

# Counterfactuals

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# Association (1)

- Statistical dependence between two or more events, characteristics, or other variables.
- An association is present if the probability of occurrence of an event or characteristic, or the quantity of a variable, varies with the occurrence of one or more other events, the presence of one or more other characteristics, or the quantity of one or more other variables

(Porta M. “A dictionary of Epidemiology”, 6th edition)

# Association (2)

Exposure A and outcome Y

- A and Y are independent if:

$$\Pr(Y=1 \mid A=1) = \Pr(Y=1 \mid A=0) = \Pr(Y=1)$$

- For example the risk of lung cancer is the same among drinkers and non-drinkers

- A and Y are associated if:

$$\Pr(Y=1 \mid A=1) \neq \Pr(Y=1 \mid A=0)$$

- For example the risk of lung cancer differs between smokers and non-smokers

# Explanations for an association

Hernan et al, Epidemiology 2004;15:615-25

An association between an exposure and an outcome can be produced by 3 casual structures:

- 1) Cause and effect: A causes Y or Y causes A
- 2) Common causes: A and Y share a common cause
- 3) Common effects: A and Y have a shared effect

# Simpson's paradox

EH Simpson . The interpretation of interaction in contingency tables.  
J Royal Stat Soc Series B; 1951; 2:238-41

8. If, however, there is no second order interaction, there is considerable scope for paradox and error. The dangers of amalgamating  $2 \times 2$  tables are well known and are referred to, for example, on page 317 of Kendall (1945), vol. I. Kendall's example illustrates that if  $A$  and  $B$  are associated positively in  $C$  and negatively in  $\bar{C}$  they may appear as independent in the whole population; but a more curious case than this can be constructed. Consider the following artificial example.

TABLE 4						
			<i>Male</i>		<i>Female</i>	
			<i>Untreated</i>	<i>Treated</i>	<i>Untreated</i>	<i>Treated</i>
Alive	.	.	4/52	8/52	2/52	12/52
Dead	.	.	3/52	5/52	3/52	15/52

# Simpson's paradox

	Male		Female	
	Untreated	Treated	Untreated	Treated
Dead	4	8	2	12
Alive	3	5	3	15

OR in males = 0.83

OR in females = 0.83

OR in all = 1.00

*“This time we say that there is a positive association between treatment and survival among both males and females; but if we combine tables we again find that there is no association between treatment and survival in the combined populations. What is the “sensible” interpretation here? The treatment can be hardly rejected as valueless to the race when it is beneficial when applied to males and females” [p. 241]*

# Note

- Simpson's paper was mainly on interaction
- the label "Simpson's paradox" was given in the 1970s
- Similar results were shown before Simpson (as also acknowledged in his article)
- The main issue with these results is that, statistically, it cannot be decided which answer is correct: does the treatment work or not? If we do not know the gender than it does not, if we know the gender it works! [→ paradox]
- We need external information to identify the correct answer

# External information

“ What is the data generating process?”

For example:

Is it possible that gender was affected by treatment?

Is it possible that something affected both gender and treatment?

Is it possible that gender affected the treatment?

All these questions imply an association between gender and treatment. Gender and treatment are associated in the data. Thus statistical analysis cannot answer these questions



# Causal framework

We need to have a framework or a set of considerations to help to guide judgments about causality

# Causation

## Individual level

A patient takes an aspirin and has a stroke

*Was the stroke caused by the aspirin?*

# Causation

At the individual level, the **causal effect** of an exposure on the outcome is defined as the difference in the outcome if the same individual was exposed versus unexposed.

## **Example:**

A patient takes an aspirin and has a stroke

*Was the stroke caused by the aspirin?*

**Usually we reason that:**

the aspirin caused the stroke if the stroke  
would have not occurred had the patient not  
taken the aspirin

However

we cannot observe the same subject under  
both exposures at the same time – the  
comparison is hypothetical

# Individual causal effect

- Given an exposure  $A$  with values 0 or 1 the subject's outcome is  $Y^a$ , in which there are two potential outcomes:

$Y^1 \rightarrow$  the potential outcome under the exposure

$Y^0 \rightarrow$  the potential outcome under no exposure

- The aspirin causes the stroke if

$$Y^1 \neq Y^0$$

- The aspirin does not cause the stroke if

$$Y^1 = Y^0$$

# Individual causal effect

- If for all individuals in a population

$$Y^1 = Y^0$$

- Then the exposure does not have a causal effect on the outcome:
- “Sharp causal null hypothesis”

**1. For example, consider 4 patients with the following distribution**

<b>Patient</b>	<b>E</b>	<b>Y</b>	<b>Y<sup>0</sup></b>	<b>Y<sup>1</sup></b>
a	0	1		
b	0	0		
c	1	1		
d	1	0		

Complete the table with the potential outcomes assuming that the exposure does not have a causal effect on the outcome

# Population causal effect

- Only 1 potential outcome can be observed → no casual effect estimate at the individual level
- We can estimate an **aggregated causal** effect in the population

