Estimation of causal effects

Arvid Sjölander

Department of Medical Epidemiology and Biostatistics
Karolinska Institutet

A short course on concepts and methods in Causal Inference

Ideal data

- Let Y_a be the outcome that we would observe, for a given subject, if the subject potentially received exposure level a
  - Y_1 is the outcome under exposure
  - Y_0 is the outcome under non-exposure
- Y_1 and Y_0 are referred to as **potential outcomes**
- Ideally - **and very unrealistically** - we could observe both potential outcomes for any given subject

Subject	Y_1	Y_0
August	1	0
Selma	0	0
Fjodor	1	1

Subject-specific causal effects

Subject	Y_1	Y_0
August	1	0
Selma	0	0
Fjodor	1	1

- A has a causal effect on Y, for a given subject, if the potential outcomes Y_1 and Y_0 differ for this subject
  - for August, the exposure has an effect: $Y_1 \neq Y_0$
  - for Selma and Fjodor, the exposure has not effect; $Y_1 = Y_0$

Observed data

- August is exposed ($A = 1$). Thus, for August
  - Y_1 is observed and equal to the factual outcome Y
  - Y_0 is unobserved, or **counterfactual**
- Selma and Fjodor are unexposed ($A = 0$). Thus, for Selma and Fjodor
  - Y_0 is observed and equal to the factual outcome Y
  - Y_1 is unobserved, or **counterfactual**

Subject	A	Y	Y_1	Y_0
August	1	1	1	?
Selma	0	0	?	0
Fjodor	0	1	?	1

A fundamental problem of causation

- It is very difficult to say whether the exposure causes the outcome for a specific subject
  - because we cannot observe the same subject under two exposure levels simultaneously
- Fortunately, it is much easier to justify causal claims on population levels
  - e.g. 'if everybody would quit smoking, then the incidence of liver cancer would decrease by 15%'

Population causal effects

- $\Pr(Y_a = 1)$ is the proportion of subjects that would develop the outcome, if **everybody** would receive exposure level a
  - the probability of the outcome if everybody would receive a
- A has a population causal effect on Y if

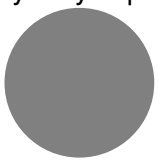
$$\Pr(Y_1 = 1) \neq \Pr(Y_0 = 1)$$

- A has no population causal effect on Y if

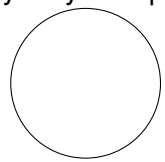
$$\Pr(Y_1 = 1) = \Pr(Y_0 = 1)$$

How to estimate population causal effects

Everybody exposed



Everybody unexposed



$$\Pr(Y_1 = 1) \text{ vs } \Pr(Y_0 = 1)$$

- Direct computation of population causal effects requires comparing
  - the whole population under exposure, with
  - the whole population under no exposure
- But just like for any given subject, we cannot in general observe the whole population under two exposure levels
- *How can we estimate population causal effects?*

Outline

Outline

Example

- Ideal data:

ID	Y_1	Y_0
1	0	0
2	1	0
3	0	0
4	1	1
5	0	0
6	1	1
7	1	1
8	1	1
9	0	0
10	1	0

- *Compute the causal risk ratio*

Solution

ID	Y_1	Y_0
1	0	0
2	1	0
3	0	0
4	1	1
5	0	0
6	1	1
7	1	1
8	1	1
9	0	0
10	1	0

$$\Pr(Y_1 = 1) = 6/10 = 0.6$$

$$\Pr(Y_0 = 1) = 4/10 = 0.4$$

$$\text{causal risk ratio} = \frac{0.6}{0.4} = 1.5$$

Example, cont'd

- Data obtained from a **randomized trial**:

