Confounding II

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The Structure of Confounding

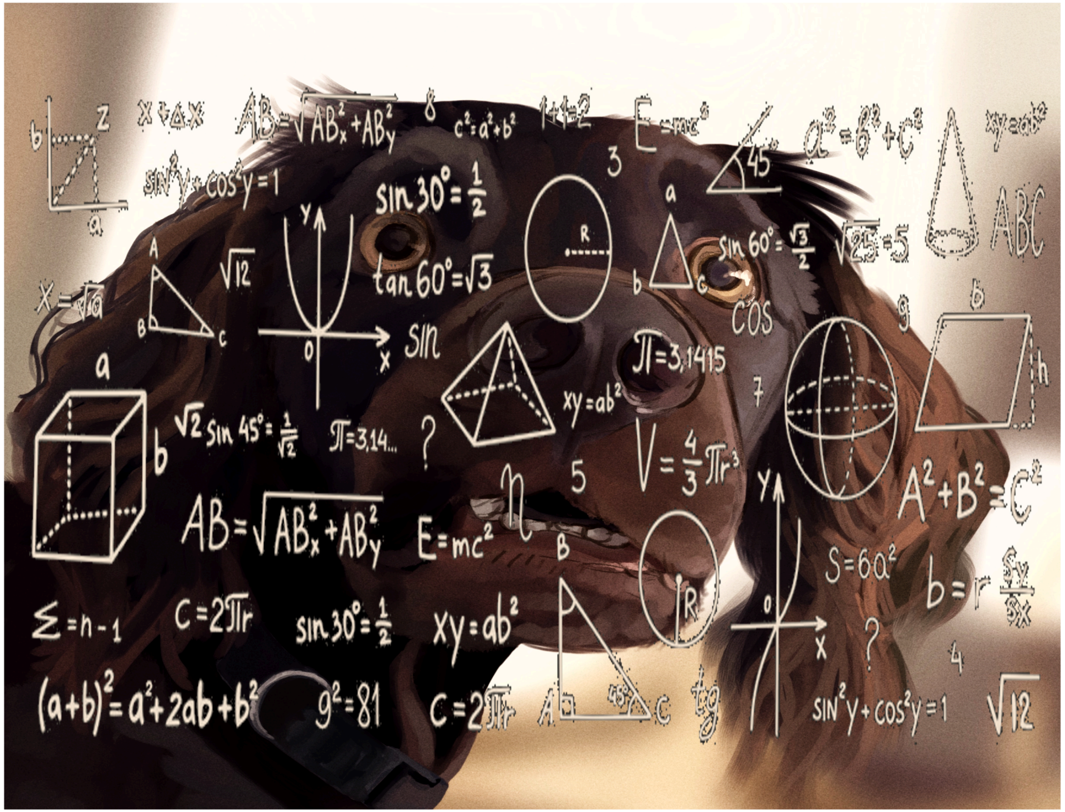
and worked examples !

Conditions that allow a variable to be a confounder:

📣 **Modern Epidemiology 4th, page 268** 💡

> *The developments in causal inference over the past decades, summarized in Chapter 3, have made clear that this definition [...the traditional criteria described from ME3...] of a “confounder” is inadequate. It is inadequate because there can be a pre-exposure variable associated with the exposure and the outcome, the control of which introduces, rather than eliminates, bias* [ME4;p268]

The Structure of Confounding??



The Structure of Confounding

$$A \leftarrow L \rightarrow Y$$

This diagram shows two sources of association between treatment and outcome:

1. The path $A \rightarrow Y$ that represents the causal effect of A on Y , and

2. The path $A \leftarrow L \rightarrow Y$ between A and Y that includes the common cause L

   - The path $A \leftarrow L \rightarrow Y$ links A and Y through the common cause L, is the ***"backdoor path"***

The structure of Confounding

- In a causal DAG, a backdoor path is a non-causal path between treatment and outcome that remains even if all arrows pointing from treatment to other variables (i.e., the descendants of treatment) are removed.
- That is, the path has an arrow pointing into treatment.

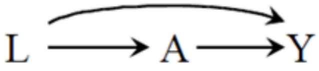


Figure 7.1

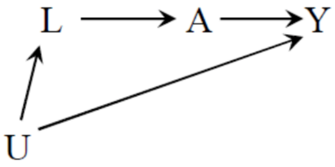


Figure 7.2

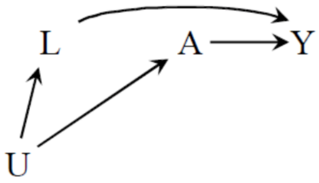


Figure 7.3

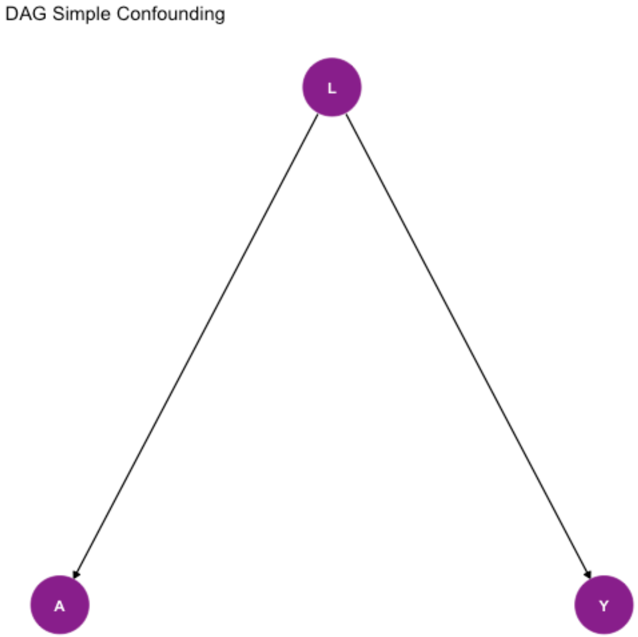
Confounding and exchangeability

- The backdoor criterion, **does not** answer questions regarding the magnitude or direction of confounding.

- It is possible that some unblocked backdoor paths are weak and thus induce little bias, or that several strong backdoor paths induce bias in opposite directions and thus result in a weak net bias.

- Because unmeasured confounding is not an “all or nothing” issue, in practice, it is important to consider the expected direction and magnitude of the bias.

Confounders ($Y \leftarrow L \rightarrow A$)



Simulated Example

```r
set.seed(704); N <- 100;
L <- rbinom(N,1,0.5)
A <- ifelse(L==0,rbinom(N,1,0.25),
            rbinom(N,1,0.75))
Y <- ifelse(L==0,rbinom(N,1,0.20),
            rbinom(N,1,0.8))
#summary(L)
data <- data.frame(N, A, L, Y)
tab <- table(data$A, data$Y)
#tab; tab/margin.table(tab)
l6conf1<-epi.2by2(tab,
                  method = "cohort.count")
```

```
##              Outcome +    Outcome -      Total                 Inc risk *
## Exposed +           39           13         52     75.00 (61.05 to 85.97)
## Exposed -           14           34         48     29.17 (16.95 to 44.06)
## Total               53           47        100     53.00 (42.76 to 63.06)
```

*Outcomes per 100 population units

Confounders

Crude

```
tabl6conf1 <- data.table::as.data.table(l6c
kable(tabl6conf1, digits = 2) %>%
  kable_paper()
```

var	est	lower	upper
Inc risk ratio	2.57	1.61	4.11
Inc odds ratio	7.29	3.01	17.63
Attrib inc risk *	45.83	28.40	63.26
Attrib fraction in exposed (%)	61.11	37.90	75.64
Attrib inc risk in population *	23.83	7.68	39.99
Attrib fraction in population (%)	44.97	21.55	61.40

```
l6strtab1<- data %>%
  tbl_summary(by= L,
  label=list(Y ="Outcome",  A ="Exposure"),
  #type = all_continuous() ~ "continuous1",
  statistic =  all_categorical() ~ c( "{n}
  missing = "no") %>%
  modify_spanning_header(c("stat_1", "stat_
  modify_caption("**Summary of covars distr
l6strtab1
```

Summary of covars distribution

	L=0/L=1	
Characteristic	[1]">**0** *N = 51*[1]	[1]">**1** *N = 49*[1]
N		
100	51 / 51 (100%)	49 / 49 (100%)
Exposure	10 / 51 (20%)	38 / 49 (78%)
Outcome	9 / 51 (18%)	38 / 49 (78%)

[1] n / N (%)

Confounders

L=0

Exposure	Outcome; L=0	
	0	1
0	36	5
1	6	4

L=1

Exposure	Outcome; L=1	
	0	1
0	3	8
1	8	30

```
tab1 <- table(data$A, data$Y, data$L)
#tab1
l6conf2<-epi.2by2(tab1, method = "cohort.count")
tabl6conf2 <- data.table::as.data.table(l6conf2$massoc.summary)
```

Confounders

Adjusted

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	2.57	1.61	4.11
Inc risk ratio (M-H)	1.42	0.87	2.30
Inc risk ratio (crude:M-H)	1.81		
Inc odds ratio (crude)	7.29	3.01	17.63
Inc odds ratio (M-H)	2.46	0.84	7.21
Inc odds ratio (crude:M-H)	2.96		
Attrib inc risk (crude) *	45.83	28.40	63.26
Attrib inc risk (M-H) *	16.69	-16.33	49.71
Attrib inc risk (crude:M-H)	2.75		

*Outcomes per 100 population units

Confounders?

Consider this DAG:

$$C \rightarrow E \rightarrow Y$$

- In this case, C is not a confounder because it does not have an independent effect on Y.
  - But there will be an observed association between C and Y, by virtue of their common association with E.
  - But it is not an independent association.

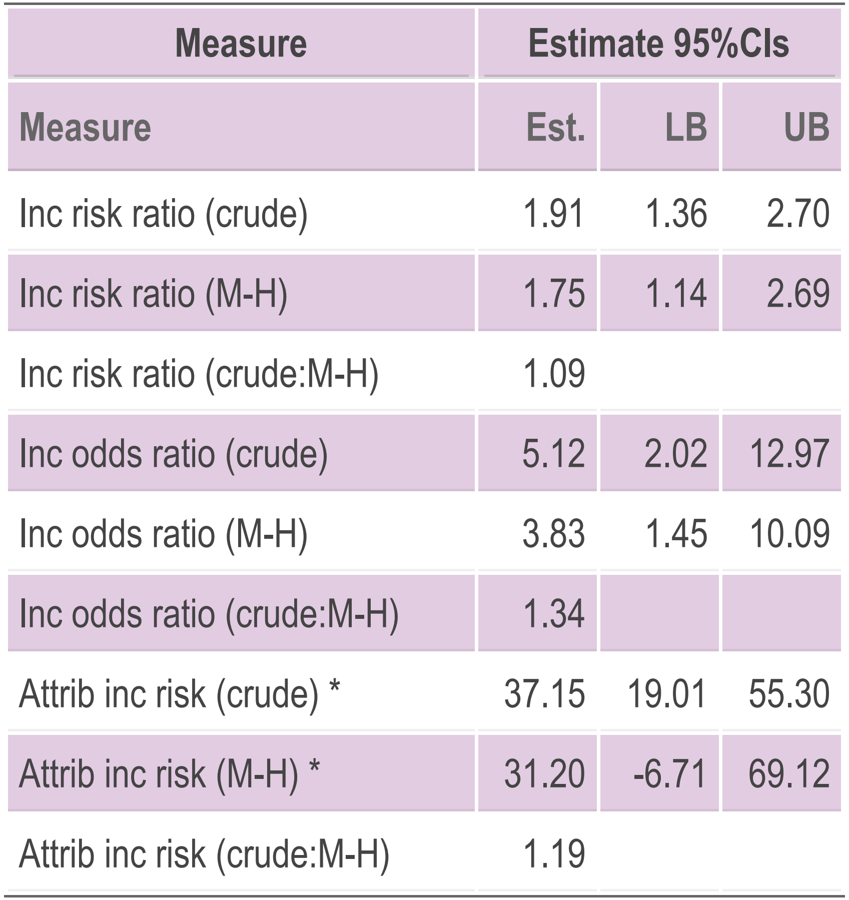
That’s why we should assess this criterion within levels of exposure.

