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Confounding and Effect Modification

John McGready
Johns Hopkins University

Confounding

Effect modification/statistical interaction



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Section A

Confounding

Confounding (Lurking Variable)

Consider results from the following (fictitious) study:

- ★ *This study was done to investigate the association between smoking and a certain disease in males and female adults*
- ★ *210 smokers and 240 non-smokers were recruited for the study*

We will first look at the results separately for males and females

Is smoking related to disease in males?

Males		
	Smoker	Non-Smoker
<i>Disease</i>	29	4
<i>No Disease</i>	131	36
<i>Totals</i>	160	40
<i>18% (29/160) of male smokers have disease</i>		
<i>10% (4/40) of male non-smokers have disease</i>		

$$\hat{RR} = 1.8, \hat{OR} = 2.0$$

Is smoking related to disease in females?

Females		
	Smoker	Non-Smoker
<i>Disease</i>	23	60
<i>No Disease</i>	27	140
<i>Totals</i>	50	200
<i>46% (23/50) of female smokers have disease</i>		
<i>30% (60/200) of female non-smokers have disease</i>		

$$\hat{RR} = 1.5, \hat{OR} = 2.0$$

Is smoking related to disease overall?

Combined Tables		
	Smoker	Non-Smoker
<i>Disease</i>	52	64
<i>No Disease</i>	158	176
<i>Totals</i>	210	240
<i>25% (52/210) of smokers have disease</i>		
<i>27% (64/240) of non-smokers have disease</i>		

$$\hat{RR} = 0.93, \hat{OR} = 0.91$$

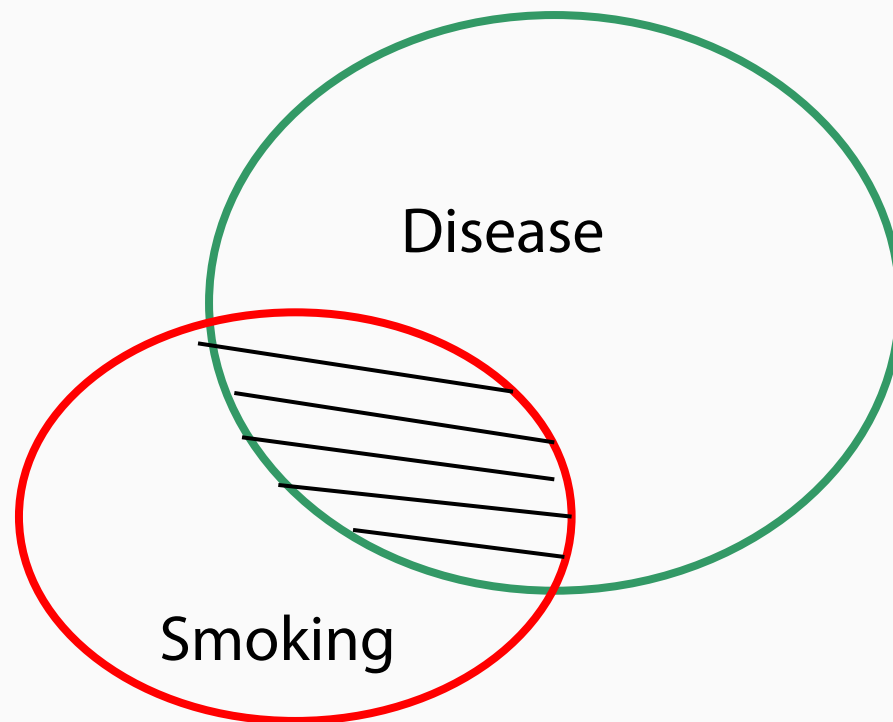
There is a much higher prevalence of disease among females

Disease and Sex		
	Disease	No Disease
<i>Male</i>	33	167
<i>Female</i>	83	167
<i>Totals</i>	116	334

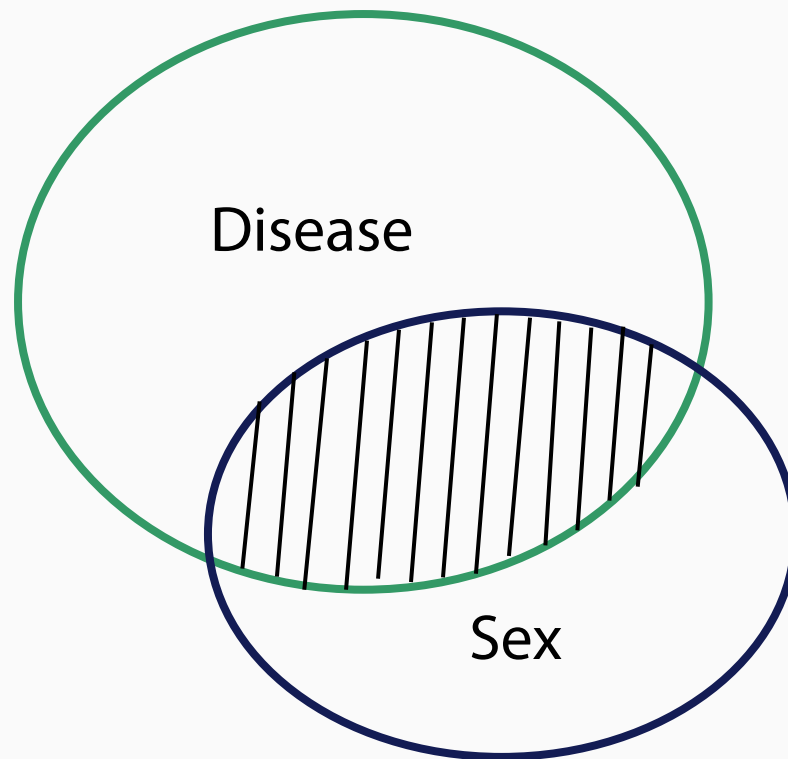
Most of the non-smokers are female

Smoking and Sex		
	Smoker	Non-Smoker
<i>Male</i>	160	40
<i>Female</i>	50	200
<i>Totals</i>	210	240