ID	A	Y	Y_1	Y_0
1	1	0	0	?
2	1	1	1	?
3	0	0	?	0
4	1	1	1	?
5	0	0	?	0
6	1	1	1	?
7	0	1	?	1
8	0	1	?	1
9	1	0	0	?
10	0	0	?	0

- *Compute the risk ratio*

Solution

ID	A	Y	Y_1	Y_0
1	1	0	0	?
2	1	1	1	?
3	0	0	?	0
4	1	1	1	?
5	0	0	?	0
6	1	1	1	?
7	0	1	?	1
8	0	1	?	1
9	1	0	0	?
10	0	0	?	0

$$\begin{aligned}\Pr(Y=1|A=1) &= 3/5 = 0.6 \\ &= \Pr(Y_1=1)\end{aligned}$$

$$\begin{aligned}\Pr(Y=1|A=0) &= 2/5 = 0.4 \\ &= \Pr(Y_0=1)\end{aligned}$$

$$\begin{aligned}\text{risk ratio} &= \frac{0.6}{0.4} = 1.5 \\ &= \text{causal risk ratio}\end{aligned}$$

Conclusion

- In this randomized trial, association = causation
- This is not a coincidence, it is true in all (ideal) randomized trials
- Let's look closer into why this happens

The RCT revisited

ID	A	Y	Y_1	Y_0
1	1	0	0	0 (?)
2	1	1	1	0 (?)
3	0	0	0 (?)	0
4	1	1	1	1 (?)
5	0	0	0 (?)	0
6	1	1	1	1 (?)
7	0	1	1 (?)	1
8	0	1	1 (?)	1
9	1	0	0	0 (?)
10	0	0	1 (?)	0

- *Compute all the following:*
  - $\Pr(Y=1|A=1)$
  - $\Pr(Y_1=1|A=1)$
  - $\Pr(Y_1=1|A=0)$
  - $\Pr(Y_1=1)$

Solution

ID	A	Y	Y_1	Y_0
1	1	0	0	0 (?)
2	1	1	1	0 (?)
3	0	0	0 (?)	0
4	1	1	1	1 (?)
5	0	0	0 (?)	0
6	1	1	1	1 (?)
7	0	1	1 (?)	1
8	0	1	1 (?)	1
9	1	0	0	0 (?)
10	0	0	1 (?)	0

$$\begin{aligned}\Pr(Y=1|A=1) &= 3/5 \\ \Pr(Y_1=1|A=1) &= 3/5\end{aligned}$$

- These are always equal, since $Y = Y_1$ for those who are factually exposed

Solution, cont'd

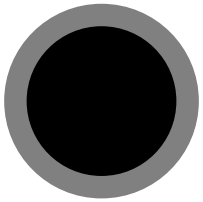
ID	A	Y	Y_1	Y_0
1	1	0	0	0 (?)
2	1	1	1	0 (?)
3	0	0	0 (?)	0
4	1	1	1	1 (?)
5	0	0	0 (?)	0
6	1	1	1	1 (?)
7	0	1	1 (?)	1
8	0	1	1 (?)	1
9	1	0	0	0 (?)
10	0	0	1 (?)	0

$$\begin{aligned}\Pr(Y_1 = 1|A = 1) &= 3/5\\ \Pr(Y_1 = 1|A = 0) &= 3/5\\ \Pr(Y_1 = 1) &= 6/10 = 3/5\end{aligned}$$

- That these are equal means that Y_1 has the same distribution in
  - those who are factually exposed; **observable**
  - those who are factually unexposed; **unobservable**
  - the whole population; **unobservable**
- Rather remarkable!
- We can use $\Pr(Y_1 = 1|A = 1) = \Pr(Y = 1|A = 1)$ as a surrogate for $\Pr(Y_1 = 1)$

In a picture

Everybody exposed; 60% have $Y_1 = 1$



Factually exposed; 60% have $Y_1 = 1$

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1)$$

The RCT revisited

ID	A	Y	Y_1	Y_0
1	1	0	0	0 (?)
2	1	1	1	0 (?)
3	0	0	0 (?)	0
4	1	1	1	1 (?)
5	0	0	0 (?)	0
6	1	1	1	1 (?)
7	0	1	1 (?)	1
8	0	1	1 (?)	1
9	1	0	0	0 (?)
10	0	0	1 (?)	0