- Stratified by E, the association between C and Y is null if there is no direct effect (as shown in the DAG).

Confounders ?

$C \to E \to Y$

```
set.seed(704)
N <- 100
C <- rbinom(N,1,0.5)
E <- ifelse(C==0,rbinom(N,1,0.8),
            rbinom(N,1,0.5))
Y <- ifelse(E==0,rbinom(N,1,0.2),
            rbinom(N,1,0.5))
#summary(C)
data1 <- data.frame(N, C, E,Y)
tab1C <- table(data1$E, data1$Y, data1$C)
```



Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	1.91	1.36	2.70
Inc risk ratio (M-H)	1.75	1.14	2.69
Inc risk ratio (crude:M-H)	1.09		
Inc odds ratio (crude)	5.12	2.02	12.97
Inc odds ratio (M-H)	3.83	1.45	10.09
Inc odds ratio (crude:M-H)	1.34		
Attrib inc risk (crude) *	37.15	19.01	55.30
Attrib inc risk (M-H) *	31.20	-6.71	69.12
Attrib inc risk (crude:M-H)	1.19		

Confounders ?

Figure 7.4 A version of the famous M-diagram again. No confounding, despite backdoor paths.

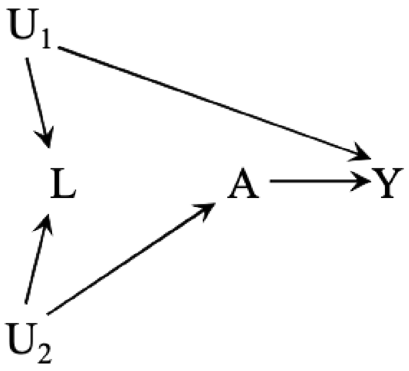


Figure 7.4

Here there are no common causes of treatment A and outcome Y, and therefore there is no confounding.

The back door path between A ← U2 → L ← U1 → Y is locked because L is a collider on that path.

Confounders

No common causes but L is a collider
$U1 \rightarrow L \leftarrow U2$

```
set.seed(704)
N <- 100
U1 <- rbinom(N,1,0.5)
U2 <- rbinom(N,1,0.5)
L <- ifelse(U1==1, rbinom(N,1,0.6),
     ifelse(U2==1, rbinom(N,1,0.6),
     rbinom(N,1,0.5))) #L is affected by U1
A <- ifelse(U2==1, rbinom(N,1,0.5),
     rbinom(N,1,0.5)) #A is affected by U2
Y <- ifelse(A==1, rbinom(N,1,0.6),
     ifelse( U1==1,  rbinom(N,1,0.6),
     rbinom(N,1,0.5))) # Y is affected by A

#summary(C)
datanoconf2 <- data.frame(N, U1, U2, L, A,Y
tab.noconf2<- table(datanoconf2$A,
              datanoconf2$Y,
              datanoconf2$L)
```

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	1.73	1.05	2.86
Inc risk ratio (M-H)	1.70	1.04	2.78
Inc risk ratio (crude:M-H)	1.02		
Inc odds ratio (crude)	2.53	1.11	5.74
Inc odds ratio (M-H)	2.46	1.08	5.61
Inc odds ratio (crude:M-H)	1.03		
Attrib inc risk (crude) *	22.00	3.21	40.79
Attrib inc risk (M-H) *	21.33	0.74	41.92
Attrib inc risk (crude:M-H)	1.03		

Confounders

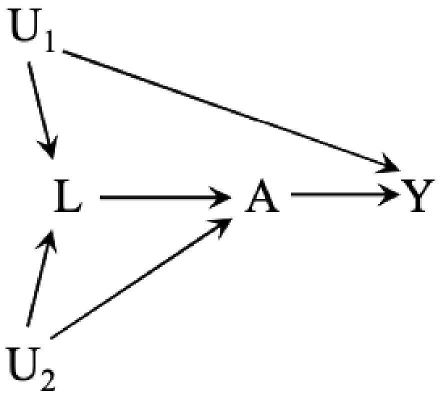


Figure 7.5

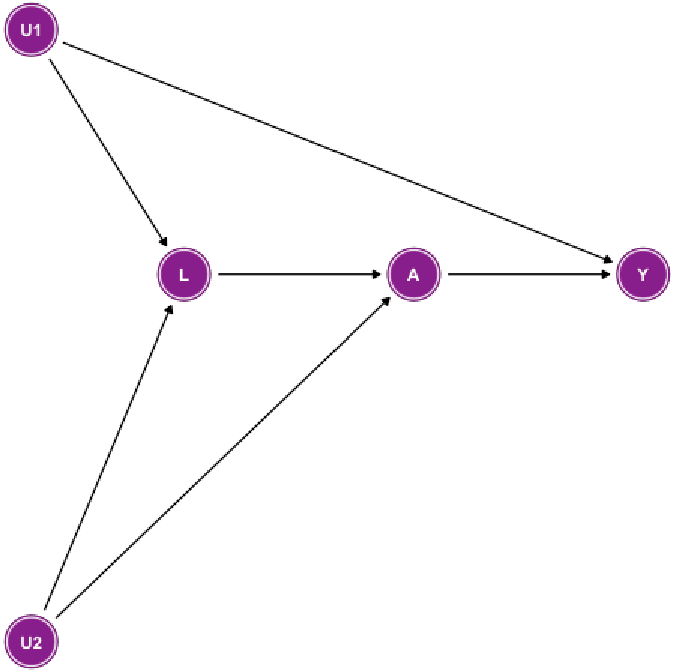
There is an arrow $L \to A$. The presence of this arrow creates an open backdoor path:

- A ← L ← U1 → Y, because U1 is a common cause of A and Y, and so **confounding exists.**
- Conditioning on L would block that backdoor path but would simultaneously open a backdoor path on which L is a collider (A ← U2 → L ← U1 → Y)

The bias is **intractable:** attempting to block the confounding path opens a selection bias path.

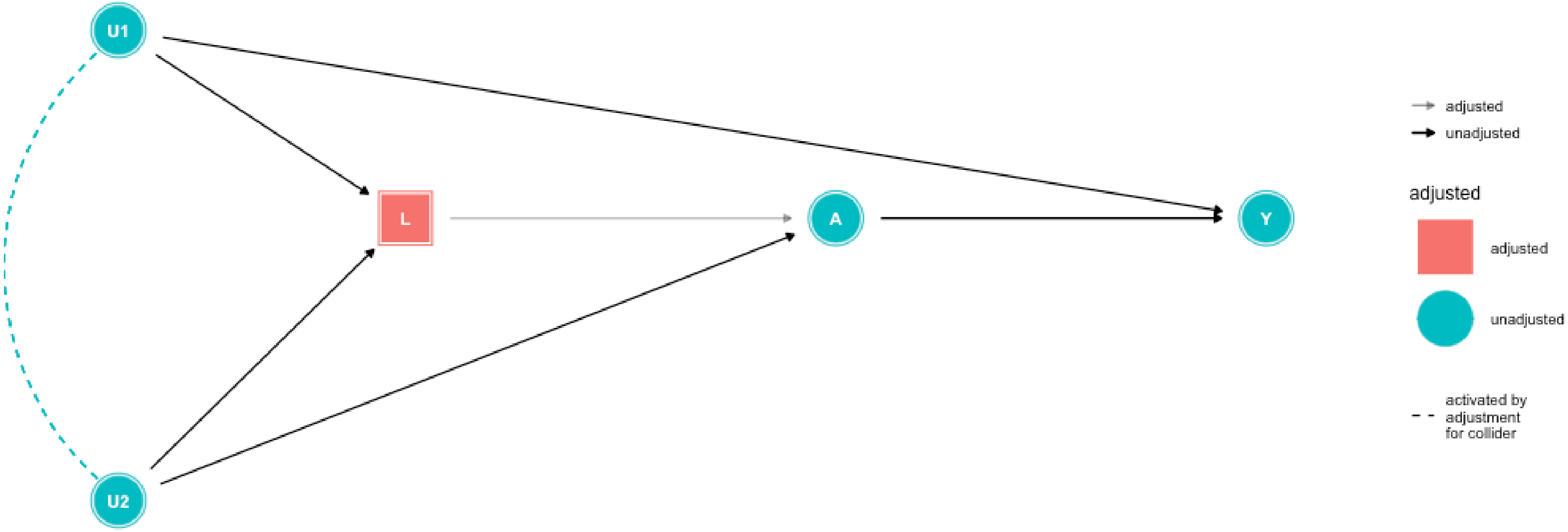
Confounding ? Colliders?

```
dag <- ggdag::dagify(Y ~ A + U1,
       A ~ L + U2,
       L ~ U1 + U2,
       exposure = "A", outcome = "Y",
       latent = c("U1", "U2"),
       coords = list(x = c(L = 3.2, Y = 3.8
       y = c(U2 = 1, L = 1.3,  A=1.3, Y=1.3
dag_plot <- dag %>%
  ggdag::tidy_dagitty(layout = "manual",
  seed = 704) %>% arrange(name) %>%
  ggplot(aes(x = x, y = y, xend = xend,
  yend = yend)) + geom_dag_point() +
  geom_dag_edges() +  theme_dag() +
  geom_dag_node(color="darkmagenta") +
  geom_dag_text(color="white")
```



Confounding ? Colliders?

```
#control_for(dag, var = "L")
#ggdag_paths(dag) +theme_dag()
ggdag_adjust(dag, var = "L", stylized = T, collider_lines = T) + theme_dag()
```



R can help ...

```r
g <- dagitty::paths(dag, "A", "Y")
a <- paste0("There are ", length(g$paths),
            " pathways from A to Y")
b <- paste0("Of these backdoor pathways ",
            sum(g$open=="TRUE"), " are open")
c <- paste0("The adjustment sets are ",
            adjustmentSets(dag, "A", "Y", type = "canonical"))

print(c(a,b,c))
```

```
## [1] "There are 3 pathways from A to Y"
## [2] "Of these backdoor pathways 2 are open"
## [3] "The adjustment sets are "
```

The bias is **intractable:** attempting to block the confounding path opens a selection bias path.