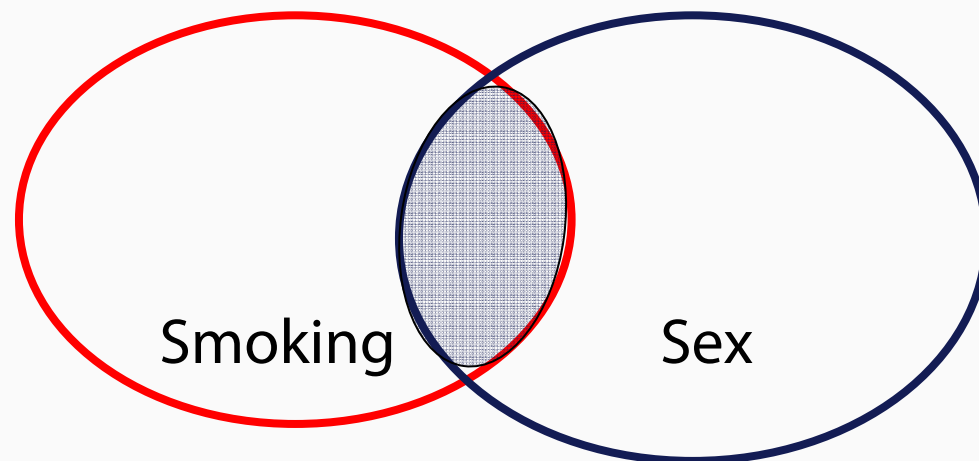
A picture



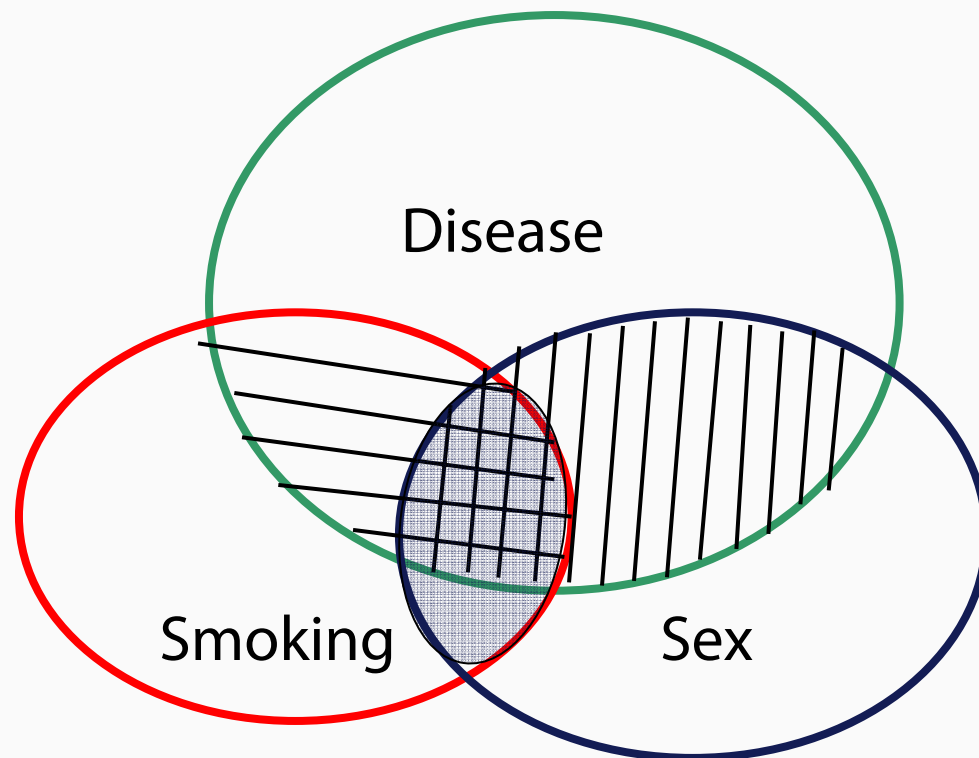
A picture



A picture



A picture



The nature of an association can change (and even reverse direction) or disappear when data from several groups are combined to form a single group

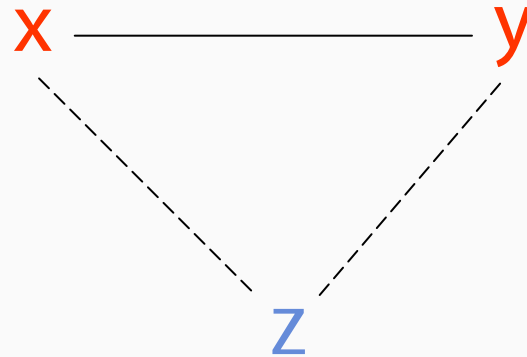
Confounding (Lurking Variable)

An association between an exposure **X** and a disease **Y** can be confounded by another lurking (hidden) variable **Z**

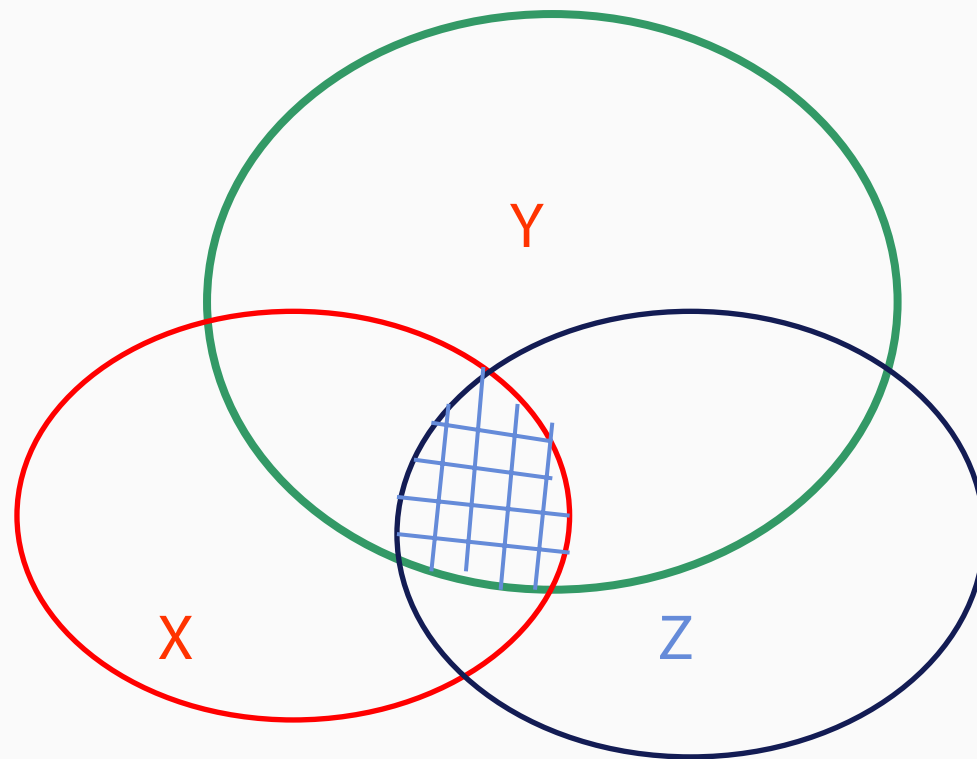
Confounding (Lurking Variable)

A confounder Z distorts the true relation between X and Y

This can happen if Z is related both to X and to Y



A picture



What is the Solution for Confounding?

