# Estimation of causal effects

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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

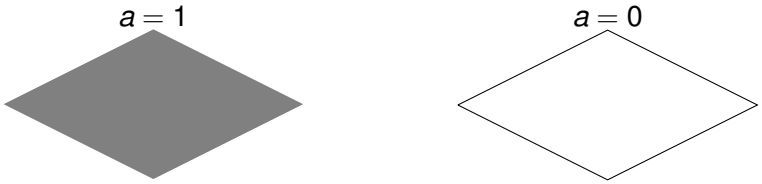
$$\Pr(Y_1 = 1) \neq \Pr(Y_0 = 1)$$

- $A$ 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

# 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 CRR*



# Solution



# 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 |

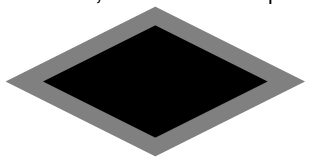
- *Compute RR*

# Solution

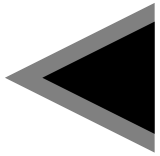


# In a picture

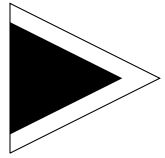
$a = 1$; 60% have $Y_1 = 1$



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



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

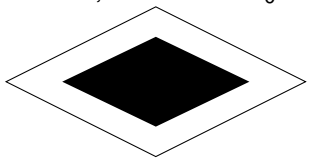


$$\underbrace{\Pr(Y_1 = 1|A = 1)}_{=\Pr(Y=1|A=1)} = \Pr(Y_1 = 1|A = 0) = \Pr(Y_1 = 1)$$

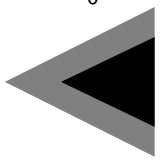


# In a picture, cont'd

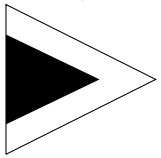
$a = 0$; 40% have $Y_0 = 1$



$A = 1$; 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 $A$

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

- 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 $A$

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

- *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 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:

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

## 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 |

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

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

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



# 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*

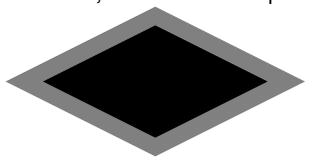


# Solution

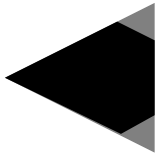


# In a picture

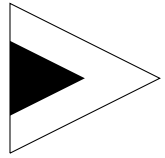
$a = 1$; 60% have $Y_1 = 1$



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



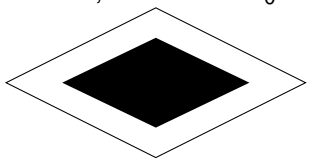
$A = 0$; 40% have $Y_1 = 1$



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

## In a picture

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



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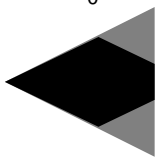
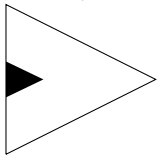


$A = 0$; 20% have $Y_0 = 1$



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



## 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

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

- 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 $L$:

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

- 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



## 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



# 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

## 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