Confounders

```
set.seed(704)
N <- 100
U1 <- rbinom(N,1,0.5)
U2 <- rbinom(N,1,0.5)
L <- ifelse(U1==1, rbinom(N,1,0.65),
     ifelse(U2==1,  rbinom(N,1,0.65),
     rbinom(N,1,0.15))) #L is affected by U
A <- ifelse(L==1, rbinom(N,1,0.65),
     ifelse(U2==1, rbinom(N,1,0.65),
     rbinom(N,1,0.45))) #A is affected by L
Y <- ifelse(A==1,  rbinom(N,1,0.65),
      ifelse(U1==1, rbinom(N,1,0.6),
      rbinom(N,1,0.3))) # Y is affected by

#summary(C)
data2 <- data.frame(N, U1, U2, L, A,Y)
tabL.intract <- table(data2$A, data2$Y,
                data2$L)
```

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	1.91	1.16	3.13
Inc risk ratio (M-H)	2.12	1.18	3.80
Inc risk ratio (crude:M-H)	0.90		
Inc odds ratio (crude)	3.00	1.31	6.88
Inc odds ratio (M-H)	3.13	1.35	7.28
Inc odds ratio (crude:M-H)	0.96		
Attrib inc risk (crude) *	25.97	7.09	44.85
Attrib inc risk (M-H) *	28.01	5.35	50.67
Attrib inc risk (crude:M-H)	0.93		

Confounders

Figure 7.7 is another non confounding example in which the traditional criteria lead to selection bias due to adjustment for L.

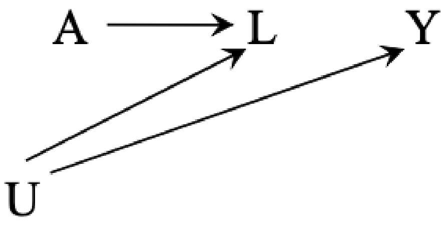


Figure 7.7

- The traditional criteria would not have resulted in bias had condition (3) been replaced by the condition that L is not caused by treatment.
  - *(3) it does not lie on a causal pathway between treatment and outcome.*

> Replace condition (3) by the condition that “there exist variables A and Y such that there is conditional exchangeability within their joint levels $Y^a \perp A|L,U$". H&R, Technical Point 7.2

Confounders

L is not on the "pathway" $A \rightarrow Y$

```r
set.seed(704)
N <- 100
U <- rbinom(N,1,0.5)
A <-rbinom(N,1,0.55) #A affects L
L <- ifelse(U==1, rbinom(N,1,0.65),
     ifelse(A==1, rbinom(N,1,0.65),
     rbinom(N,1,0.25))) #L is affected by U
Y <- ifelse(U==1, rbinom(N,1,0.6),
     rbinom(N,1,0.25)) # Y is affected by U

datanoconf3 <- data.frame(N, U, L, A,Y)
tabL.noconf3 <- table(datanoconf3$A,
                      datanoconf3$Y,
                      datanoconf3$L)
```

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	0.98	0.67	1.42
Inc risk ratio (M-H)	0.98	0.61	1.57
Inc risk ratio (crude:M-H)	1.00		
Inc odds ratio (crude)	0.96	0.42	2.18
Inc odds ratio (M-H)	0.97	0.42	2.23
Inc odds ratio (crude:M-H)	0.99		
Attrib inc risk (crude) *	-1.10	-21.55	19.36
Attrib inc risk (M-H) *	-0.85	-25.69	23.99
Attrib inc risk (crude:M-H)	1.30		

Surrogate confounders (Is L a confounder?)

In Figure 7.8, confounding of A on Y via unmeasured common cause U .

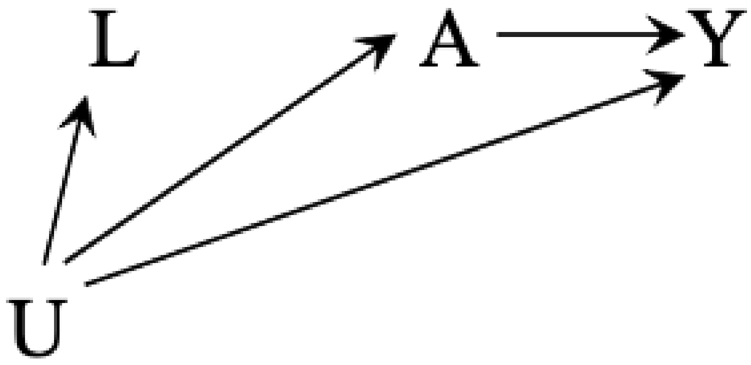


Figure 7.8

- Measured variable L is a proxy or surrogate for U . Adjust for the variable L?
- On the one hand, L is not a confounder because it does not lie on a backdoor path between A and Y .

Confounders

Surrogates when L is not highly correlated with U

```
set.seed(704)
N <- 100
U <- rbinom(N,1,0.8)
A <- ifelse(U==1, rbinom(N,1,0.65),
     rbinom(N,1,0.5)) #A is affected by  U
L <- ifelse(U==1, rbinom(N,1,0.65),
     rbinom(N,1,0.5)) #L is affected by U
Y <- ifelse(A==1,  rbinom(N,1,0.65),
     ifelse(U==1, rbinom(N,1,0.65),
     rbinom(N,1,0.15))) # Y is affected by
dataconf4 <- data.frame(N, U, L, A,Y)
tabL.conf4 <- table(dataconf4$A,
                    dataconf4$Y,
                    dataconf4$L)
```

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	1.94	1.22	3.08
Inc risk ratio (M-H)	2.01	1.23	3.30
Inc risk ratio (crude:M-H)	0.97		
Inc odds ratio (crude)	3.29	1.39	7.78
Inc odds ratio (M-H)	3.46	1.41	8.50
Inc odds ratio (crude:M-H)	0.95		
Attrib inc risk (crude) *	28.52	8.61	48.44
Attrib inc risk (M-H) *	29.58	-5.76	64.92
Attrib inc risk (crude:M-H)	0.96		

Surrogate confounders (Is L a confounder?)

- On the other hand, adjusting for L, which is associated with U , will indirectly adjust for some of the confounding caused by U .

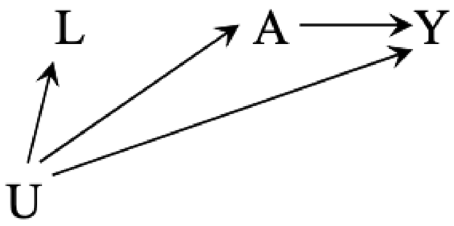


Figure 7.8

- In the extreme case that L were perfectly correlated with U then adjusting for L = adjusting for U.
- Therefore we will typically prefer to adjust, rather than not to adjust, for L.

Confounders

Surrogates when L and U correlated

```
set.seed(704)
N <- 100
U <- rbinom(N,1,0.8)
A <- ifelse(U==1, rbinom(N,1,0.65),
rbinom(N,1,0.5)) #A is affected by U
L <- ifelse(U==1, rbinom(N,1,0.95),
rbinom(N,1,0.5)) #L is affected by U
Y <- ifelse(A==1,  rbinom(N,1, 0.65),
ifelse(U==1, rbinom(N,1,0.65),
rbinom(N,1,0.15))) # Y is affected by U and

dataconf5 <- data.frame(N, U, L, A,Y)
tabL.conf5 <- table(dataconf5$A,
              dataconf5$Y,
              dataconf5$L)
```

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	1.94	1.22	3.08
Inc risk ratio (M-H)	1.74	1.06	2.88
Inc risk ratio (crude:M-H)	1.11		
Inc odds ratio (crude)	3.29	1.39	7.78
Inc odds ratio (M-H)	2.69	1.11	6.53
Inc odds ratio (crude:M-H)	1.22		
Attrib inc risk (crude) *	28.52	8.61	48.44
Attrib inc risk (M-H) *	23.16	-8.90	55.21
Attrib inc risk (crude:M-H)	1.23		

Confounders cannot be descendants of treatment, but can be in the future of treatment

In Figure 7.11. L is a descendant of treatment A that blocks all backdoor paths from A to Y.

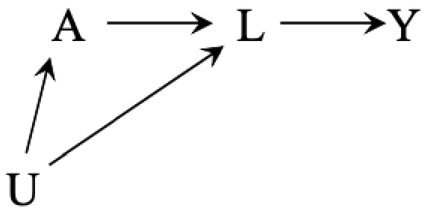
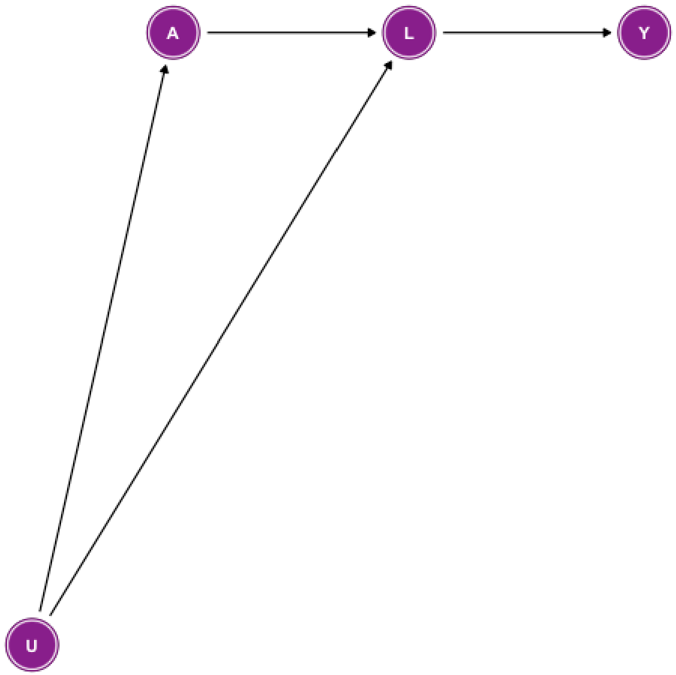


Figure 7.11

- Conditioning on L does not cause selection bias because no collider path is opened.
- Since the causal effect of A on Y is only through L, conditioning on L completely blocks this pathway.
- This shows that adjusting for a variable L that blocks all backdoor paths does not eliminate bias when L is a descendant of A.
- Since $Y^a \perp\!\!\!\perp A|L$ implies adjustment for L eliminates all bias, there must not be conditional exchangeability,
- **and thus $E[Ya = 1] - E[Ya = 0]$ is not identified.**