If you **DON'T KNOW** what the potential confounders are, there's not much you can do after the study is over

★ *Randomization is the best protection*

What is the Solution for Confounding?

If you can't randomize but **KNOW** what the potential confounders are, or there are statistical methods to help control (adjust for confounders)

What is the Solution for Confounding?

Stratify

- ★ *Look at tables separately*
- ★ *For example, male and females, clinic*
- ★ *Take weighted average of stratum specific estimates*

Regression methods

- ★ *Just around the corner!*

Example: Arm Circumference and Height

An observational study to arm circumference and height in Nepali children

- ★ *94 randomly selected subjects, ages 3 months—6.5 years, had arm circumference, weight and height measured*
- ★ *This study is observational—it is not possible to randomize subjects to weight groups!*

Example: Arm Circumference and Height

The data

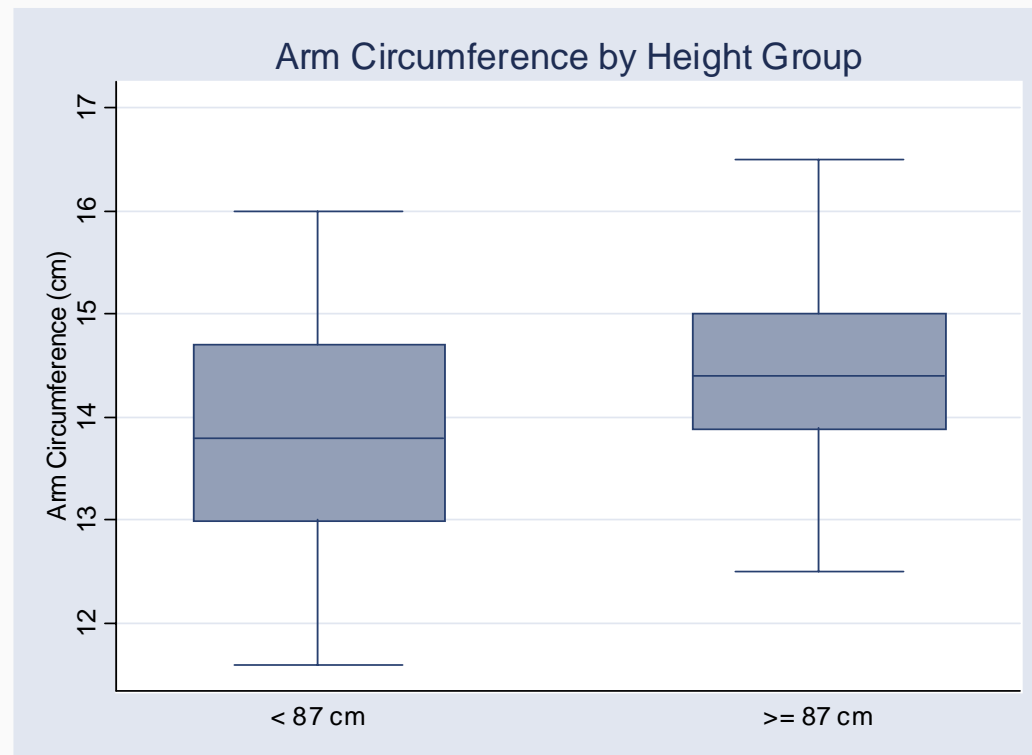
- ★ *Arm circumference range: 11.6–16.5 cm*
- ★ *Height range: 57–109 cm*
- ★ *Weight range: 5–18 kg*

To perform analysis

- ★ *Dichotomize height at median: i.e., subjects will be classified as “less than” or “greater than or equal to” median height of 87 cm*
- ★ *Dichotomize weight at median: i.e., subjects will be classified as “less than” or “greater than or equal to” median weight of 11.4 kg*

Example: Arm Circumference and Height

Boxplot arm circumference by height group



Example: Arm Circumference and Height

Mean arm circumference (AC) by height group

<u>Height Group</u>	<u>n</u>	<u>Mean AC</u>	<u>SD</u>
< 87 cm	47	13.8	1.1
≥ 87 cm	47	14.5	0.9

Example: Arm Circumference and Height

Results from a t-test

```
. ttest armcirc, by( ht_group)
```

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
< 87 cm	47	13.78298	.1581378	1.084138	13.46466	14.10129
>= 87 cm	47	14.47021	.1304271	.8941634	14.20768	14.73275
combined	94	14.1266	.1079877	1.04698	13.91215	14.34104
diff		-.687234	.2049849		-1.094352	-.2801163