Where

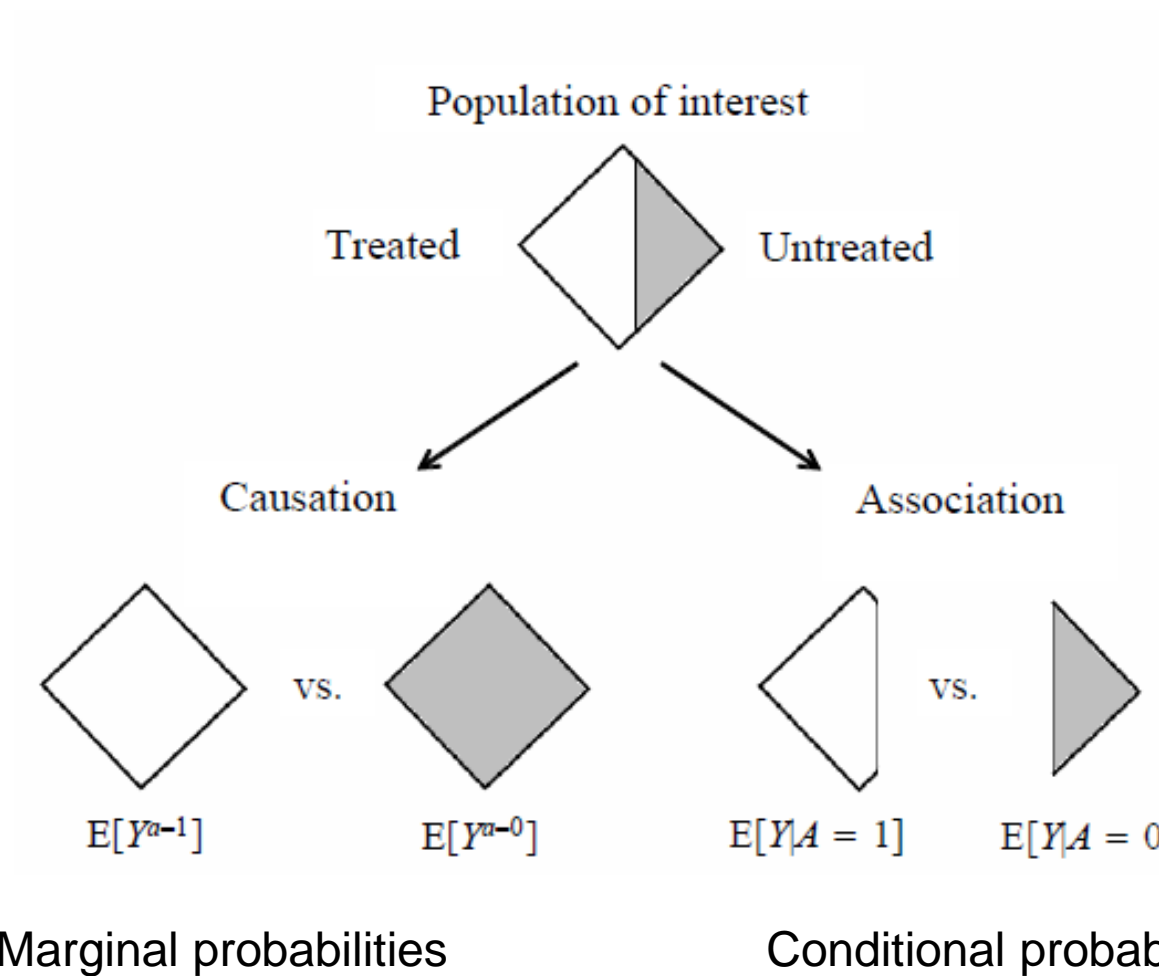
- $\Pr[Y^1=1]$  is the probability of the outcome under the scenario where everybody is exposed
- $\Pr[Y^0=1]$  is the probability of the outcome under the scenario where everybody is unexposed

There is no need of assuming the same effect in all subjects: e.g. the exposure may have a causal effect for some subjects but no aggregated effect



# Example

- consider 100 patients taking the aspirin and the same patients not taking the aspirin
- The probability of stroke if they take the aspirin is  $\Pr[Y^1=1]$ ; the probability of stroke had they not taken the aspirin is  $\Pr[Y^0=1]$
- Taking the aspirin in the population does not cause stroke if  $\Pr[Y^1=1] = \Pr[Y^0=1]$ , while it causes stroke if  $\Pr[Y^1=1] \neq \Pr[Y^0=1]$
- Causal null hypothesis:  $\Pr[Y^1=1] = \Pr[Y^0=1]$ ,



## However:

- We cannot compare the whole population under the exposure with the whole population under no exposure
- We should assume that:
  - the probability of the outcome among those **factually exposed** and the counterfactual outcome under the exposure in the whole population are the same
  - the probability of the outcome among those **factually unexposed** and the counterfactual outcome under no exposure in the whole population are the same

$$\Pr[Y=1 \mid A=1] = \Pr[Y^1=1]$$

and

$$\Pr[Y=1 \mid A=0] = \Pr[Y^0=1]$$

# Exchangeability

$$\Pr[Y^1=1 \mid A=0] = \Pr[Y^1=1 \mid A=1] = \Pr[Y^1=1]$$

and

$$\Pr[Y^0=1 \mid A=0] = \Pr[Y^0=1 \mid A=1] = \Pr[Y^0=1]$$

	Exposed		Unexposed	
	Actual	CounterF	Actual	CounterF
Outcome				
Y=1	30	20	20	30
Y=0	70	80	80	70
Total	100	100	100	100
Risk	0.30	0.20	0.20	0.30

The only difference in terms of the outcome between the exposed and the unexposed is the exposure

How can we achieve exchangeability?