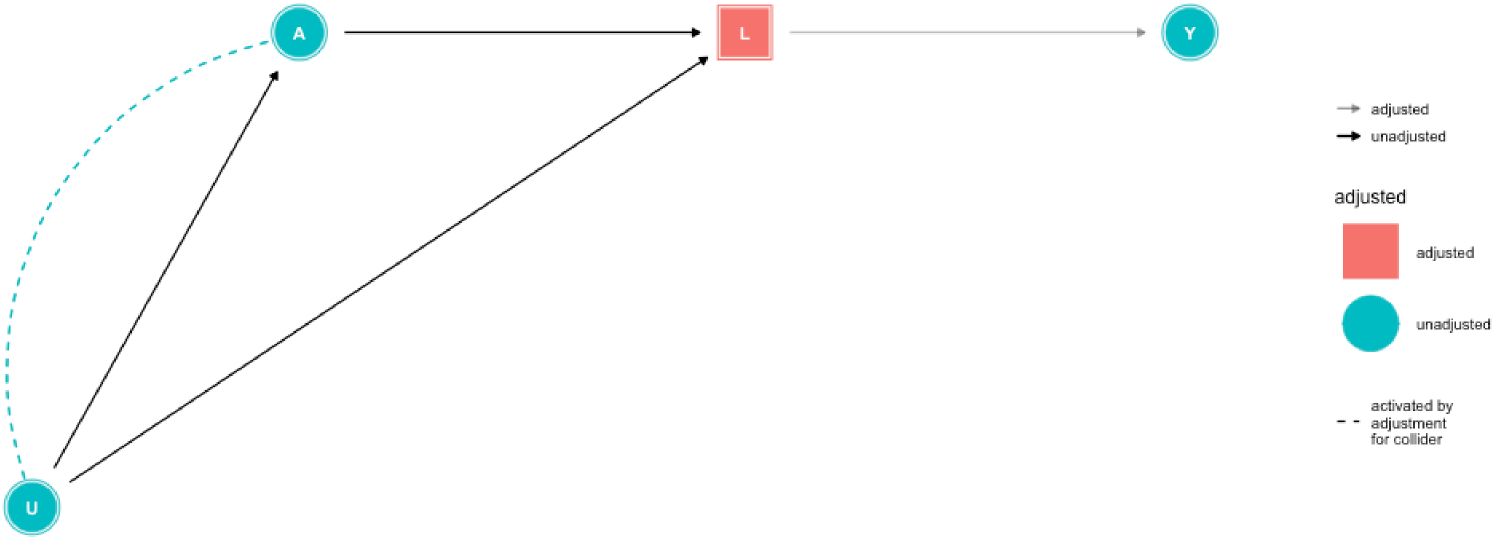
Confounders as descendants?

```
dag1 <- ggdag::dagify(Y ~ L,
       A ~ U,
       L ~ U + A,
       exposure = "A", outcome = "Y",
       latent = "U",
       coords = list(x = c(L = 2, Y = 2.5,
       y = c(U = 1.3, L = 1.5,  A=1.5, Y=1.
dag_plot1 <- dag1 %>%
  ggdag::tidy_dagitty(layout = "manual",
                      seed = 704) %>%
  arrange(name) %>%
  ggplot(aes(x = x, y = y, xend = xend,
   yend = yend)) + geom_dag_point() +
  geom_dag_edges() + theme_dag() +
  geom_dag_node(color="darkmagenta") +
  geom_dag_text(color="white")
```



Confounders as descendants ? Colliders?

```
#control_for(dag1, var = "L")
#ggdag_paths(dag1) +theme_dag()
ggdag_adjust(dag1, var = "L", stylized = T, collider_lines = T) +  theme_dag()
```



R can help ...

```r
g1 <- dagitty::paths(dag1, "A", "Y")
a1 <- paste0("There are ", length(g$paths),
            " pathways from A to Y")
b1 <- paste0("Of these backdoor pathways ",
            sum(g1$open=="TRUE"), " are open")
c1 <- paste0("The adjustment sets are ",
            adjustmentSets(dag1, "A", "Y", type = "canonical"))

print(c(a1,b1,c1))
```

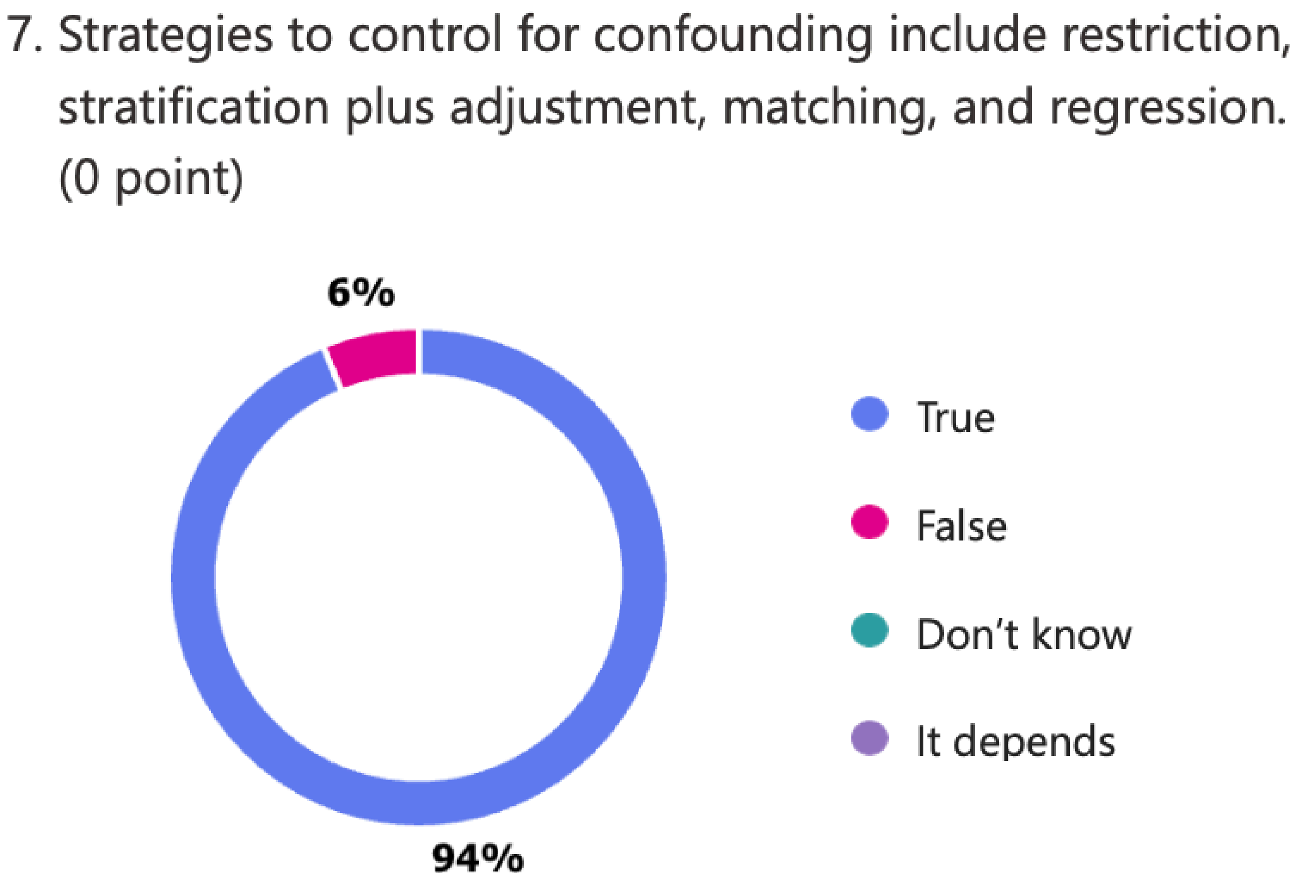
```
## [1] "There are 3 pathways from A to Y"
## [2] "Of these backdoor pathways 2 are open"
## [3] "The adjustment sets are "
```

The bias is **and thus `(E[Ya=1] - E[Ya=0])` is not identified.** attempting to block the confounding path opens a selection bias path.

Do we know what a confounder is?

Confounding Variable Joke

How to adjust for confounding



7. Strategies to control for confounding include restriction, stratification plus adjustment, matching, and regression. (0 point)

How to adjust for confounding

- **Randomization is the best method.**
    - In conditionally randomized experiments given covariates L, the common causes (i.e., the covariates L) are measured and thus the adjusted (standardization or IP weighting) association measure is expected to equal the effect measure.
- Subject-matter knowledge to identify adjustment variables is ***discretionary*** **in "ideal" randomized experiments**.
- On the other hand, **subject-matter knowledge is key (a must!) in observational studies** in order to identify and measure adjustment variables (e.g., for regression adjustment).

How to adjust for confounding

- Causal inference from observational data relies on the **uncheckable assumption** that we have used our knowledge to identify and measure a set of variables L that is a sufficient set for confounding adjustment:

    - The set of non-descendants of treatment that includes enough variables to block all backdoor paths.

- Under this assumption of no unmeasured confounding or of conditional exchangeability given L, standardization and Inverse Probability (IP) weighting can be used to compute the average causal effect in the population.

Standardization

Why standardize?

- To control for confounding
- To summarize many estimates into one

- Is a weighted average of measures of occurrence across a distribution (say, age).
- Can be applied to any measure of occurrence or measure of effect
- Weights are chosen based on the population of interest

(ME3, pg. 49)

Standardized measures of association and effect

- Let I_k represent strata specific incidence rates and
- let I_k^* represent another schedule of such rates (perhaps based on a different exposure distribution)
- Let Tk represent person-time at risk in each strata

$$I_s = \left(\frac{\sum_{k=1}^{K} T_k I_k}{\sum_{k=1}^{K} T_k} \right)$$

$$I_s^* = \left(\frac{\sum_{k=1}^{K} T_k I_k^*}{\sum_{k=1}^{K} T_k} \right)$$

- Then the standardized rate ratio is: $IR_s = I_s / I_s^*$
- The standardized rate difference is: $IR_s = I_s - I_s^* = \sum T_k (I_k - I_k^*)$

(ME3, pg. 67)

Standardized measures of association and effect

- Note that the standardized rate difference is a weighted average of stratum-specific rate differences

Interpretation of both measures:

- Effects of exposure on this population.
    - For the standardized rate ratio we need to assume that the relative distribution of person-time would be unaffected by exposure.

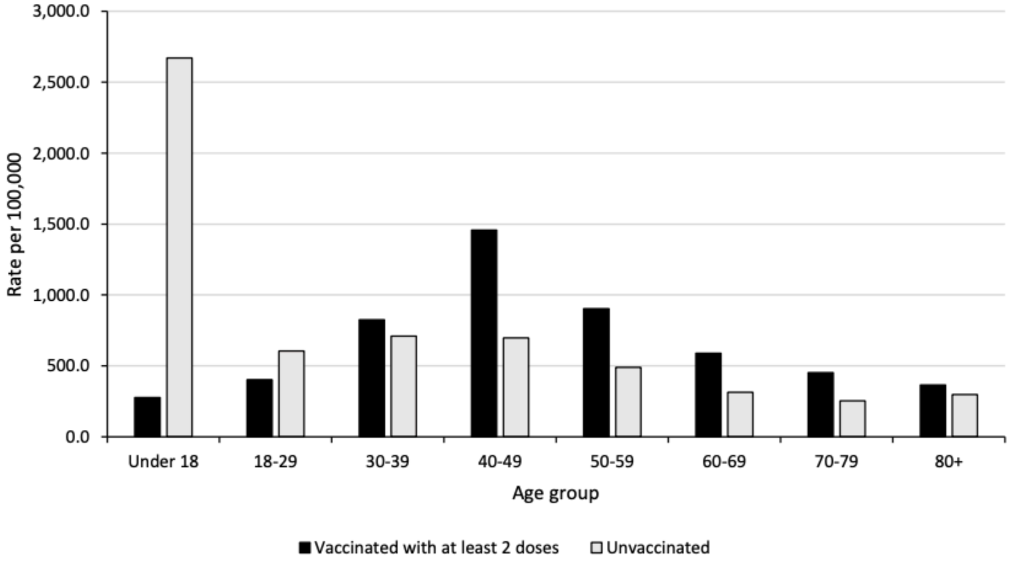
– Standardized risk ratios do not require this assumption because the denominators do not use person-time.