Degrees of freedom: 92

Ho: mean(< 87 cm) - mean(>= 87 cm) = diff = 0

Ha: diff < 0
t = -3.3526
P < t = 0.0006

Ha: diff != 0
t = -3.3526
P > |t| = 0.0012

Ha: diff > 0
t = -3.3526
P > t = 0.9994

Continued

Example: Arm Circumference and Height

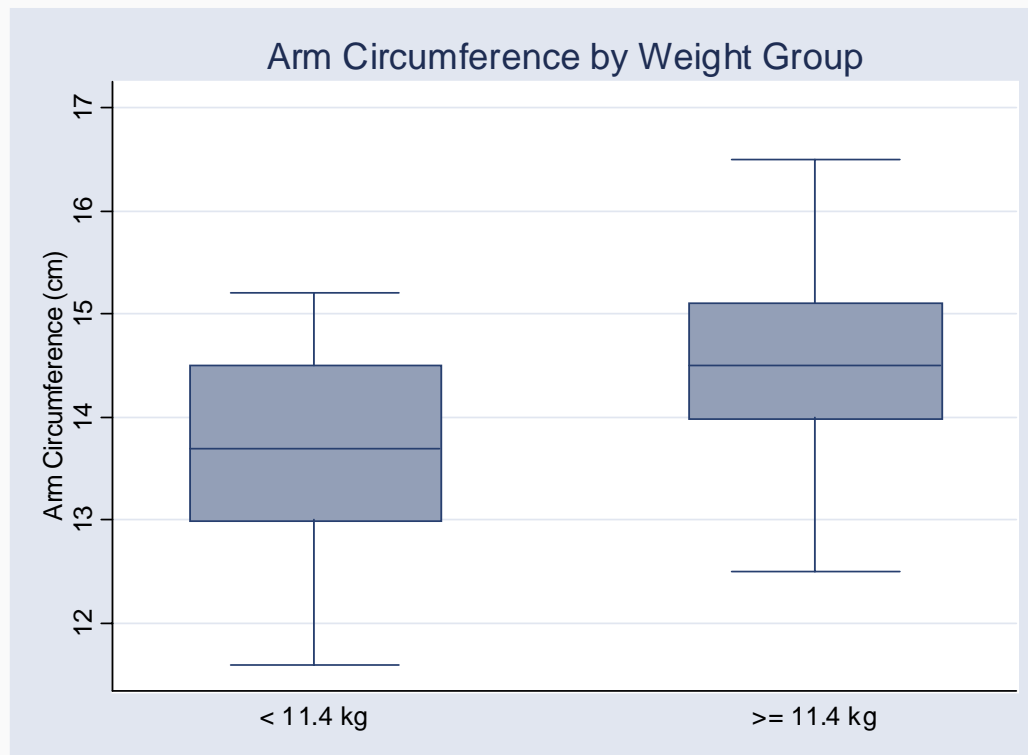
Results from a t-test

- ★ *Children below the median height had arm circumferences of .69 cm lower on average than children (equal to or) above the median height (95% CI : 0.28 cm–1.29 cm lower)*

Example: Arm Circumference and Height

What about weight?

★ *Boxplot: arm circumference by weight group*



Continued

Example: Arm Circumference and Height

Mean arm circumference (AC) by weight group

<u>Weight Group</u>	<u>n</u>	<u>Mean AC</u>	<u>SD</u>
< 11.4 kg	47	13.6	1.0
≥ 11.4 kg	47	14.6	0.9

Continued

Example: Arm Circumference and Height

Results from a t-test

```
. ttest armcirc, by( wt_group)
```

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
< 11.4 k	47	13.65319	.1468715	1.0069	13.35755	13.94883
>= 11.4	47	14.6	.1258459	.8627559	14.34669	14.85331
combined	94	14.1266	.1079877	1.04698	13.91215	14.34104
diff		-.9468085	.1934126		-1.330943	-.5626745

Degrees of freedom: 92

Ho: mean(< 11.4 k) - mean(>= 11.4) = diff = 0

Ha: diff < 0
t = -4.8953
P < t = 0.0000

Ha: diff != 0
t = -4.8953
P > |t| = 0.0000

Ha: diff > 0
t = -4.8953
P > t = 1.0000

Continued

Example: Arm Circumference and Height

Results from a t-test

- ★ *Children below the median weight had lower arm circumferences .95 cm on average than children (equal to or) above the median weight (95% CI : .56 cm–1.33 cm lower)*

Example: Arm Circumference and Height

So lower weight subjects have smaller arm circumferences on average: i.e., not only is arm circumference related to height, but it is also related to weight

If height is related to weight, then it's possible that part of the relationship we saw between arm circumference and height is because of the arm circumference-height-weight relationship—in other words, it is possible that the arm circumference/height relationship is confounded by weight

Example: Arm Circumference and Height

Two-by-two table of height group versus weight group

wt_group	ht_group		Total
	< 87 cm	>= 87 cm	
< 11.4 kg	41	6	47
>= 11.4 kg	6	41	47
Total	47	47	94

Continued

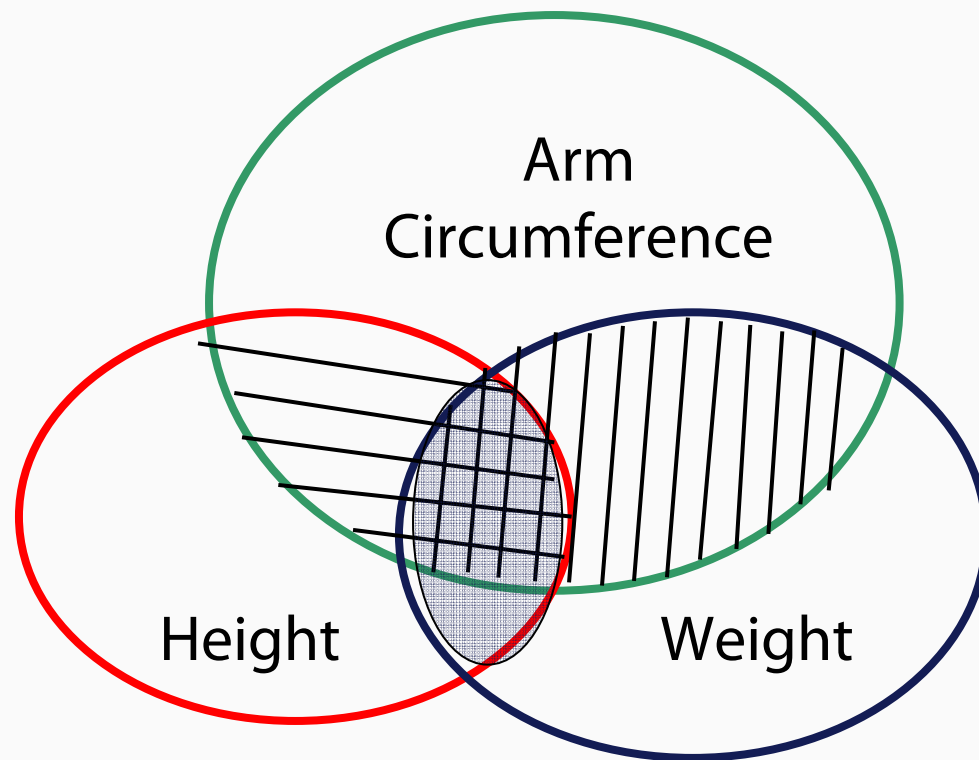
Example: Arm Circumference and Height

87% of the heavier children are taller versus 13% of the younger subjects (difference = 74%, 95% CI 61%–88%)

So it appears that weight is also related to height

Example: Arm Circumference and Height

Possible diagram of this scenario



Continued

Example: Arm Circumference and Height

Recall the original finding—children below the median height had arm circumferences of .69 cm lower on average than children (equal to or) above the median height

To investigate whether this estimate is being fueled in part by weight differences in the height groups, and the arm circumference/weight relationship, let's stratify by weight group, and estimate the arm circumference/height association in each weight group

Example: Arm Circumference and Height

Mean arm circumference (AC) by height group

★ *Children below median weight*

<u>Height Group</u>	<u>n</u>	<u>Mean AC</u>	<u>SD</u>
< 87 cm	41	13.65	1.1
≥ 87 cm	6	13.63	.62