- *Compute all the following:*
  - $\Pr(Y = 1|A = 0)$
  - $\Pr(Y_0 = 1|A = 0)$
  - $\Pr(Y_0 = 1|A = 1)$
  - $\Pr(Y_0 = 1)$

Solution

ID	A	Y	Y_1	Y_0
1	1	0	0	0 (?)
2	1	1	1	0 (?)
3	0	0	0 (?)	0
4	1	1	1	1 (?)
5	0	0	0 (?)	0
6	1	1	1	1 (?)
7	0	1	1 (?)	1
8	0	1	1 (?)	1
9	1	0	0	0 (?)
10	0	0	1 (?)	0

$$\begin{aligned}\Pr(Y = 1|A = 0) &= 2/5\\ \Pr(Y_0 = 1|A = 1) &= 2/5\end{aligned}$$

- These are always equal, since $Y = Y_0$ for those who are factually unexposed

Solution, cont'd

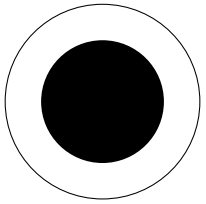
ID	A	Y	Y_1	Y_0
1	1	0	0	0 (?)
2	1	1	1	0 (?)
3	0	0	0 (?)	0
4	1	1	1	1 (?)
5	0	0	0 (?)	0
6	1	1	1	1 (?)
7	0	1	1 (?)	1
8	0	1	1 (?)	1
9	1	0	0	0 (?)
10	0	0	1 (?)	0

$$\begin{aligned}\Pr(Y_0 = 1|A = 0) &= 2/5\\ \Pr(Y_0 = 1|A = 0) &= 2/5\\ \Pr(Y_0 = 1) &= 4/10 = 2/5\end{aligned}$$

- That these are equal means that Y_0 has the same distribution in
  - those who are factually unexposed; **observable**
  - those who are factually exposed; **unobservable**
  - the whole population; **unobservable**
- Rather remarkable!
- We can use $\Pr(Y_0 = 1|A = 0) = \Pr(Y = 1|A = 0)$ as a surrogate for $\Pr(Y_0 = 1)$

In a picture

Everybody unexposed; 40% have $Y_0 = 1$



Factually unexposed; 40% have $Y_0 = 1$

$$\underbrace{\Pr(Y_0 = 1|A = 0)}_{=\Pr(Y=1|A=0)} = \Pr(Y_0 = 1)$$

Conclusion

- In the randomized trial, we had that

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1)$$

$$\underbrace{\Pr(Y_0 = 1|A = 0)}_{=\Pr(Y=1|A=0)} = \Pr(Y_0 = 1)$$

  so that the risk ratio was equal to the causal risk ratio
- **Association = causation!**
- This is always true in randomized trials (motivation to follow)

Exchangeability

- If

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1)$$

  and

$$\underbrace{\Pr(Y_0 = 1|A = 0)}_{=\Pr(Y=1|A=0)} = \Pr(Y_0 = 1)$$

  then Y_0 and Y_1 are independent of A:

$$(Y_0, Y_1) \amalg A$$

- We say that the exposed and unexposed are **exchangeable**
- Under exchangeability, association = causation

Example

ID	A	Y
1	1	0
2	1	1
3	0	0
4	1	1
5	0	0
6	1	1
7	0	1
8	0	1
9	1	0
10	0	0

- *Assume exchangeability, and compute the causal risk ratio. Where in the calculation do you use the assumption of exchangeability?*

Solution

ID	A	Y
1	1	0
2	1	1
3	0	0
4	1	1
5	0	0
6	1	1
7	0	1
8	0	1
9	1	0
10	0	0

$$\begin{aligned}\frac{\Pr(Y_1=1)}{\Pr(Y_0=1)} &= \{(Y_0, Y_1) \amalg A\} \\ &= \frac{\Pr(Y_1=1|A=1)}{\Pr(Y_0=1|A=0)} \\ &= \frac{\Pr(Y=1|A=1)}{\Pr(Y=1|A=0)} \\ &= \frac{3/5}{2/5} = 1.5\end{aligned}$$