Example: COVID-19 vaccine effectiveness in the UK

UK Health Security Agency "COVID-19 vaccine surveillance report", Week 41

Figure 2. Rates (per 100,000) by vaccination status from week 37 to week 40 2021

(a) COVID-19 cases



Rates (per 100,000) by vaccination status from week 37 to week 40 2021

Example: COVID-19 vaccine effectiveness in the UK (2)

Numbers by variant are reported by Public Health England.

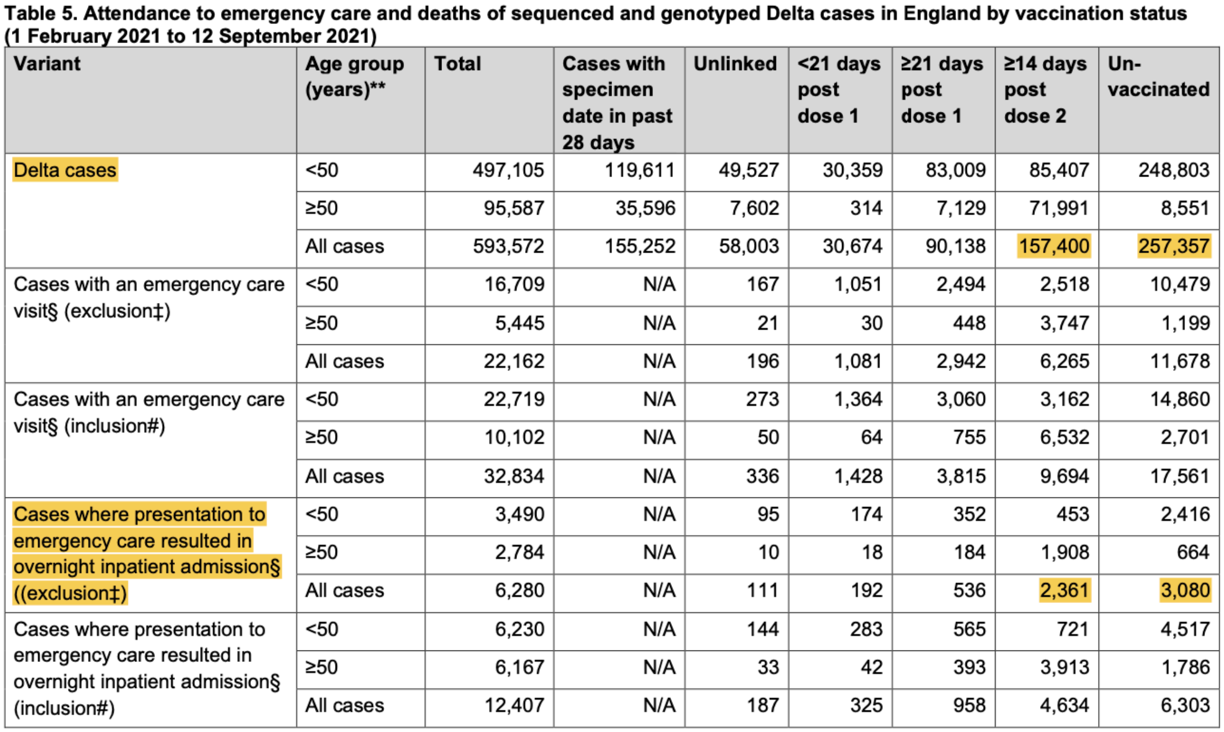


Table 5. Attendance to emergency care and deaths of sequenced and genotyped Delta cases in England by vaccination status (1 February 2021 to 12 September 2021)

Variant	Age group (years)**	Total	Cases with specimen date in past 28 days	Unlinked	<21 days post dose 1	≥21 days post dose 1	≥14 days post dose 2	Un-vaccinated
Delta cases	<50	497,105	119,611	49,527	30,359	83,009	85,407	248,803
	≥50	95,587	35,596	7,602	314	7,129	71,991	8,551
	All cases	593,572	155,252	58,003	30,674	90,138	157,400	257,357
Cases with an emergency care visit§ (exclusion‡)	<50	16,709	N/A	167	1,051	2,494	2,518	10,479
	≥50	5,445	N/A	21	30	448	3,747	1,199
	All cases	22,162	N/A	196	1,081	2,942	6,265	11,678
Cases with an emergency care visit§ (inclusion#)	<50	22,719	N/A	273	1,364	3,060	3,162	14,860
	≥50	10,102	N/A	50	64	755	6,532	2,701
	All cases	32,834	N/A	336	1,428	3,815	9,694	17,561
Cases where presentation to emergency care resulted in overnight inpatient admission§ ((exclusion‡)	<50	3,490	N/A	95	174	352	453	2,416
	≥50	2,784	N/A	10	18	184	1,908	664
	All cases	6,280	N/A	111	192	536	2,361	3,080
Cases where presentation to emergency care resulted in overnight inpatient admission§ (inclusion#)	<50	6,230	N/A	144	283	565	721	4,517
	≥50	6,167	N/A	33	42	393	3,913	1,786
	All cases	12,407	N/A	187	325	958	4,634	6,303

From: Table 5. Attendance to emergency care and deaths of sequenced and genotyped Delta cases in England by vaccination status (1 February 2021 to 12 September 2021) here.)

Example: COVID-19 vaccine effectiveness in the UK

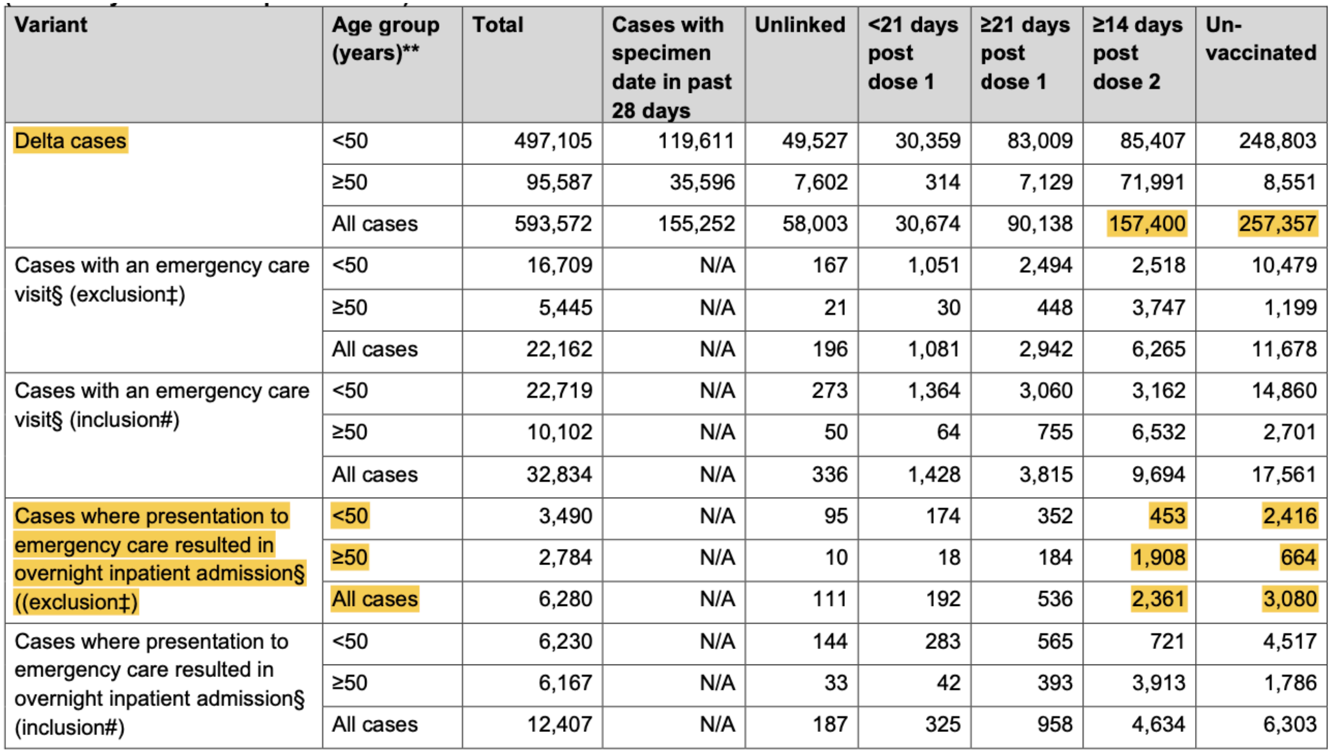
Let's play with the numbers (1): check the risk difference (RD)

```
#157400 - 2361 #exposed without outcome
#257357 - 30801 #unexposed without outcome
l6UKdata<-c(2361,155039, 3080, 254277)
l6UKest<- epi.2by2(l6UKdata, method = "cohort.count")
l6UKest
```

```
##              Outcome +    Outcome -      Total                 Inc risk *
## Exposed +         2361       155039     157400      1.50 (1.44 to 1.56)
## Exposed -         3080       254277     257357      1.20 (1.16 to 1.24)
## Total             5441       409316     414757      1.31 (1.28 to 1.35)
##
## Point estimates and 95% CIs:
## -------------------------------------------------------------------
## Inc risk ratio                                 1.25 (1.19, 1.32)
## Inc odds ratio                                 1.26 (1.19, 1.33)
## Attrib risk in the exposed *                   0.30 (0.23, 0.38)
## Attrib fraction in the exposed (%)            20.21 (15.85, 24.35)
## Attrib risk in the population *                0.12 (0.06, 0.17)
## Attrib fraction in the population (%)         8.77 (6.64, 10.86)
## -------------------------------------------------------------------
## Uncorrected chi2 test that OR = 1: chi2(1) = 69.360 Pr>chi2 = <0.001
## Fisher exact test that OR = 1: Pr>chi2 = <0.001
##  Wald confidence limits
##  CI: confidence interval
##  * Outcomes per 100 population units
```

Example: COVID-19 vaccine effectiveness in the UK

- **Missing something?**



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	All cases	12,407	N/A	187	325	958	4,634	6,303

From: Table 5. Attendance to emergency care and deaths of sequenced and genotyped Delta cases in England by vaccination status (1 February 2021 to 12 September 2021) here.) Note: The totals do not exactly sum up to the previous table, as age was missing in a few cases.