★ *Shorter subjects below the median weight have arm circumferences on average .02 cm larger than taller subjects below the median weight (95% CI: – .87 cm (lower) to .92 cm (higher))*

Example: Arm Circumference and Height

Mean arm circumference (AC) by height group

★ *Children above median weight*

<u>Height Group</u>	<u>n</u>	<u>Mean AC</u>	<u>SD</u>
< 87 cm	6	14.65	.92
≥ 87 cm	41	14.59	.87

★ *Shorter subjects at or above the median weight have arm circumferences on average .06 cm larger than taller subjects at or above the median weight (95% CI: - .71 cm (lower) to .83 cm (higher))*

Example: Arm Circumference and Height

A recap

- ★ *Ignoring weight, children below the median height had arm circumferences of .69 less on average than children at or above the median height and this difference was statistically significant*
- ★ *When stratified by weight children below the median height had arm circumferences marginally larger on average than children with or above the median height in both weight groups, but these estimates were very close to 0 and not statistically significant*

Example: Arm Circumference and Height

So, it appears as though the association between arm circumference and height “disappears” or at least gets much smaller after accounting for weight

Example: Arm Circumference and Height

One approach—take a weighted average of the average arm circumference differences between subjects below and above the median weight within weight groups, weighted by size of each group

However, this is a pain, and if there are more potential confounders we could spend our life stratifying and computing such estimates

Example: Arm Circumference and Height

Better approach—multiple regression methods
(forthcoming!)

Example: Arm Circumference and Height

For completeness—let's look at the relationship between arm circumference and weight, adjusted to height

Example: Arm Circumference and Height

Mean arm circumference (AC) by weight group

★ *Children below median height*

<u>Weight Group</u>	<u>n</u>	<u>Mean AC</u>	<u>SD</u>
< 11.4 kg	41	13.65	1.1
≥ 11.4 kg	6	14.65	.92

★ *Lower weight children below the median height have arm circumferences on average one cm smaller than higher weight children below the median height (95% CI: .07 cm (lower) to 1.91 cm (lower))*

Continued

Example: Arm Circumference and Height

Mean arm circumference (AC) by weight group

★ *Children above median height*

<u>Weight Group</u>	<u>n</u>	<u>Mean AC</u>	<u>SD</u>
< 11.4 kg	6	13.63	.62
≥ 11.4 kg	41	14.59	.89

★ *Lower weight children at or above the median height have arm circumferences on average .96 cm smaller than higher weight children at or above the median height (95% CI: .22 cm (lower to 1.7 cm (lower))*

Continued

Example: Arm Circumference and Height

A recap

- ★ *Ignoring height, children below the median weight had arm circumferences of .95 cm less on average than children at or above the median height and this difference was statistically significant*
- ★ *When stratified by height children below the median weight had arm circumferences similarly smaller on average than children at or above the median height in both height groups, and these estimates were statistically significant*

Example: Arm Circumference and Height

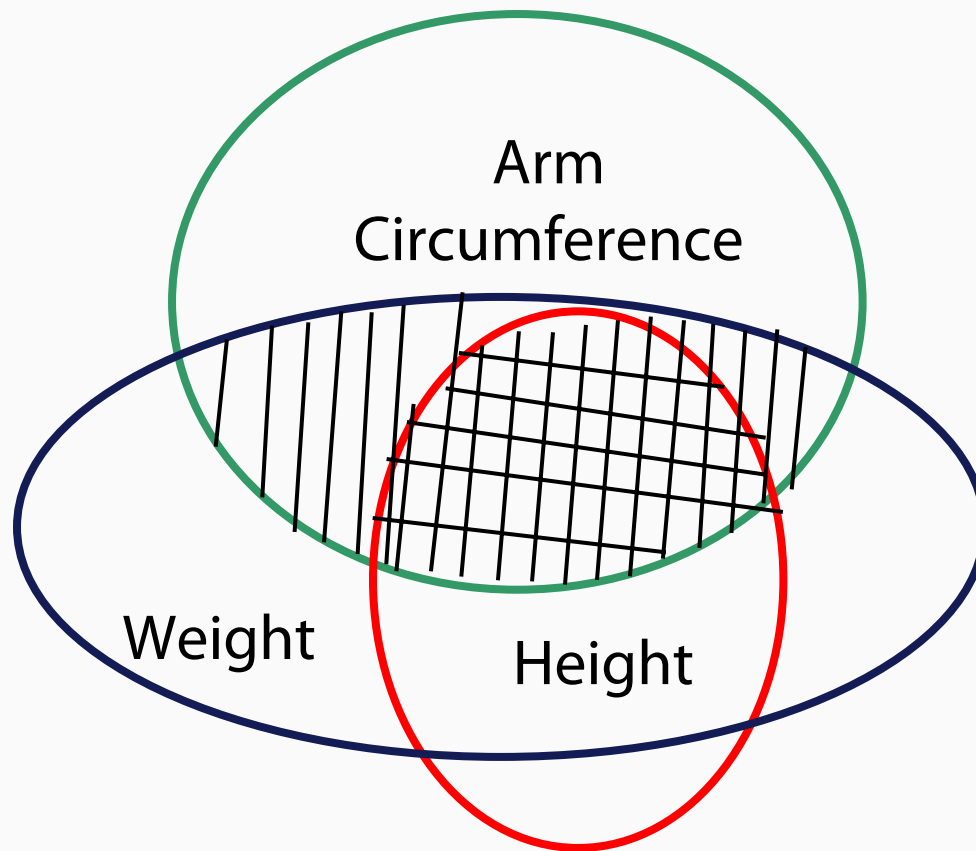
A weighted overall average height adjusted difference in arm circumference between the two weight groups is .98 cm (children below median weight have smaller arm circumference on average), with 95% CI .40 cm to 1.55 cm

Interesting:

- ★ *When adjusted for weight, the arm circumference/height association disappears*
- ★ *When adjusted for height, the arm circumference/weight association is almost the same as the unadjusted arm circumference/weight association*

Example: Arm Circumference and Height

This is an interesting case, perhaps better illustrated by this picture:



Continued

Example: Arm Circumference and Height

This is not always the case—many times when there is confounding between an outcome and two (or more) grouping variables, all of the adjusted outcome/group relationships will differ from the unadjusted associations