## **RANDOMIZATION**

**Methods to adjust for  
confounding**

## 2. Consider again the 4 patients

Patient	E	Y	$Y^0$	$Y^1$
a	0	1	1	1
b	0	0	0	0
c	1	1	1	1
d	1	0	0	0

Calculate:

$$\Pr[Y^1=1]$$

$$\Pr[Y^0=1]$$

$$\Pr[Y^1=1 \mid E=0]$$

$$\Pr[Y^1=1 \mid E=1]$$

$$\Pr[Y=1 \mid E=0]$$

### 3. Hypothetical data of an exposure with a causal effect on the outcome

Patient	E	Y	$Y^0$	$Y^1$
a	0	1	1	1
b	0	0	0	1
c	1	1	1	1
d	1	0	0	0

Calculate:

$$\Pr[Y^1=1]$$

$$\Pr[Y^0=1]$$

$$\Pr[Y^1=1 \mid E=0]$$

$$\Pr[Y^1=1 \mid E=1]$$

$$\Pr[Y=1 \mid E=0]$$

$$\Pr[Y=1 \mid E=1]$$

**Comment the results**

# Note: hot debate

- we need a clear definition of exposure and lack of exposure → clear definition of the contrast
- Example: height and testicular cancer → what is the unexposed group? Short people, average height?
- When we say that the risk of risk testicular cancer increases by 13% per 5-cm increase in height we do not define the counterfactual scenarios
- In addition height is only partly manipulable and, even for the manipulable part, there is no specification on how height is changed (e.g. diet, better prenatal environment, etc..)
- However.....



# Note 1: However

- it is often possible to imagine a hypothetical (infeasible) intervention... e.g. climate change being present --- what if the climate change were not present? → No necessity of manipulation
- We should have a pragmatic approach on the level of precision – vagueness of the counterfactuals:
  - when is the treatment sufficiently well defined? “it depends on the question and context” – do not be too strict
  - can a state act as an exposure? “I would say yes”
- The potential outcome framework is not the only possible framework to make causal claims

# Hill's considerations or viewpoints (1965)

Hill AB. The environment and disease: Association or causation?  
Proceed Royal Soc Medicine – London 1965;58:295-300.

*“[...] we see that the event  $B$  is associated with the environmental feature  $A$  [...]. In what circumstances can we pass from this observed association to a verdict of causation”*

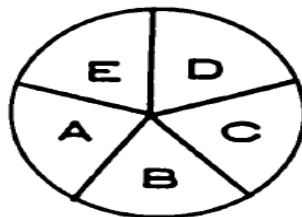
*“I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'”!*

*“[...] the decisive question is whether the frequency of the undesirable event  $B$  will be influenced by a change in the environmental feature  $A$ .”*

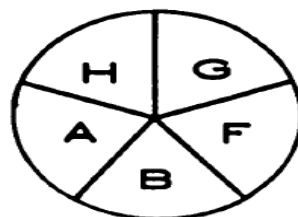
# Sufficient-component cause model

- A cause is “an antecedent event, condition, or characteristic that was necessary for the occurrence of the disease at the moment it occurred, given that other conditions are fixed” (Rothman 1976)
- INUS “Insufficient but Necessary part of an Unnecessary but Sufficient condition” (Mackie, 1965)
- Sufficient cause: “minimal set of conditions and events that are sufficient for the outcome to occur” (Rothman 1976)