Example: COVID-19 vaccine effectiveness in the UK

Let's play with the numbers (2) - Standardization

Outcomes among people under 50 years

```
l6UKdatu50<-c(453,84954, 2416,  246387)
l6UKt1u50<- epi.2by2(l6UKdatu50, method = "cohort.count")
l6UKt1u50$tab
```

```
##              Outcome +    Outcome -      Total                 Inc risk *
## Exposed +          453        84954      85407        0.53 (0.48 to 0.58)
## Exposed -         2416       246387     248803        0.97 (0.93 to 1.01)
## Total             2869       331341     334210        0.86 (0.83 to 0.89)
```

Outcomes among people $\geq$ 50 years

```
l6UKdatm50<-c(1908 , 70083, 664,   7887)
l6UKt1m50<- epi.2by2(l6UKdatm50, method = "cohort.count")
l6UKt1m50$tab
```

```
##              Outcome +    Outcome -      Total                 Inc risk *
## Exposed +         1908        70083      71991        2.65 (2.53 to 2.77)
## Exposed -          664         7887       8551        7.77 (7.21 to 8.35)
## Total             2572        77970      80542        3.19 (3.07 to 3.32)
```

Example: COVID-19 vaccine effectiveness in the UK

Let's play with the numbers (3) check the risk differences (RD)

Outcomes among people under 50 years

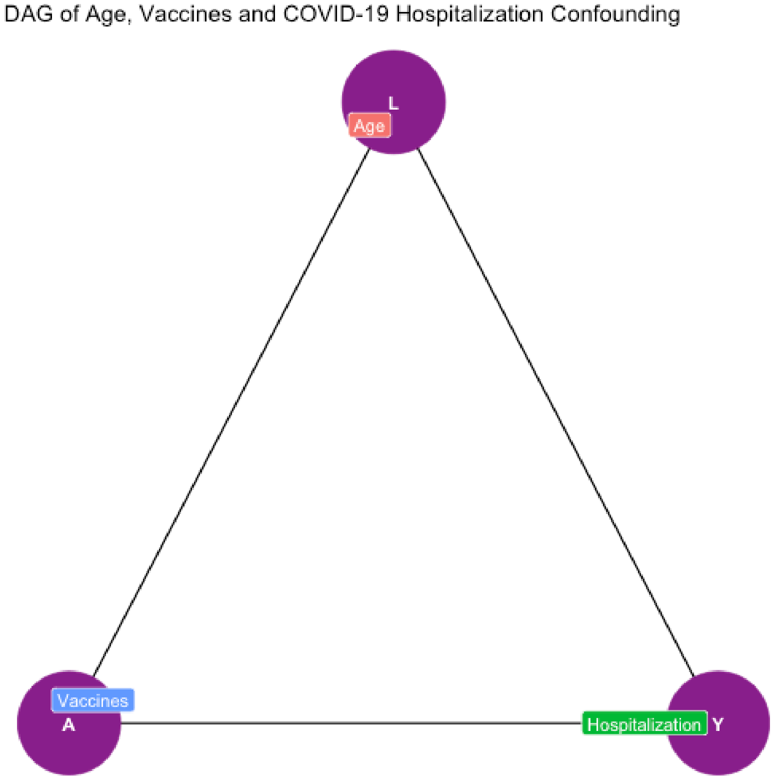
Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio	0.55	0.49	0.60
Inc odds ratio	0.54	0.49	0.60
Attrib inc risk *	-0.44	-0.50	-0.38
Attrib fraction in exposed (%)	-83.08	-102.34	-65.65
Attrib inc risk in population *	-0.11	-0.16	-0.06
Attrib fraction in population (%)	-13.12	-14.92	-11.34

Outcomes among people $\geq$ 50 years

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio	0.34	0.31	0.37
Inc odds ratio	0.32	0.30	0.35
Attrib inc risk *	-5.11	-5.69	-4.54
Attrib fraction in exposed (%)	-192.99	-219.11	-169.00
Attrib inc risk in population *	-4.57	-5.15	-3.99
Attrib fraction in population (%)	-143.17	-159.10	-128.21

Example: COVID-19 vaccine effectiveness in the UK

Confounding?


DAG of Age, Vaccines and COVID-19 Hospitalization Confounding
L
Age
Vaccines
A
Hospitalization
Y

We know that IRL the "L" includes a vector / set of potential covariates that could be considered as Confounders... this is an illustration only!

Direct standardization

Suppose we want to estimate $E[Y^a = 1] - E[Y^a = 0] = RD$.

The conditional exchangeability allows us to say $Y^a \perp\!\!\!\perp A|L$

According to the law of total expectation:

$E[Y^a = 1] = \sum_x E[Y^a = 1|X = x]Pr(x)$;

$E[Y^a = 0] = \sum_x E[Y^a = 0|X = x]Pr(x)$

- $\sum_x$ means sum over all values x that occur in the study population.
- $Pr(x)$ refers to the distribution of x in that population.

$RD = E[Y^a = 1] - E[Y^a = 0] =$

$\sum_x E[Y^a = 1|X = x]P(x) - \sum_x E[Y^a = 0|X = x]P(x)$

Example: COVID-19 vaccine effectiveness in the UK

Let's play with the numbers - Standardization

Outcomes among people under 50 years

```
##              Outcome +    Outcome -      Total                 Inc risk *
## Exposed +          453        84954      85407        0.53 (0.48 to 0.58)
## Exposed -         2416       246387     248803        0.97 (0.93 to 1.01)
## Total             2869       331341     334210        0.86 (0.83 to 0.89)
```

Outcomes among people $\geq$ 50 years

```
##              Outcome +    Outcome -      Total                 Inc risk *
## Exposed +         1908        70083      71991        2.65 (2.53 to 2.77)
## Exposed -          664         7887       8551        7.77 (7.21 to 8.35)
## Total             2572        77970      80542        3.19 (3.07 to 3.32)
```

Example: COVID-19 vaccine effectiveness in the UK

Let's play with the numbers (4) - Standardization

To compute the PO using observed data, we need the consistency assumption

$$RD = \sum_x E[Y|A=1, X=x]P(x) - \sum_x E[Y|A=0, X=x]Pr(x)$$

Standardized risk in the vaccinated :
$(453/85,407 \times 334,210/414,752 + 1,908/71,991 \times 80,542/414,752) \approx 0.94\%$

R_{vax} = 0.94

Standardized risk in the unvaccinated :
$(2,416/248,803 \times 334,210/414,752 + 664/8,551 \times 80,542/414,752) \approx 2.29\%$

R_{unvax} = 2.29

Standardized RD = -1.35 from (`0.94% - 2.29% = -1.35%`) $\neq 0.3$ in the crude estimates.

Standardized RR = 0.41 from (`0.0094 / 0.0229`) $\neq 1.25$ in the crude estimates.

Example: COVID-19 vaccine effectiveness in the UK

UK Health Security Agency "COVID-19 vaccine surveillance report", Week 41

(b) Cases presenting to emergency care (within 28 days of a positive test) resulting in overnight inpatient admission

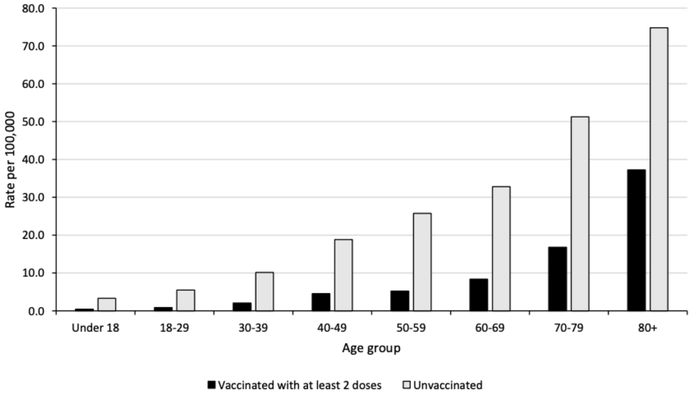
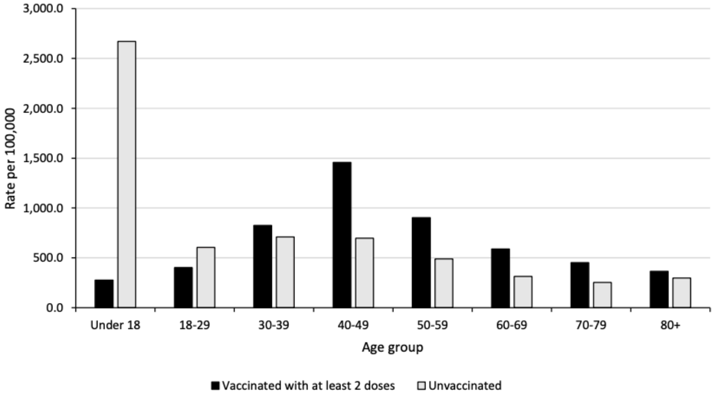


Figure 2. Rates (per 100,000) by vaccination status from week 37 to week 40 2021

(a) COVID-19 cases



Cases presenting to emergency care (within 28 days of a positive test) resulting in overnight inpatient admission.here.

What about the Mantel-Haenzel Methods?

- *Cochran-Mantel-Haenzel* methods are useful for associations, when only few covariates are involved in the calculation.
- Takes the effect in each strata of L or Z (our third variable),
- Combines these measures across L using calculated weights [1], for example example:

$$RD_{M-H} = \left(\frac{\sum_l (RD_l w_l)}{\sum_l w_l} \right) = \left(\frac{RD_0 w_0 + RD_1 w_1}{w_0 + w_1} \right)$$

- Are expected to work in closed cohorts and **assumes homogeneity across strata!!**
    - Limited use in a set of covariates L and in presence of Effect measure modification and or interaction.

[1] There are specific formulas for RD, RR and ORs as well

Standardized measures of association and effect

- No assumption of homogeneity, "agnostic of the distribution", Model-based direct standardization [1] are used when $L(X, E, A)$ consists of a large vectors of covariates.

Involves two steps:

- Fitting a regression model for the outcome given exposure and covariates

- Averaging the exposure effect over the covariate distribution of the standard population.

[1] More on "advanced" techniques to address confounding empirically after we deal with regressions.

Standardized Morbidity Ratio (SMR)

- A generalization to standardization when the standard population is the exposed sub-population.
- In this case, the standardized rate ratio becomes:

$$I_s = \left(\frac{\sum_{k=1}^{K} T_k I_k}{\sum_{k=1}^{K} T_k I_k^*} \right) = \left(\frac{\sum_{k=1}^{K} A_k}{\sum_{k=1}^{K} T_k I_k^*} \right)$$

[Numerator] cases occurring in exposed (**Observed**)

[Denominator] cases **expected** to occur in absence of exposure if exposure doesn’t affect person time at risk

(ME3, pg. 68-69)

How to adjust for confounding

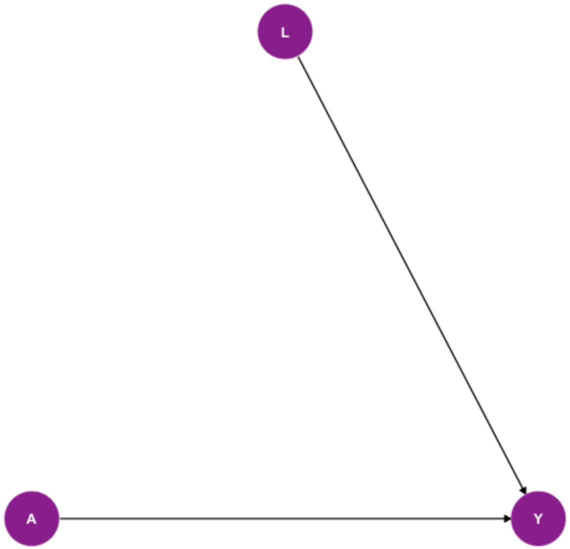
Standardization and Inverse Probability (IP) weighting are not the only methods.

$$IPW_z = \left(\frac{1}{Pr(A = a | L = z)} \right)$$

Often using regression models, **assuming the model specification is correct!** 😬

IPW removes the arrow from $L \to A$:

DAG - effect of IPW on Confounding



How to adjust for confounding

Two categories of methods for confounding adjustment:

1) G-methods (including G-formula, IP weighting, and G-estimation). These exploit conditional exchangeability in subsets defined by L to estimate the causal effect of A on Y in the entire population or in any subset of the population.