Why randomization works

- Under randomization, all pre-exposure variables are equally distributed across levels of A
  - all pre-exposure variables are independent of A
- **The potential outcomes** (Y_0, Y_1) **are pre-exposure variables**
- They describe how the subject 'reacts' to $A = 0$ and $A = 1$
- This reaction depends on numerous factors which are determined before the factual exposure level is received
  - genes,lifestyle, age, etc
- Thus, under randomization (Y_0, Y_1) are independent of A

$$(Y_0, Y_1) \amalg A$$

- *This is amazing! Why then not always randomize?*

Example

- **Does heart transplant** (A) **increase 5-year survival** (Y)?
- Select a large population of potential recipients of a transplant
- Get funding and ethical approval
- Randomly allocate each subject to either transplant $(A = 1)$ or medical treatment $(A = 0)$
- 5 years later, calculate the causal risk ratio
- *Is this feasible?*

Non-ignorable drop out

- Some people may drop out of the study ($D = 1$) before end of follow up
  - can compute $\Pr(Y = 1|A, D = 0)$, but not $\Pr(Y = 1|A)$
- Problematic because among those who remain in the study, exposed and unexposed may not be exchangeable:

$$(Y_0, Y_1) \not\perp\!\!\!\perp A \mid D = 0$$

Unblinding

- When the study subjects are aware of what treatment they receive, they may change their behavior accordingly
  - e.g. transplant receivers may change their diet to keep their new heart healthy
- The causal effect of A on Y combines the effect of the exposure and the behavior change
- Even if treated and untreated behave similarly, pure knowledge of treatment received may affect the outcome
  - placebo effect

Non-compliance

- Some subjects who are assigned to the new treatment may take the old treatment, and vice versa
- Traditional analyses:
  - Intention To Treat (ITT)
  - As Treated (AT)
- Both these analyses are likely to be biased
  - alternative 'causal inference methods' exist (beyond the scope of this course)

Conclusion

- Real randomized trials often suffer from several important problems
- Observational studies are needed
  - in fact, most human knowledge comes from observations, e.g. evolution theory, smoking causes lung cancer etc
- And so are methods for causal inference from observational studies

Outline

Example

- Ideal data:

ID	Y_1	Y_0
1	0	0
2	1	0
3	0	0
4	1	1
5	0	0
6	1	1
7	1	1
8	1	1
9	0	0
10	1	0

$$\Pr(Y_1 = 1) = 6/10 = 0.6$$

$$\Pr(Y_0 = 1) = 4/10 = 0.4$$

$$\text{causal risk ratio} = \frac{0.6}{0.4} = 1.5$$

Example, cont'd

- Data obtained from an **observational study**:

ID	A	Y	Y_1	Y_0
1	0	0	?	0
2	1	1	1	?
3	0	0	?	0
4	1	1	1	?
5	1	0	0	?
6	1	1	1	?
7	0	1	?	1
8	1	1	1	?
9	0	0	?	0
10	0	0	?	0

- *Compute the risk ratio*

Solution

ID	A	Y	Y_1	Y_0
1	0	0	?	0
2	1	1	1	?
3	0	0	?	0
4	1	1	1	?
5	1	0	0	?
6	1	1	1	?
7	0	1	?	1
8	1	1	1	?
9	0	0	?	0
10	0	0	?	0

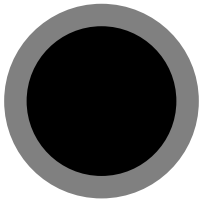
$$\begin{aligned} \Pr(Y = 1|A = 1) &= 4/5 = 0.8 \\ &> \Pr(Y_1 = 1) \end{aligned}$$

$$\begin{aligned} \Pr(Y = 1|A = 0) &= 1/5 = 0.2 \\ &< \Pr(Y_0 = 1) \end{aligned}$$

$$\begin{aligned} \text{risk ratio} &= \frac{0.8}{0.2} = 4 \\ &> \text{causal risk ratio} \end{aligned}$$