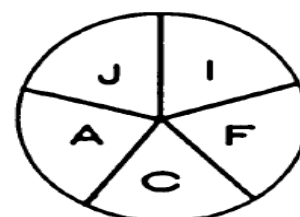
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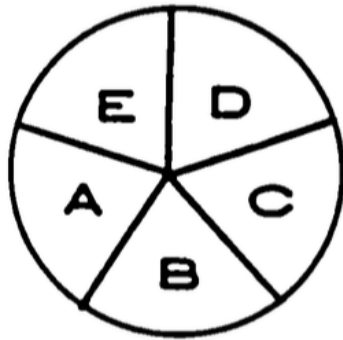
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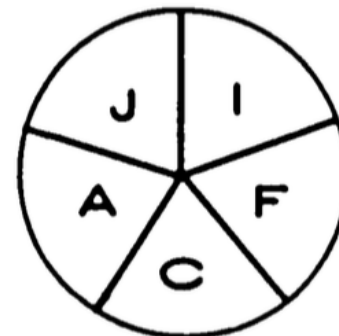
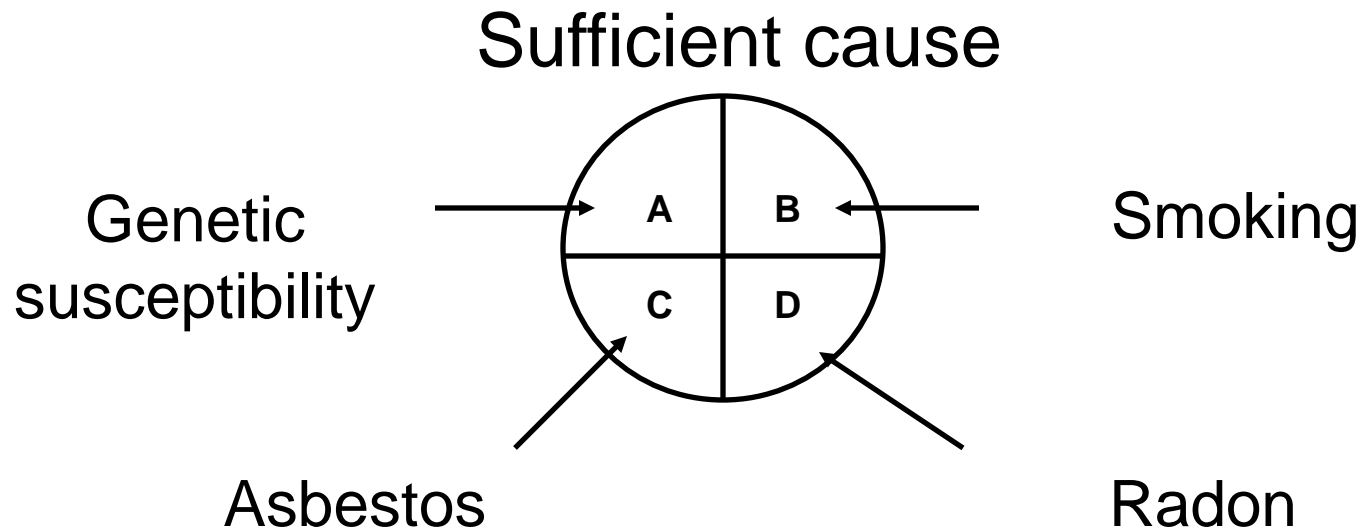


FIGURE 1. Conceptual scheme for the causes of a hypothetical disease.

- A, B,.... J are all INUS
- A is a necessary cause
- There are three possible Unnecessary but Sufficient conditions

# Example: at the individual level

Causal mechanism for lung cancer in an individual:



Each factor is a component cause. Each factor is not sufficient to determine the disease

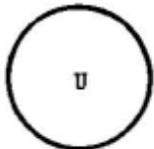

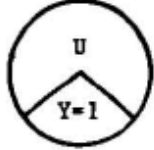
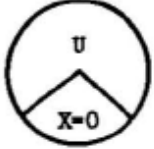
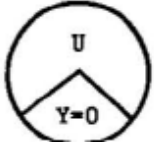
# From Mackie 1965

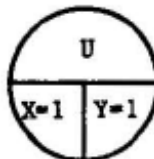
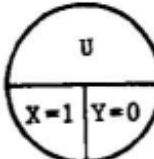
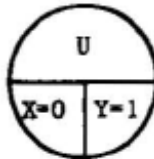
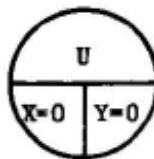
*“In analyzing our ordinary causal statements, we must admit that the field is often taken for granted or only roughly indicated, rather than specified precisely”*

*“If we are looking for the cause of the fire in this house, we may similarly dismiss as irrelevant the fact that a proposed cause would not have produced a fire if the house had been radically different [...]”*

*“This modification enables us to deal with the well-known difficulty that it is impossible, without including in the cause the whole environment, the whole prior state of the universe (and so excluding any likelihood of repetition), to find a genuinely sufficient condition, one which is “by itself, adequate to secure the effect.”*

# Example of two factors - SCC model

	SUFFICIENT CAUSE TYPE	DESCRIPTION
1		X and Y irrelevant
2		X = 1 necessary, Y irrelevant
3		Y = 1 necessary, X irrelevant
4		X = 0 necessary, Y irrelevant
5		Y = 0 necessary, X irrelevant

6		X = 1 and Y = 1 necessary
7		X = 1 and Y = 0 necessary
8		X = 0 and Y = 1 necessary
9		X = 0 and Y = 0 necessary

U = all other components of the sufficient cause

**Figure 1.** Enumeration of the nine types of sufficient causes for two dichotomous exposure variables.

# Example of two factors – counterfactual model

Type	$X^1Y^1$	$X^0Y^1$	$X^1Y^0$	$X^0Y^0$
1	1	1	1	1
2	1	1	1	0
3	1	1	0	1
4	1	1	0	0
5	1	0	1	1
6	1	0	1	0
7	1	0	0	1
8	1	0	0	0
9	0	1	1	1
10	0	1	1	0
11	0	1	0	1
12	0	1	0	0
13	0	0	1	1
14	0	0	1	0
15	0	0	0	1
16	0	0	0	0