- Under the assumption of conditional exchangeability given L, g-methods simulate $A - Y$ associations in the population if backdoor paths involving variables L did not exist; simulated $A - Y$ associations can then be attributed to the effect of A on Y.

- IP weighting achieves this by creating a pseudo-population in which A is independent of measured confounders L, by “deleting” the arrow from $L \rightarrow A$.

How to adjust for confounding

2) Stratification-based methods (including Stratification, Restriction, Matching).

Methods that exploit conditional exchangeability in subsets defined by L to estimate the association between A and Y in those subsets only.

Stratification-based methods estimate the association between A and Y in one or more subsets of the population in which the treated and the untreated are assumed to be exchangeable.

- Hence the $A \to Y$ association in each subset is entirely attributed to the effect of A on Y .

- Stratification/restriction do not delete the arrow from $L \to A$, but instead calculate the association within strata of L, since within each level of L, there is no $L \to A$ association to cause confounding.

How to adjust for confounding

All these methods require conditional exchangeability given the measured covariates L to identify the effect of treatment A on outcome Y.

- When interested in the effect in the entire population, conditional exchangeability is required in all strata defined by L;
- When interested in the effect in a subset of the population, conditional exchangeability is required in that subset only.
- Achieving conditional exchangeability may be an unrealistic goal in many observational studies but expert knowledge can be used to get as close as possible to that goal.
- At the very least, investigators should generally avoid adjustment for variables affected by either the treatment or the outcome.

How to adjust for confounding

Thoughtful and knowledgeable investigators could believe that various causal structures, possibly leading to different conclusions regarding confounding, are equally plausible.

- DAGs simply allow us to have that discussion.

- Existence of common causes of treatment and outcome does not depend on the adjustment method (although it does depend on the target population).
- Adjustment for measured confounding will generally imply a change in the estimate, but not necessarily the other way around.
- Changes in estimates may occur for reasons other than confounding,
  - **including selection bias when adjusting for non-confounders and the use of non-collapsible effect measures.**

H & R write:

> *"Attempts to define confounding based on change in estimates have been long abandoned because of these problems." This is overstated. When using a DAG and collapsible measures, the method is a reasonable and practical strategy."*

A note on stratification and non-collapsibility

Comparing crude to adjusted estimates is reliable for RR and RD, but not for OR unless: a) rare outcome or b) OR ≈ RR due to design (e.g. case-cohort).

Recall the case of $C \rightarrow E \rightarrow Y$

Measure	Estimate 95%CIs		
Measure	Est.	LB	UB
Inc risk ratio (crude)	1.91	1.36	2.70
Inc risk ratio (M-H)	1.75	1.14	2.69
Inc risk ratio (crude:M-H)	1.09		
Inc odds ratio (crude)	5.12	2.02	12.97
Inc odds ratio (M-H)	3.83	1.45	10.09
Inc odds ratio (crude:M-H)	1.34		
Attrib inc risk (crude) *	37.15	19.01	55.30
Attrib inc risk (M-H) *	31.20	-6.71	69.12
Attrib inc risk (crude:M-H)	1.19		

A note on stratification and non-collapsibility

- We can say a measure of the association between A and Y is collapsible across L if the adjusted association, $RR_{AY}|L$, is equal to the crude association, RR_{AY}, where L is not a confounder — This means that a crude measure of association will not change if we adjust for a variable that is not a confounder (L)

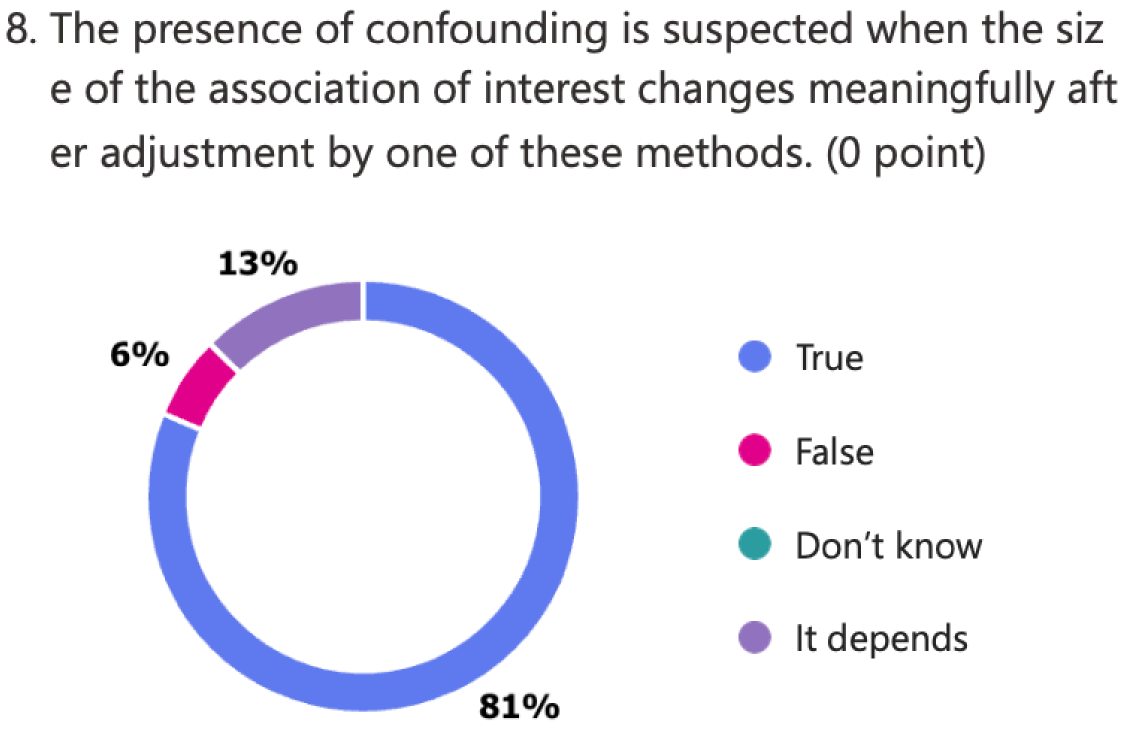
- The odds (OR) and incidence density ratios (IDR) fail this property and are considered non collapsible effect measures

- For the OR, the crude measure may be closer to the null than the pooled/adjusted OR, particularly with a common outcome

- Therefore, for some measures, our simple crude vs. adjusted comparison **may suggest confounding when there really isn't!**

Change in estimate??

Not Really!!!



8. The presence of confounding is suspected when the size of the association of interest changes meaningfully after adjustment by one of these methods. (0 point)

Structural confounding, violation of Positivity

High correlations between confounder and exposure: violation of the “positivity assumption”. When this is “structural” (in the sense of a high correlation that exists because of causal relations in the source population), Oakes calls this “structural confounding”.

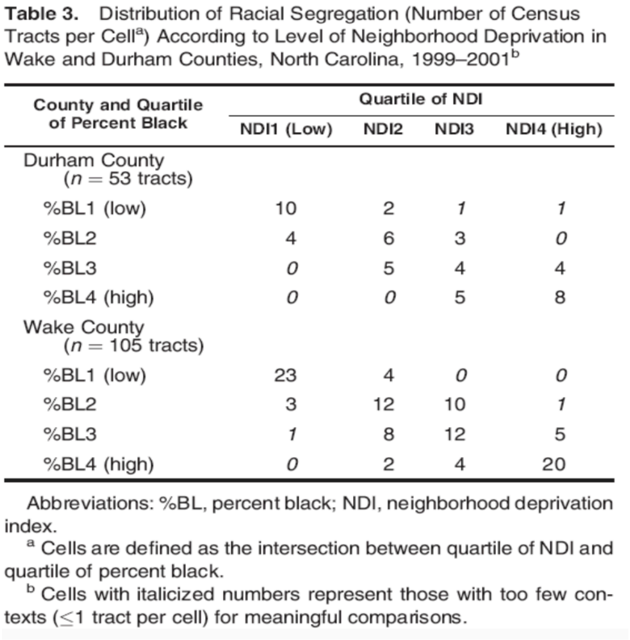


Table 3. Distribution of Racial Segregation (Number of Census Tracts per Cell[a]) According to Level of Neighborhood Deprivation in Wake and Durham Counties, North Carolina, 1999–2001[b]

County and Quartile of Percent Black	Quartile of NDI			
	NDI1 (Low)	NDI2	NDI3	NDI4 (High)
Durham County (n = 53 tracts)				
%BL1 (low)	10	2	*1*	*1*
%BL2	4	6	3	*0*
%BL3	*0*	5	4	4
%BL4 (high)	*0*	*0*	5	8
Wake County (n = 105 tracts)				
%BL1 (low)	23	4	*0*	*0*
%BL2	3	12	10	*1*
%BL3	*1*	8	12	5
%BL4 (high)	*0*	2	4	20

Abbreviations: %BL, percent black; NDI, neighborhood deprivation index.

[a] Cells are defined as the intersection between quartile of NDI and quartile of percent black.

[b] Cells with italicized numbers represent those with too few contexts (≤1 tract per cell) for meaningful comparisons.

Oakes JM. Advancing neighbourhood-effects research selection, inferential support, and structural confounding. Int J Epidemiol. 2006 Jun;35(3):643-7.
Messer et al. Effects of Socioeconomic and Racial Residential Segregation on Preterm Birth: A Cautionary Tale of Structural Confounding AJE 2010; Mar 15;171(6):664-73.

Structural confounding, violation of Positivity

Data Generation Process

```
set.seed(704); n=500
ses1 <- sample(1:12, n, replace = TRUE);
ses1[ses1>=10]<-0
ses2 <- cut(ses1, breaks = c(0, 5, 10, 15),
        labels = c("0", "1", "2"))
ses2[is.na(ses2 )]<- "2"
exposure<- ifelse(ses2=="1",
    rbinom(n,1,0.45),
    ifelse(ses2=="0", rbinom(n,1,0.5),
    ifelse(ses2=="2", rbinom(n,1,0.0001),
    rbinom(n,1,0.2))))
outcome<- ifelse(ses2=="0", rbinom(n,1,0.75
    ifelse(ses2=="1", rbinom(n,1,0.25),
    rbinom(n,1,0.25)))
data.strconf <- data.frame(outcome, exposur
table(exposure, ses2)
```

```
##          ses2
## exposure   0   1   2
##        0 101 107 123
##        1 104  65   0
```

```
strconf2 <- glm(outcome ~ exposure,
```

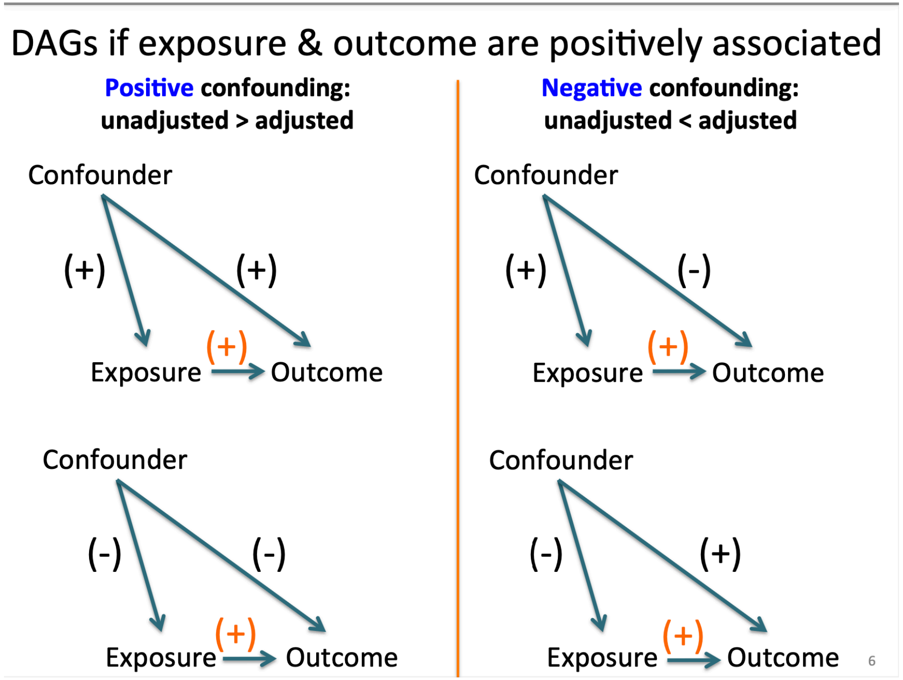
Regression Results Crude/Unadjusted

	exp(Est.)	2.5%	97.5%	z val.	p
(Intercept)	0.663	0.532	0.827	-3.657	0.000
exposure	1.677	1.154	2.437	2.713	0.007

Adjusted

	exp(Est.)	2.5%	97.5%	z val.	p
(Intercept)	2.461	1.676	3.612	4.598	0.000
exposure	1.011	0.634	1.613	0.046	0.963
as.factor(ses2)1	0.119	0.074	0.190	-8.860	0.000
as.factor(ses2)2	0.168	0.097	0.290	-6.399	0.000

Which way will the confounding go?



