

# 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 make 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

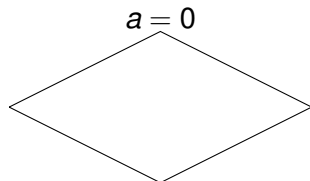
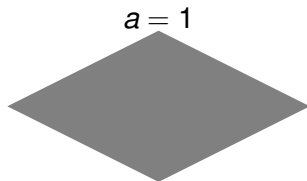
- $\Pr(Y_a = 1)$  is the proportion of subjects that would develop the outcome, if **everybody** would receive exposure level  $a$ 
  - The probability of the outcome if everybody would receive  $a$
- $A$  has a population causal effect on  $Y$  if

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

- $A$  has no population causal effect on  $Y$  if

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

# Population causal effects



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

- 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

Randomized trials

Observational studies



# Outline

Randomized trials

Observational studies

## 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 CRR*

# 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

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

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

$$CRR = \frac{0.6}{0.4} = 1.5$$

## 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 RR*

# 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

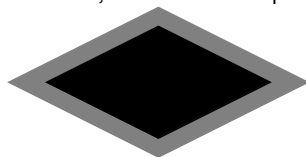
$$\begin{aligned}\Pr(Y = 1|A = 1) &= 3/5 = 0.6 \\ &= \Pr(Y_1 = 1)\end{aligned}$$

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

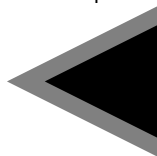
$$RR = \frac{0.6}{0.4} = 1.5 = CRR$$

# In a picture

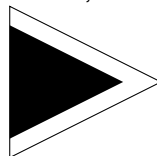
$a = 1$ ; 60% have  $Y_1 = 1$



$A = 1$ ; 60% have  $Y_1 = 1$



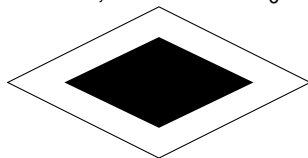
$A = 0$ ; 60% have  $Y_1 = 1$



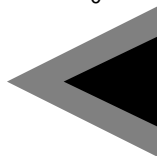
$$\underbrace{\Pr(Y_1 = 1 | A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1 | A = 0) = \Pr(Y_1 = 1)$$

# In a picture, cont'd

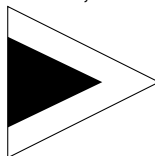
$a = 0$ ; 40% have  $Y_0 = 1$



$A = 1$ ; 40% have  $Y_0 = 1$



$A = 0$ ; 40% have  $Y_0 = 1$



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

# Conclusion

- In the randomized trial, we had that

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1|A = 0) = \Pr(Y_1 = 1)$$

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

so that

$$RR = CRR$$

- Association = causation!**
- This is always true in randomized trials (motivation to follow)



# Exchangeability

- In randomized trials, we have that

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1|A = 0) = \Pr(Y_1 = 1)$$

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

- $Y_0$  and  $Y_1$  are independent of  $A$

$$(Y_0, Y_1) \perp\!\!\!\perp A$$

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

## 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  $A$

$$(Y_0, Y_1) \perp\!\!\!\perp A$$

- *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 calculate  $\Pr(Y = 1|A, D = 0)$ , but not  $\Pr(Y = 1|A)$
- Problematic because among those who remain in the study, exposed and unexposed may not be exchangeable:

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

# 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

Randomized trials

Observational studies



# 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

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

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

$$CRR = \frac{0.6}{0.4} = 1.5$$

## 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  $RR$

# 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

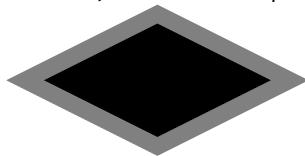
$$\begin{aligned}\Pr(Y = 1|A = 1) &= 4/5 = 0.8 \\ &> \Pr(Y_1 = 1)\end{aligned}$$

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

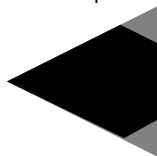
$$RR = \frac{0.8}{0.2} = 4 > CRR$$

# In a picture

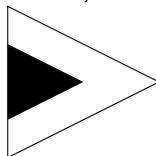
$a = 1$ ; 60% have  $Y_1 = 1$



$A = 1$ ; 80% have  $Y_1 = 1$



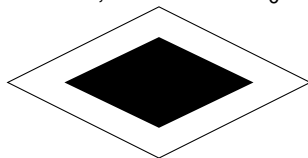
$A = 0$ ; 40% have  $Y_1 = 1$



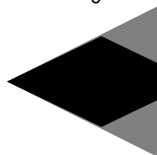
$$\underbrace{\Pr(Y_1 = 1 | A = 1)}_{=\Pr(Y=1|A=1)} \neq \Pr(Y_1 = 1 | A = 0) \neq \Pr(Y_1 = 1)$$

# In a picture

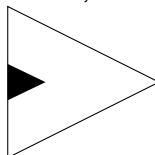
$a = 0$ ; 40% have  $Y_0 = 1$



$A = 1$ ; 60% have  $Y_0 = 1$



$A = 0$ ; 20% have  $Y_0 = 1$



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

# Conclusion

- In the observational study, we had that

$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} \neq \Pr(Y_1 = 1|A = 0) \neq \Pr(Y_1 = 1)$$

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

- In other words, we had non-exchangeability

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

- As a consequence,

$$RR \neq CRR$$

- 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 ( $Y$ )
- If so, then there will be an association between  $A$  and  $Y$ , 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 not independent
- That is, if

$$\Pr(Y_1 = 1|A = 1) \neq \Pr(Y_1 = 1|A = 0)$$

or

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

- 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  $L$ :

$$(Y_0, Y_1) \perp\!\!\!\perp A \mid L$$

- 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

# Stratification

- The conceptually simplest way to adjust for a potential confounder  $L$  is by **stratification**
  - The study population is partitioned into strata (groups), one for each level of  $L$
- Each stratum is analyzed separately
- Within strata, there is no variation in  $L$ 
  - and hence no imbalance in  $L$  across exposure levels

# 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

- Compute  $CRR(L)$  for  $L = 1$  and  $L = 0$ , assuming conditional exchangeability, given  $L$

## 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

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

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

# Regression model for the outcome

- E.g.

$$\text{logit}\{\Pr(Y = 1|A, L)\} = \alpha + \beta A + \gamma L$$

$$\beta = \log\{OR(L)\}$$

- Asymptotically equivalent to stratification by  $L$ , if the model is correct
  - If the model is incorrect, then it may not produce anything interpretable
- Regression models are useful for finite samples and sparse data
  - more later

# 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

- Compute *CRR*, assuming conditional exchangeability, given  $L$

## 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

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

# Stratification-based standardization

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

- Explicit use of the standardization formula leads to a two step procedure
  - First,  $\Pr(Y = 1|A = a, L)$  is calculated for all levels of  $L$ , by stratification on  $L$
  - Then, these probabilities are averaged over the population distribution of  $L$
- We refer to this method of standardization as **stratification-based**

# Weighting-based standardization

- $\Pr(Y_a = 1)$  can also be calculated using a method called ‘Inverse Probability Weighting’ (IPW)
  - Assuming conditional exchangeability, given  $L$
- IPW uses weighting instead of stratification
  - more later
- We refer to this method of standardization as **weighting-based**

# Summary

- Under **exchangeability**, association is equal to causation
- 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 our adjustment is sufficient or not is untestable
- **Stratification** produces subpopulation (conditional) effects
- **Standardization** produces population (marginal) effects