See

Hernan M, Robins J. Causal Inference. February 16, 2012

Greenland et al. Concepts of Interaction. In “Modern Epidemiology” 2008

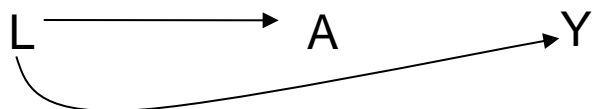
Greenland et al. Scand J Work Environ Health 1988;14:125-9



# Some differences between the SCC and the counterfactual model

- In the SCC model the basic unit of analysis is the mechanism that causes an event
- in the counterfactual model the basic unit of analysis is the individual
- Thus different mechanisms may lead to the same potential outcome for an individual unless the potential outcome is specified for all the INUS of a sufficient cause
- In SCC there is no (need of) specification of the counterfactual level of exposure

# Conditional exchangeability



L	A	Y
0	0	0
0	1	1
0	0	0
1	0	0
1	1	1
1	1	1

L=1 is more frequent among the exposed (2/3) than the unexposed (1/3)

To have exchangeability we now need:

$$L=1: \rightarrow \Pr[Y^a=1 \mid A=0, L=1] = \Pr[Y^a=1 \mid A=1, L=1] = \Pr[Y^a=1 \mid L=1]$$

$$L=0: \rightarrow \Pr[Y^a=1 \mid A=0, L=0] = \Pr[Y^a=1 \mid A=1, L=0] = \Pr[Y^a=1 \mid L=0]$$

This is called conditional exchangeability

# 4. Consider the following patients

N	L	E	Y	Y <sup>0</sup>	Y <sup>1</sup>	
a	0	0	0			A. Complete the table with the potential outcomes assuming that the exposure does not have a causal effect on the outcome
b	0	0	1			
c	0	0	0			
d	0	0	0			B. Calculate 1) CRR 2) ARR 3) Comment on the difference between CRR and ARR
f	0	1	0			
g	0	1	0			
h	0	1	0			
i	0	1	1			
l	1	0	1			C. Check that there is conditional exchangeability
m	1	0	1			
n	1	0	0			
o	1	1	1			
p	1	1	1			
q	1	1	1			D. Calculate 1) ARR in L=1 2) CRR in L=1
r	1	1	1			
s	1	1	1			
t	1	1	1			
u	1	1	0			
v	1	1	0			E. Y <sup>0</sup> and Y <sup>1</sup> are not observed; how would you estimate them from these data?
z	1	1	0			

# Causal effects under conditional exchangeability

## 1) Stratum-specific causal effects

comparison of, say,  $\Pr[Y^1=1 \mid L=1]$  with  $\Pr[Y^0=1 \mid L=1]$

→ e.g. stratification, regression models

## 2) Causal effect in the entire population:

comparison of  $\Pr[Y^1=1]$  with  $\Pr[Y^0=1]$ , (whole population being exposed vs. whole population being unexposed)

→ standardization, IPW

NOTE: conditional exchangeability is always assumed to identify these effects

# Standardization and IPW

- Standardization

The risks  $\Pr[Y^a=1]$  are obtained as weighted averages of the stratum specific risks  $\Pr[Y^a=1 | L=1]$ , using the proportions of  $L=1$  as the weighting function, and then compared: e.g.  $\Pr[Y^1=1] - \Pr[Y^0=1]$

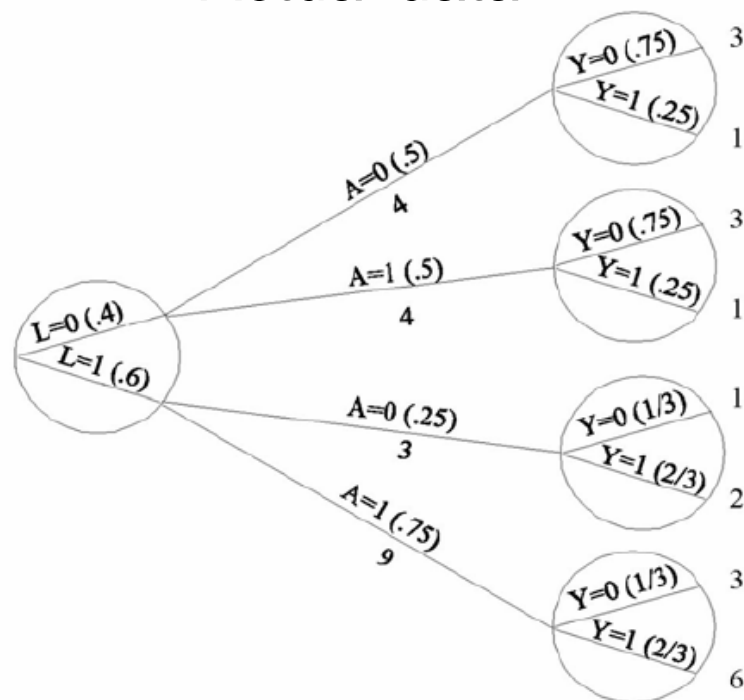
- IPW

The risks  $\Pr[Y^a=1]$  are obtained by weighting each individual by the inverse of the conditional [on  $L$ ] probability of receiving the treatment the he/she actually had