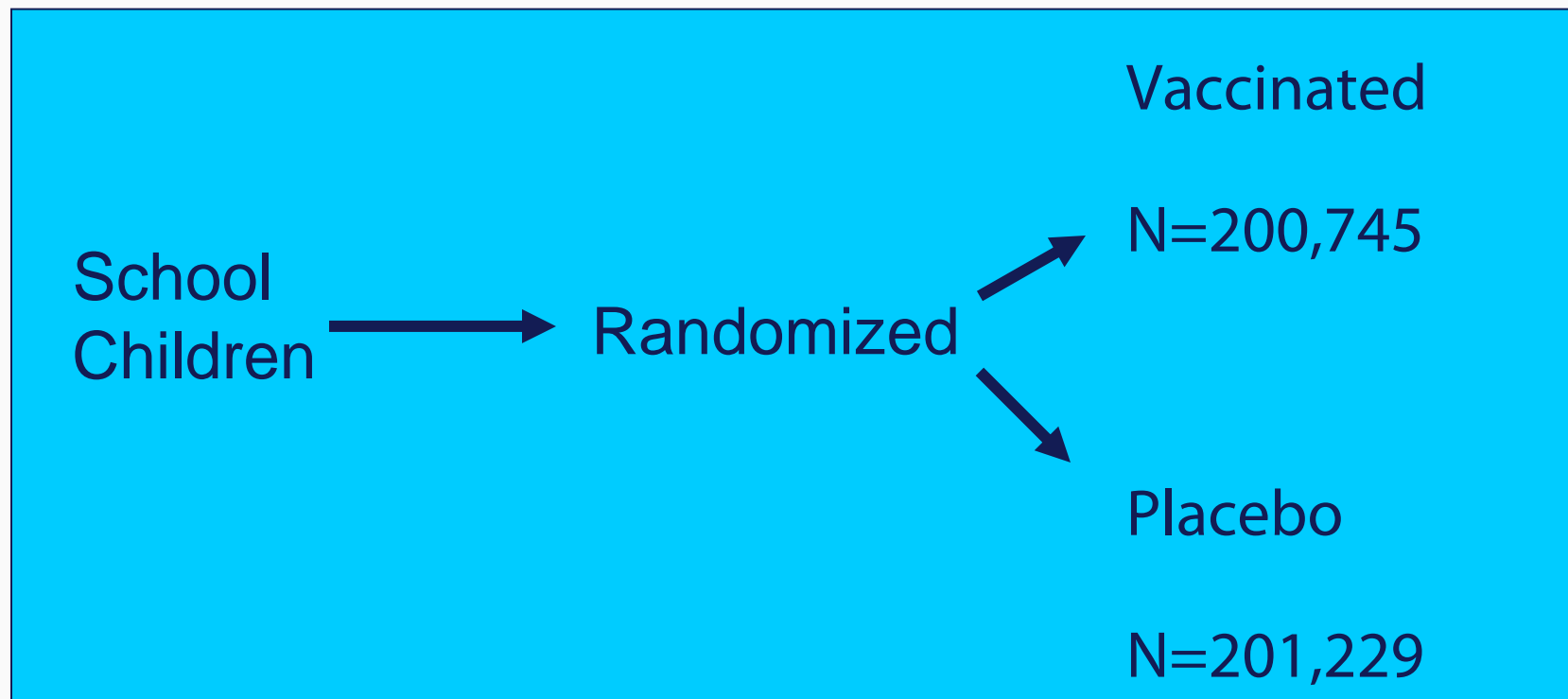
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Section A

Practice Problems

1. Can you explain confounding to a classmate or other acquaintance? Can you think of an example to help with your explanation?

2. Consider a large, randomized study such as the Salk polio vaccine trial.



2. How does randomization help to ensure that the outcome/treatment group relationship observed is not confounded by any factors known or unknown? More specifically, what part of the necessary conditions for confounding does randomization eliminate?

3. Suppose a study were performed to assess the relationship between a diet choice (vegan, lacto-ovo vegetarian, neither) and cholesterol level. Subjects were not randomized to a dietary group. Before interpreting the relationship, can you name some potential factors for which it would be advisable to control?



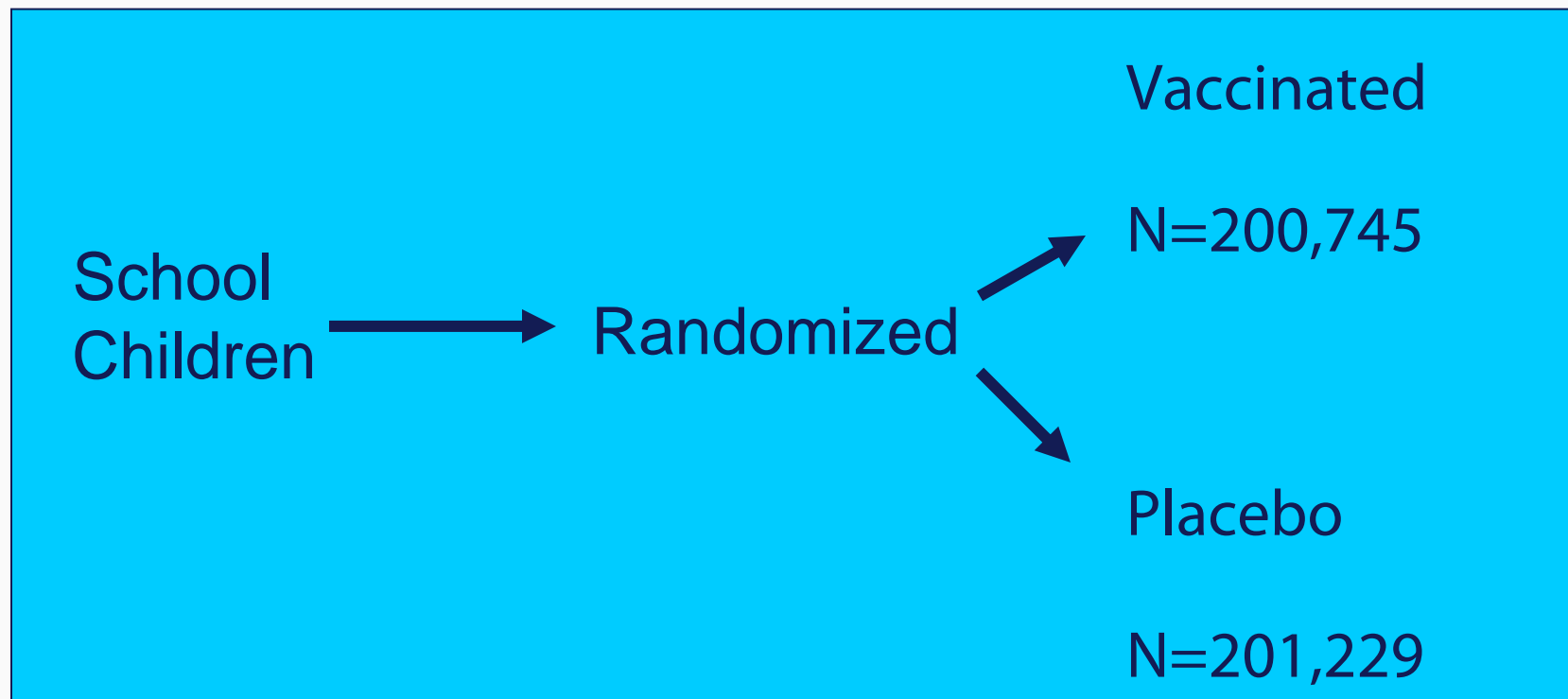
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Section A

Practice Problem Solutions

1. Can you explain confounding to a classmate or other acquaintance? Can you think of an example to help with your explanation?