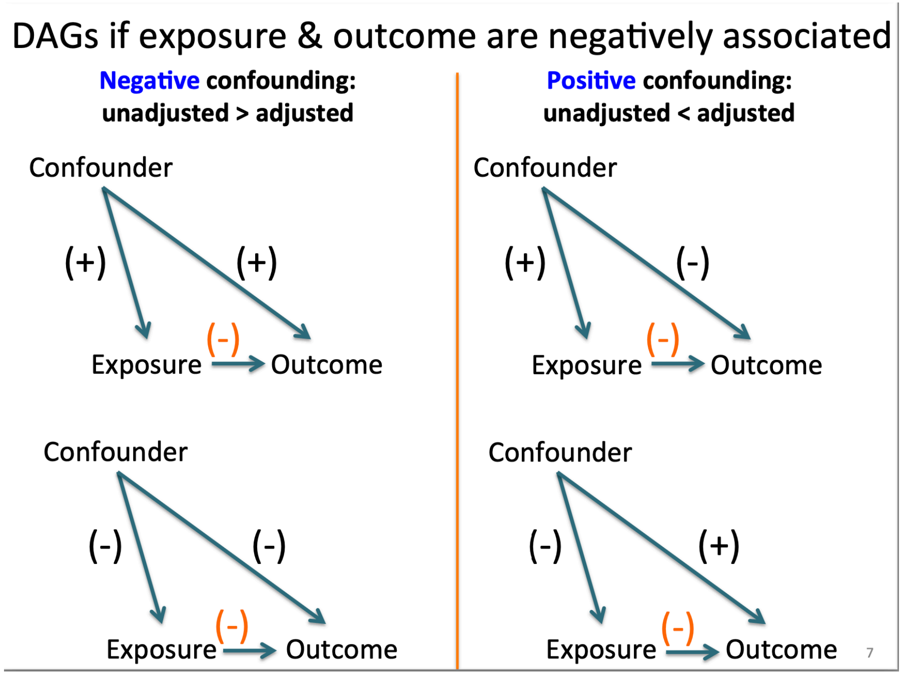
DAGs if exposure & outcome are positively associated

Positive confounding: unadjusted > adjusted

Negative confounding: unadjusted < adjusted

Vander Stoep A, et al. A didactic device for teaching epidemiology students how to anticipate the effect of a third factor on an exposure-outcome relation. AJE 1999; 15;150(2):221.

Which way will the confounding go?



DAGs if exposure & outcome are negatively associated

Negative confounding:
unadjusted > adjusted

Confounder
(+)
(+)
Exposure
(-)
Outcome

Confounder
(-)
(-)
Exposure
(-)
Outcome

Positive confounding:
unadjusted < adjusted

Confounder
(+)
(-)
Exposure
(-)
Outcome

Confounder
(-)
(+)
Exposure
(-)
Outcome

7

These schematics are just illustrations, it depends on the strength (degree of correlation) of the covariates!!, simulations works better than "blanket" type of statements

Positive, negative, and “qualitative” confounding

- Confounding may lead to an overestimation or an underestimation of the true magnitude of an effect.

- **Positive confounding:** the magnitude of the unadjusted vis-à- vis the adjusted association is exaggerated.

- **Negative confounding:** the magnitude of the unadjusted vis-à- vis the adjusted association is underestimated.

- **Qualitative confounding:** An extreme case when confounding results in an inversion of the direction of the association.

Magnitude of confounding

- The magnitude of confounding will depend on the strength of the confounder-exposure AND confounder-outcome associations.

- Conversely, if there is no association between the confounder - exposure OR no association between the confounder-outcome then no confounding of the main effect could be present.

- The strength of the confounder-exposure and confounder- outcome associations bounds the confounding effect
  - e.g., if RRcrude = 2 and the confounder-outcome relation is 2 (a doubling of risk), then the confounder would have to be perfectly correlated with the exposure in order to fully explain the main effect of RR=2

How strong the the *unmeasured confounding* should be to explain away my estimated association?

E values: respond to this question for ratio [1] measures, how?

$$E - value = RR + \sqrt{RR \times (RR - 1)}$$

- E-value is the minimum value of the association between $U \rightarrow A$ and $U \rightarrow Y$ that will be capable of attenuating the observed association towards the null.

- Example: RR=1.33; $1.33 + \sqrt{1.33 \times (1.33 - 1)} =$ 1.99 then, if there was an U, it should:

  1) double the risk among unexposed and/or exposed ($RR_{UY} = 2$), AND

  2) be twice as prevalent among exposed than among unexposed ($RR_{AU} = 2$)

To completely explain away the observed association, but a weaker confounder (given the E-value), say 1.5 or 1.3, would not.

[1] E values are debatable for some but still a straightforward calculation and useful information to have. Versions of the E-value exists for ORs and HRs. E-value calculator.

Statistical significance?

In general, NO!

- But if you MUST use p-values, set the criteria on the high side (e.g. p < 0.30). This way you adjust for some non-confounders, but you don't miss many true confounders.

`Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. AJE 1989;129(1):125-37.`

- Residual confounding (unmeasured L's (U1, U2, etc), categorization, measurement error, etc):

`Kaufman JS, et al. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. Epidemiology 1997; 8(6):621-8. Ogburn EL, Vanderweele TJ. Bias attenuation results for nondifferentially mismeasured ordinal and coarsened confounders. Biometrika. 2013;100(1):241- 248. PMID: 24014285`

Residual confounding

Residual confounding occurs when adjustment does not completely remove the confounding effect of a given variable(s):

1) Misclassification of confounding variables

- (e.g., the variable is an imperfect proxy for the characteristic we want to adjust for)

2) Improper modeling of the confounding variable

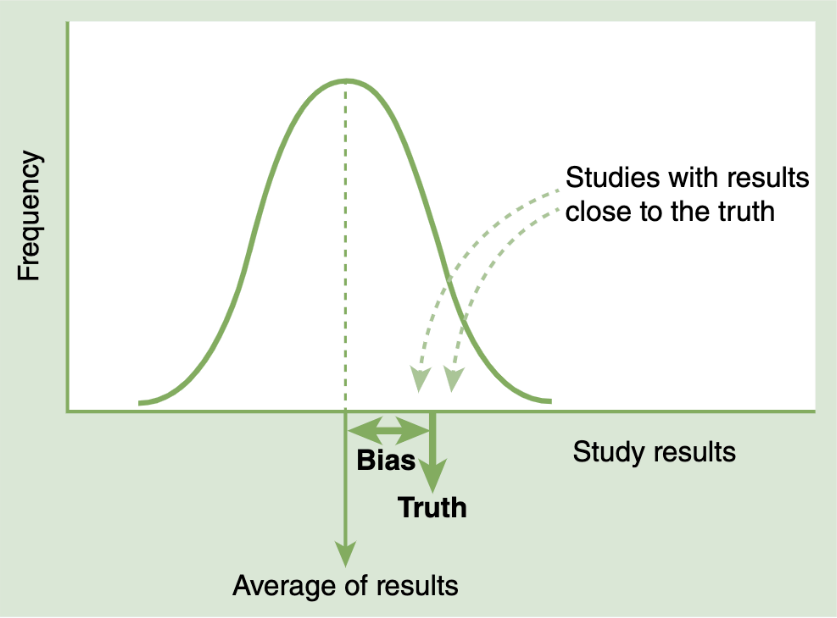
- (e.g., if we are studying air pollution and lung cancer and want to control for smoking, we should measure smoking in a way that best predicts lung cancer—i.e., pack-years not ever-never)

3) Other important confounders are not included (also known as unmeasured confounding or omitted variable bias)

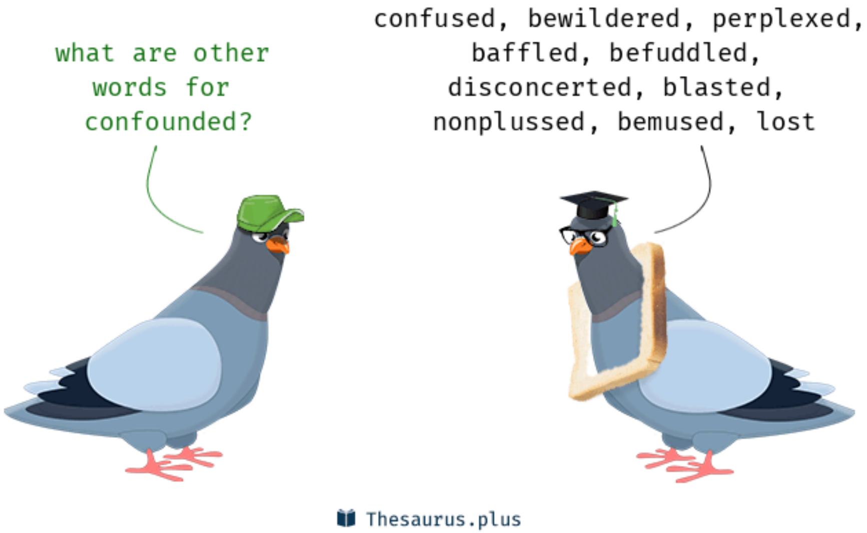
Validity and Bias:

- The epidemiologist's goal: the most **VALID and PRECISE** estimate possible of the causal effect of exposure on disease.

- Error comes from sampling variability (lack of precision) and bias (lack of validity).



Confounded [1] ?


what are other words for confounded?
confused, bewildered, perplexed, baffled, befuddled, disconcerted, blasted, nonplussed, bemused, lost
Thesaurus.plus

[1] We all are!! We will have more on this and empirical examples after we deal with regressions.

QUESTIONS?

COMMENTS?

RECOMMENDATIONS?