Note: the two methods give the same results

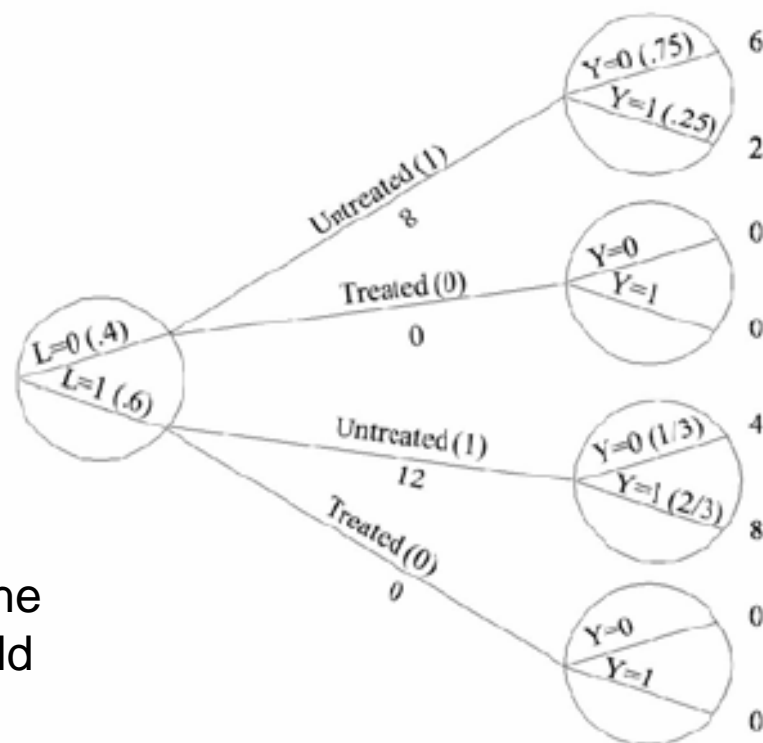
# From Hernan M, Robins J. Causal Inference. February 16, 2012

Actual data



$\Pr [Y^0=1]$

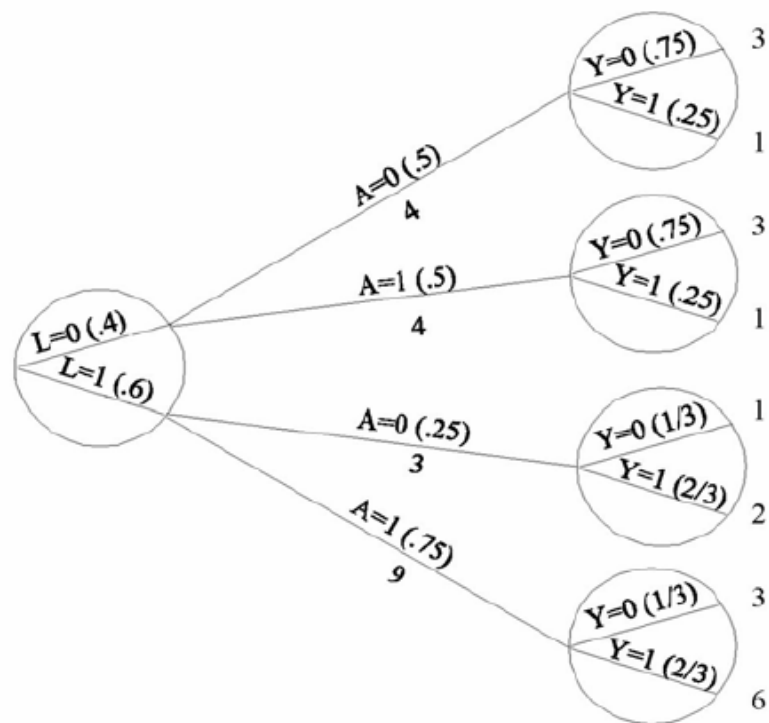
(10/20 = 50%)



e.g. in  $L=0$  the probability of  $A=0$  is 50%. If the untreated were 8 (instead of 4) then we would have expected 2 deaths