In a picture

Everybody exposed; 60% have $Y_1 = 1$

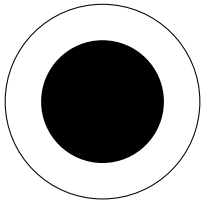


Factually exposed; 80% have $Y_1 = 1$

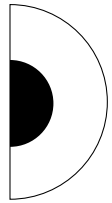
$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} \neq \Pr(Y_1 = 1)$$

In a picture, cont'd

Everybody unexposed; 40% have $Y_0 = 1$



Factually unexposed; 20% have $Y_0 = 1$



$$\underbrace{\Pr(Y_0 = 1|A = 0)}_{=\Pr(Y=1|A=0)} \neq \Pr(Y_0 = 1)$$

Conclusion

- In the observational study, we had that

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} \neq \Pr(Y_1 = 1)$$

$$\underbrace{\Pr(Y_0 = 1|A = 0)}_{=\Pr(Y=1|A=0)} \neq \Pr(Y_0 = 1)$$

- In other words, we had non-exchangeability

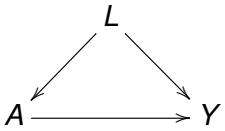
$$(Y_0, Y_1) \not\perp\!\!\!\perp A$$

- As a consequence, the risk ratio was not equal to the causal risk ratio
- **Association $\neq$ causation!**
- This is typical for observational studies

Three important questions

- What is the cause of non-exchangeability in observational studies?
- Can we identify non-exchangeability in a population/sample?
- How can we estimate causal effects in the presence of non-exchangeability?

What is the cause of non-exchangeability in observational studies?



- Suppose that there is a covariate, L, which affects both A and Y
  - e.g. L = 'age'; old people have higher BMI (A) than young people, and are more likely to develop cancer (Y)
- A and Y will then be associated, even if A has no causal effect on Y
- The association between A and Y suffers from **confounding** by L
  - more on confounding later
- **Confounding causes non-exchangeability**

Can we identify non-exchangeability in a population/sample?

- By definition we have non-exchangeability if (Y_0, Y_1) and A are associated
- That is, if

$$\Pr(Y_1 = 1|A = 1) \neq \Pr(Y_1 = 1)$$

or

$$\Pr(Y_0 = 1|A = 0) \neq \Pr(Y_0 = 1)$$

- But Y_1 is not observed for the unexposed ($A = 0$), and Y_0 is not observed for the exposed ($A = 1$)
- Thus, **the observed data can never tell us whether we have exchangeability or not**
  - or whether we have unmeasured confounding
- To judge whether exchangeability is plausible, we must rely on subject matter knowledge

How can we estimate causal effects in the presence of non-exchangeability?

- There are several ways to 'adjust' the analysis for potential confounders
  - stratification
  - matching
  - standardization
  - propensity scores
  - regression modeling
  - inverse probability weighting
  - etc

Conditional exchangeability

- Adjusting for a potential confounder L produces a causal effect **if L is sufficient for confounding control**
  - more later
- Technically, if we have conditional exchangeability, given L:

$$(Y_0, Y_1) \amalg A \mid L$$

- Conditional exchangeability cannot be tested, and must be judged by subject matter knowledge
- Exchangeability can be achieved by adjustments, but can also be 'destroyed'
  - more later

Example

	$L=1$		$L=0$	
	$Y=1$	$Y=0$	$Y=1$	$Y=0$
$A=1$	1	3	6	3
$A=0$	2	3	2	1

- *Assume conditional exchangeability, given L, and use stratification to compute the conditional causal risk ratio, given L, for $L=1$ and $L=0$*

