c(1)\) and \(c(0)\).
- Beware implicit assumptions if \(c(1) \neq c(0)\): differential treatment effect in treated and untreated.
Application: Abciximab and death

- 996 percutaneous coronary intervention patients
  - Abciximab: 698 (70%) → 11 died (1.6% of 698)
  - No abciximab: 298 (30%) → 15 died (5.0% of 298)

- Administration of abciximab at discretion of interventionist.
- Adjust for sex, height, diabetes, recent MI, left ventricle ejection fraction, number of vessels in PCI, insertion of coronary stent using inverse probability of treatment weighting.

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2 Data from twang R package, originally analysed in Kereiakes et al, Am Heart J (2000)
Application: Abciximab and death\(^2\)

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- Administration of abciximab at discretion of interventionist.
- Adjust for sex, height, diabetes, recent MI, left ventricle ejection fraction, number of vessels in PCI, insertion of coronary stent using inverse probability of treatment weighting.

\[
\text{OR} = 0.17, \text{ 95\% CI (0.08, 0.46)}
\]

\(^2\)Data from twang R package, originally analysed in Kereiakes et al, Am Heart J (2000)
Application: Abciximab and death

\[
c(\text{Abciximab}) = \frac{P(Y^{\text{Abc}} = 1|\text{Abc})}{P(Y^{\text{Abc}} = 1|\text{No Abc})}
\]

\[
c(\text{No Abciximab}) = \frac{P(Y^{\text{No Abc}} = 1|\text{Abc})}{P(Y^{\text{No Abc}} = 1|\text{No Abc})}
\]

If both > 1, then

\[
P(Y^{\text{Abc}} = 1|\text{Abc}) > P(Y^{\text{Abc}} = 1|\text{No Abc})
\]

\[
P(Y^{\text{No Abc}} = 1|\text{Abc}) > P(Y^{\text{No Abc}} = 1|\text{No Abc})
\]

- Had they not received Abciximab, those who actually received Abciximab \textbf{more likely to die} than those who did not receive Abciximab.
Sensitivity analysis for the OR, \( c(0) = c(1) = 1 \)
**Take-home messages**

- Causal inference is useful in situations when randomised trials can’t be conducted
  - Strict assumptions, including no unmeasured confounding.
  - Problem: in most applications, the assumption of unmeasured confounders will not be satisfied!
- Turn to alternative approaches:
  - Instrumental variables; external adjustment; confounding functions.
- I’ve described the confounding function approach for binary outcomes.
  - Approach also available for continuous outcomes.
  - Provides a way to assess the sensitivity of estimates to the entire effect of unmeasured confounding.
  - Easy to apply.
  - Contact me for Stata code!
References


Propensity scores

- Propensity score for subject $i$, with observed covariates $X_i = x_i$, treatment $A_i = a_i$:

$$PS_i = P(A_i = 1 | X_i = x_i)$$

Usually estimated using logistic regression models.

- Rosenbaum & Rubin (Biometrika, 1983): adjustment for $PS$ sufficient to remove bias due to all $X$.

- Inverse probability of treatment weighting: Each subject’s observation assigned a weight:

$$w_i = \frac{a_i}{PS_i} + \frac{1 - a_i}{1 - PS_i}$$

- Each subject’s observation weighted by $1/w_i$. 