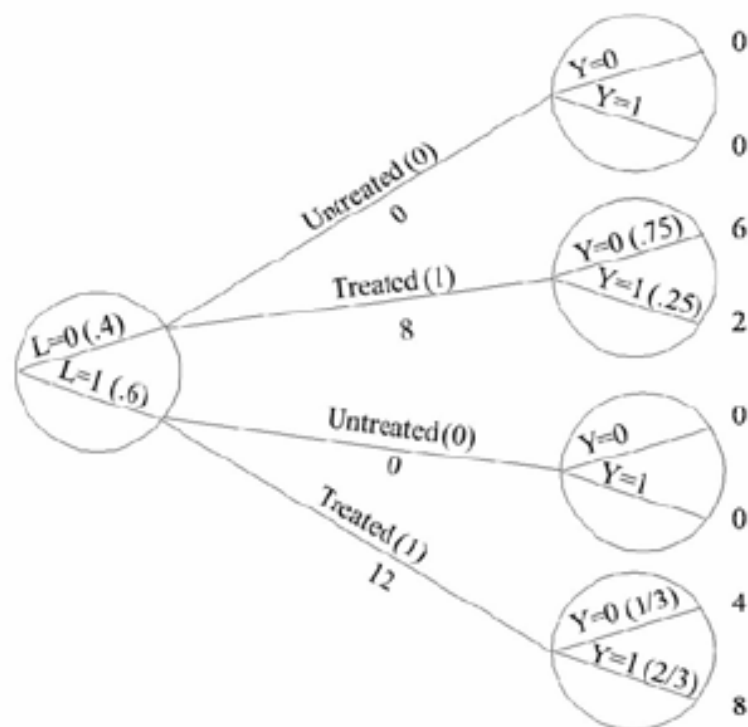
From Hernan M, Robins J. Causal Inference. February 16, 2012

Actual data



$\Pr [Y^1=1]$

(10/20 = 50%)



# Note: marginal vs. conditional effect

- If there is effect modification (i.e. the effect measure is not the same in all strata) the estimate obtained after pooling has no causal interpretation, while the stratum-specific estimates are interpretable
- Weights used for pooling have the main goal to reduce the variability of the pooled estimate
- Methods like standardization or IPW can estimate the average effect in the population, which has a causal interpretation for that population
- Let us suppose that adjustment for a variable  $L$  is necessary to obtain exchangeability but  $L$  is also an effect modifier. To obtain the average effect in the population we should use standardization



# Example

N	L	E	Y	Y <sup>0</sup>	Y <sup>1</sup>
a	0	0	0	0	0
b	0	0	1	1	1
c	0	0	0	0	0
d	0	0	0	0	1
f	0	1	0	0	0
g	0	1	1	0	1
h	0	1	0	0	0
i	0	1	1	1	1
l	1	0	1	1	1
m	1	0	1	1	1
n	1	0	0	0	0
o	1	1	1	1	1
p	1	1	1	1	1
q	1	1	1	1	1
r	1	1	1	1	1
s	1	1	1	1	1
t	1	1	1	1	1
u	1	1	0	0	0
v	1	1	0	0	0
z	1	1	0	0	0

Patient g has  $Y=1$  and  $Y^1 \neq Y^0$

Patient d has  $Y^1 = 1$

ARR in  $L=0 \rightarrow (2/4) / (1/4) = 2.00$

CRR in  $L=0 \rightarrow (4/8) / (2 / 8) = 2.00$

ARR in  $L=1 = 1.00$

CRR in  $L=1 = 1.00$

$Y^1 = 12 / 20$

$Y^0 = 10 / 20$

$CRR = 12 / 10 = 1.20$

Crude ARR = 1.43

Conditional ARR = 1.25

# Solutions 1. For example, consider 4 patients with the following distribution

Patient	E	Y	$Y^0$	$Y^1$
a	0	1	1	1
b	0	0	0	0
c	1	1	1	1
d	1	0	0	0

Complete the table with the counterfactual outcomes assuming that the exposure does not have a causal effects on the outcome

## Solutions 2. Consider again the 4 patients

Patient	E	Y	$Y^0$	$Y^1$
a	0	1	1	1
b	0	0	0	0
c	1	1	1	1
d	1	0	0	0

Calculate:

$$\Pr[Y^1=1] \rightarrow 2/4 = 50\%$$

$$\Pr[Y^0=1] \rightarrow 2/4 = 50\%$$

$$\Pr[Y^1=1 \mid E=0] \rightarrow 1/2 = 50\%$$

$$\Pr[Y^1=1 \mid E=1] \rightarrow 1/2 = 50\%$$

$$\Pr[Y=1 \mid E=0] \rightarrow 1/2 = 50\%$$

# Solutions 3. data of an exposure with a causal effect on the outcome

Patient	E	Y	Y <sup>0</sup>	Y <sup>1</sup>
a	0	1	1	1
b	0	0	0	1
c	1	1	1	1
d	1	0	0	0

$$\Pr[Y^1=1] \rightarrow 3/4 = 75\%$$

$$\Pr[Y^0=1] \rightarrow 2/4 = 50\%$$

$$\Pr[Y^1=1 \mid E=0] \rightarrow 2/2 = 100\%$$

$$\Pr[Y^1=1 \mid E=1] \rightarrow 1/2 = 50\%$$

$$\Pr[Y=1 \mid E=0] \rightarrow 2/4 = 50\%$$

$$\Pr[Y=1 \mid E=1] \rightarrow 2/4 = 50\%$$

- The CRR is  $(75\%)/(50\%) = 1.5$ ; The ARR is  $(50\%)/(50\%) = 1.0$
- There is no exchangeability  $\rightarrow \Pr[Y^1=1 \mid E=0] > \Pr[Y^1=1 \mid E=1]$