Solution

	$L=1$		$L=0$	
	$Y=1$	$Y=0$	$Y=1$	$Y=0$
$A=1$	1	3	6	3
$A=0$	2	3	2	1

Conditional causal risk ratio, given $L=1$:

$$\frac{\Pr(Y_1=1|L=1)}{\Pr(Y_0=1|L=1)} = \{(Y_0,Y_1) \amalg A|L\}$$
$$= \frac{\Pr(Y_1=1|A=1,L=1)}{\Pr(Y_0=1|A=0,L=1)} = \frac{\Pr(Y=1|A=1,L=1)}{\Pr(Y=1|A=0,L=1)}$$
$$= \frac{1/4}{2/5} = 0.63$$

Conditional causal risk ratio, given $L=0$:

$$\frac{\Pr(Y_1=1|L=0)}{\Pr(Y_0=1|L=0)} = \ldots = \frac{6/9}{2/3} = 1$$

Conditional effects vs marginal effects

- Stratification gives causal effects within subsets of the population - conditional causal effects
  - e.g. stratification by 'sex' gives the causal effect for men and women separately
- We may want to calculate the causal effect for the whole study population - a marginal causal effect
  - easier to interpret **one** marginal effect than **several** conditional effects
  - randomized trials give marginal effects, and we may want to make results from observational studies comparable
  - we may want to consider future interventions to the whole population, rather than to subsets

The standardization formula

- Under conditional exchangeability, given L, $\Pr(Y_a=1)$ can be calculated through **standardization**:

$$\Pr(Y_a=1) = \sum_L \Pr(Y=1|A=a,L)\Pr(L)$$

- Binary L:

$$\begin{aligned}\Pr(Y_a=1) &= \Pr(Y=1|A=a,L=1)\Pr(L=1) \\ &+ \Pr(Y=1|A=a,L=0)\Pr(L=0)\end{aligned}$$

Proof

- Law of total probability:

$$\Pr(Y_a = 1) = \sum_L \Pr(Y_a = 1|L)\Pr(L)$$

- Conditional exchangeability, given L:

$$\sum_L \Pr(Y_a = 1|L)\Pr(L) = \sum_L \Pr(Y_a = 1|A = a, L)\Pr(L)$$

- Definition of potential outcomes:

$$\sum_L \Pr(Y_a = 1|A = a, L)\Pr(L) = \sum_L \Pr(Y = 1|A = a, L)\Pr(L)$$

Example

	$L=1$		$L=0$	
	$Y=1$	$Y=0$	$Y=1$	$Y=0$
$A=1$	1	3	6	3
$A=0$	2	3	2	1

- *Assume conditional exchangeability, given L, and compute the marginal causal risk ratio*

Solution

	$L=1$		$L=0$	
	$Y=1$	$Y=0$	$Y=1$	$Y=0$
$A=1$	1	3	6	3
$A=0$	2	3	2	1

$$\begin{aligned}
\frac{\Pr(Y_1 = 1)}{\Pr(Y_0 = 1)} &= \{(Y_0, Y_1) \amalg A|L\} \\
&= \frac{\sum_L \Pr(Y = 1|A = 1, L)\Pr(L)}{\sum_L \Pr(Y = 1|A = 0, L)\Pr(L)} \\
&= \frac{\overbrace{1/4}^{\Pr(Y=1|A=1,L=1)} \times \overbrace{9/21}^{\Pr(L=1)} + \overbrace{6/9}^{\Pr(Y=1|A=1,L=0)} \times \overbrace{12/21}^{\Pr(L=0)}}{\underbrace{2/5}_{\Pr(Y=1|A=0,L=1)} \times \underbrace{9/21}_{\Pr(L=1)} + \underbrace{2/3}_{\Pr(Y=1|A=0,L=0)} \times \underbrace{12/21}_{\Pr(L=0)}} \\
&= 0.86
\end{aligned}$$

Summary

- Under **exchangeability**, association is equal to causation

$$(Y_0, Y_1) \amalg A$$

- Exchangeability follows by **randomization**
- We typically don't have exchangeability in observational studies
- Causal effects can be estimated in observational studies **if we make sufficient confounder adjustments**
  - but whether the adjustments are sufficient or not is untestable
- **Stratification** produces **conditional** (subpopulation) effects
- **Standardization** produces **marginal** (population) effects