2. Consider a large, randomized study such as the Salk polio vaccine trial.



2. How does randomization help to ensure that the outcome/treatment group relationship observed is not confounded by any factors known or unknown? More specifically, what part of the necessary conditions for confounding does randomization eliminate?

Remember, a necessary condition for a variable to be a confounder is that it must be related to both the outcome and the predictor of interest

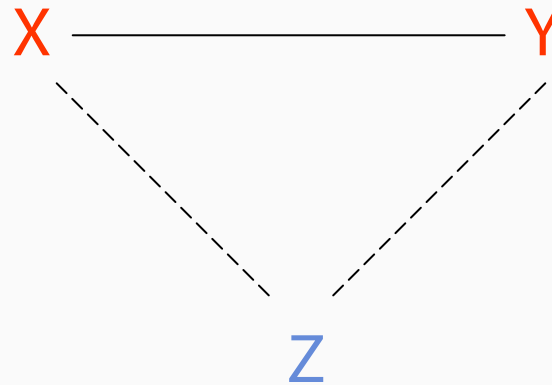
In randomized studies, the “treatment” is the predictor of interest

Randomization with a large number of potential subjects eliminates the association between the predictor of interest and any other variable besides (potentially) the outcome

In other words, randomization allows the only difference between the “treatment” groups to be the treatment of interest

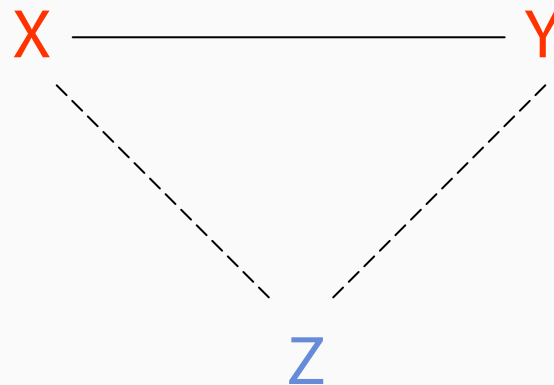
Practice Problem Solutions

In the “confounding conditions” diagram with outcome **Y**, predictor of interest **X**, and potential confounder **Z**:



Continued

Randomization eliminates the necessary link between **X** and **Z**



3. Suppose a study were performed to assess the relationship between a diet choice (vegan, lacto-ovo vegetarian, neither) and cholesterol level. Subjects were not randomized to a dietary group. Before interpreting the relationship, can you name some potential factors for which it would be advisable to control?

Remember, for a factor to be a confounder, it must be associated with both cholesterol level and with being vegetarian

Some candidates include the following:

- ★ *Gender*—females are more likely to be vegetarian and have lower cholesterol
- ★ *Smoking*—vegetarians are less likely to smoke and smoking is associated with higher cholesterol
- ★ *Income*—vegetarians are wealthier and increased wealth associated with lower cholesterol



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Section B

Statistical Interaction / Effect Modification

Let's look at the results from a fictitious data set comparing two treatments for a fatal disease as to the impact of each on reducing deaths

- ★ *The data presented is stratified by two age groups, "young" and "old"*

Effect Modification / Interaction

The data:

	YOUNG		OLD	
	Surgery	Drug	Surgery	Drug
Died	100	200	200	100
Survived	200	100	100	200
Totals	300	300	300	300

Continued

Effect Modification / Interaction

Surgery is better for this group!

	YOUNG		OLD	
	Surgery	Drug	Surgery	Drug
Died	100	200	200	100
Survived	200	100	100	200
Totals	300	300	300	300

33% (100/300) of those who had surgery died, as compared to 67% (200/300) of those taking the drug!

(RR = .50, OR = .25)

Effect Modification / Interaction

Taking the drug is better for this group!

	YOUNG		OLD	
	Surgery	Drug	Surgery	Drug
Died	100	200	200	100
Survived	200	100	100	200
Totals	300	300	300	300

67% (200/300) of those who had surgery died, as compared to 37% (100/300) of those who took the drug!

(RR = 2, OR = 4)

What happens when we combine tables?

	Combined Young and Old	
	Surgery	Drug
Died	300	300
Survived	300	300
Totals	600	600

Surgery and drug groups have identical proportions dying! (50% in each group!)

Age is an effect modifier:

- ★ *Age modifies the association between death and treatment! (Statistical interaction between age and treatment)*

The association between death and treatment depends on age

- ★ *Surgery better for younger patients, drug therapy better for the older patients*

The association between death and one variable (**TREATMENT**) depends on the level of another variable (**AGE**)

Here, it would not make sense to estimate one composite, overall measure of the association between death and treatment

Best way to look at this data is to just look at the two tables (young and old) separately and estimate two separate death/treatment associations

Example: Tree Damage and Elevation

Data on elevation and percentage of dead or badly damaged trees, from 64 Appalachian sites (reported by Committee on Monitoring and Assessment of Trends in Acid Deposition, 1986)

Eight of the 64 sites are in Southern states

Elevation information—whether the site was above or below 1,100 meters

This is an observational study (why?)