# Solution 4a

N	L	E	Y	Y <sup>0</sup>	Y <sup>1</sup>
a	0	0	0	0	0
b	0	0	1	1	1
c	0	0	0	0	0
d	0	0	0	0	0
f	0	1	0	0	0
g	0	1	0	0	0
h	0	1	0	0	0
i	0	1	1	1	1
l	1	0	1	1	1
m	1	0	1	1	1
n	1	0	0	0	0
o	1	1	1	1	1
p	1	1	1	1	1
q	1	1	1	1	1
r	1	1	1	1	1
s	1	1	1	1	1
t	1	1	1	1	1
u	1	1	0	0	0
v	1	1	0	0	0
z	1	1	0	0	0

A. Complete the table with the potential outcomes assuming that the exposure does not have a causal effect on the outcome

# Solution 4b

N	L	E	Y	Y <sup>0</sup>	Y <sup>1</sup>
a	0	0	0	0	0
b	0	0	1	1	1
c	0	0	0	0	0
d	0	0	0	0	0
f	0	1	0	0	0
g	0	1	0	0	0
h	0	1	0	0	0
i	0	1	1	1	1
l	1	0	1	1	1
m	1	0	1	1	1
n	1	0	0	0	0
o	1	1	1	1	1
p	1	1	1	1	1
q	1	1	1	1	1
r	1	1	1	1	1
s	1	1	1	1	1
t	1	1	1	1	1
u	1	1	0	0	0
v	1	1	0	0	0
z	1	1	0	0	0

B. Calculate

1) CRR  $\rightarrow \Pr[Y^1=1] / \Pr[Y^0=1]$

$$(10/20) / (10/20) = 1.00$$

2) ARR  $\rightarrow \Pr[Y=1 \mid E=1] / \Pr[Y=1 \mid E=0]$

$$(3/7) / (7/13) = 1.26$$

		Y		
		0	1	RISK
E	0	4	3	0,43
	1	6	7	0,54

There is lack of exchangeability:

e.g  $\Pr[Y^1=1 \mid E=0] = 3/7$  while  $\Pr[Y^1=1 \mid E=1] = 7/13$

# Solution 4c

N	L	E	Y	Y <sup>0</sup>	Y <sup>1</sup>
a	0	0	0	0	0
b	0	0	1	1	1
c	0	0	0	0	0
d	0	0	0	0	0
f	0	1	0	0	0
g	0	1	0	0	0
h	0	1	0	0	0
i	0	1	1	1	1
l	1	0	1	1	1
m	1	0	1	1	1
n	1	0	0	0	0
o	1	1	1	1	1
p	1	1	1	1	1
q	1	1	1	1	1
r	1	1	1	1	1
s	1	1	1	1	1
t	1	1	1	1	1
u	1	1	0	0	0
v	1	1	0	0	0
z	1	1	0	0	0

C. Check that there is conditional exchangeability

In L=1

$$\Pr[Y^1=1 \mid E=0] = \Pr[Y^1=1 \mid E=1] = 2/3$$

and

$$\Pr[Y^0=1 \mid E=0] = \Pr[Y^0=1 \mid E=1] = 2/3$$

In L=0

$$\Pr[Y^1=1 \mid E=0] = \Pr[Y^1=1 \mid E=1] = 1/4$$

and

$$\Pr[Y^0=1 \mid E=0] = \Pr[Y^0=1 \mid E=1] = 1/4$$

# Solution 4d and 4e

N	L	E	Y	Y <sup>0</sup>	Y <sup>1</sup>	D. Calculate
a	0	0	0	0	0	1) ARR in L=1
b	0	0	1	1	1	
c	0	0	0	0	0	ARR in L=1
d	0	0	0	0	0	$\Pr[Y=1 \mid E=1, L=1] / \Pr[Y=1 \mid E=1, L=1]$
f	0	1	0	0	0	
g	0	1	0	0	0	(2/3) / (4/6)
h	0	1	0	0	0	
i	0	1	1	1	1	
l	1	0	1	1	1	2) CRR in L=1
m	1	0	1	1	1	
n	1	0	0	0	0	$\Pr[Y^1 \mid L=1] / \Pr[Y^0 \mid L=1]$
o	1	1	1	1	1	
p	1	1	1	1	1	(8/12) / (8/12)
q	1	1	1	1	1	
r	1	1	1	1	1	E. Y0 and Y1 are not observed; how
s	1	1	1	1	1	would you estimate them from these
t	1	1	1	1	1	data?
u	1	1	0	0	0	IPW
v	1	1	0	0	0	
z	1	1	0	0	0	