Example: Tree Damage and Elevation

Data for the first ten sites

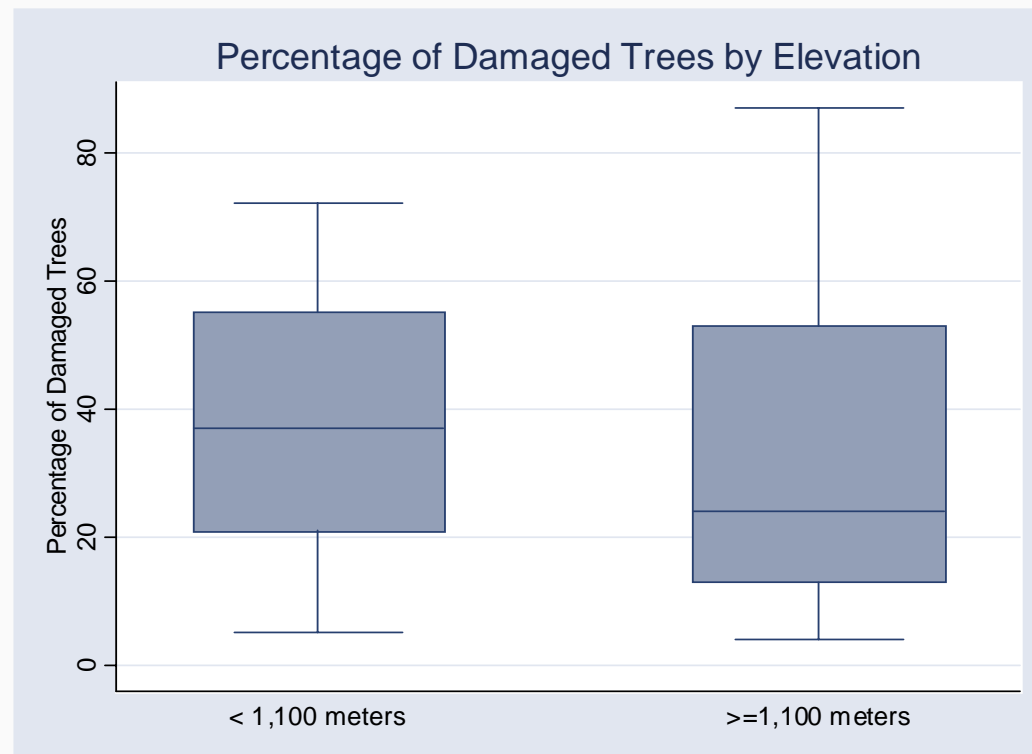
```
list damage elev_group region in 1/10
```

	damage	elev_group	region
1.	5	>=1,100 meters	South
2.	13	>=1,100 meters	South
3.	6	>=1,100 meters	South
4.	21	>=1,100 meters	South
5.	4	>=1,100 meters	South
6.	20	< 1,100 meters	South
7.	17	>=1,100 meters	South
8.	31	< 1,100 meters	South
9.	10	< 1,100 meters	North
10.	28	< 1,100 meters	North

Continued

Example: Tree Damage and Elevation

Let's try to assess the relationship between the percentage of damaged trees and elevation—here is a boxplot of the percentage of damaged trees by elevation



Continued

Example: Tree Damage and Elevation

Mean percentage of damaged trees by elevation group

<u>Elevation Group</u>	<u>n</u>	<u>Mean</u> <u>Tree Damage(%)</u>	<u>SD</u>
$< 1,100\text{ m}$	51	37.5	18.3
$\geq 1,100\text{ m}$	13	37.7	30.6

Continued

Example: Tree Damage and Elevation

Results from a t-test

```
. ttest damage, by( elev_group) unequal
```

```
Two-sample t test with unequal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
< 1,100	51	37.4902	2.56559	18.32198	32.33706	42.64334
>=1,100	13	37.69231	8.496141	30.63327	19.18081	56.20381
combined	64	37.53125	2.637392	21.09914	32.26084	42.80166
diff		-.2021116	8.875059		-19.20474	18.80051

```
Satterthwaite's degrees of freedom: 14.2598
```

```
Ho: mean(< 1,100 ) - mean(>=1,100 ) = diff = 0
```

```
Ha: diff < 0  
t = -0.0228  
P < t = 0.4911
```

```
Ha: diff != 0  
t = -0.0228  
P > |t| = 0.9821
```

```
Ha: diff > 0  
t = -0.0228  
P > t = 0.5089
```

Continued

Example: Tree Damage and Elevation

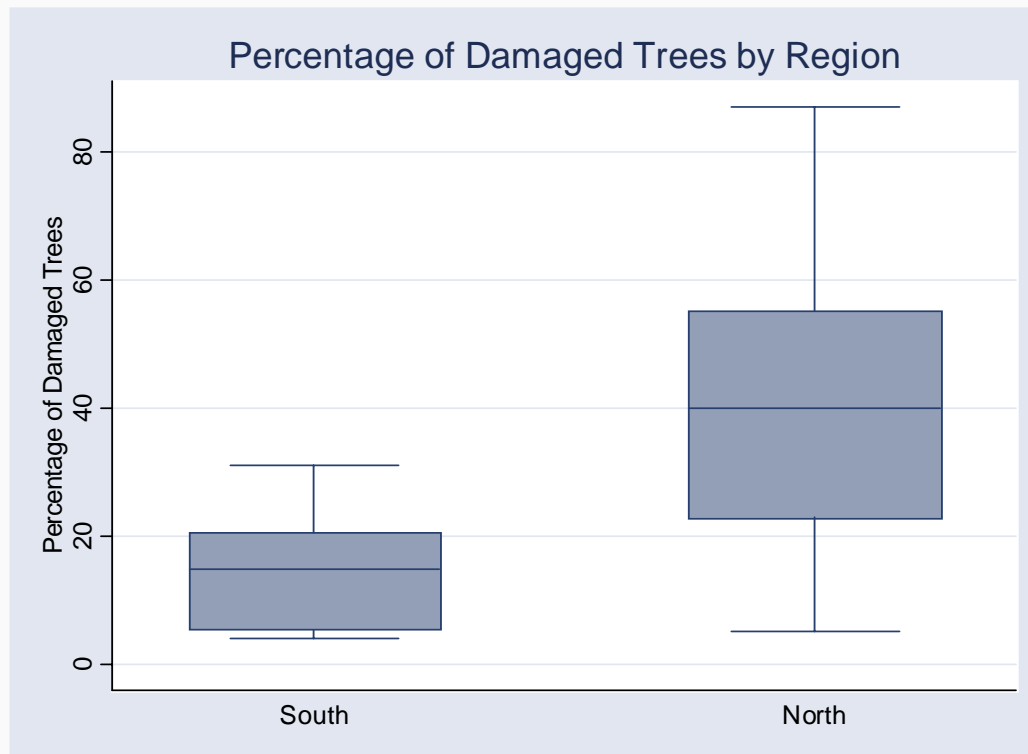
Results from a t-test

- ★ *Sites with lower elevation had marginally lower percentage of damaged trees on average: 0.2% less damaged than sites at higher elevation (95% CI: 19.2 % lower—18.8 % higher)*

Example: Tree Damage and Elevation

What about region though?

★ *Boxplot percentage of damaged trees by region*



Continued

Example: Tree Damage and Elevation

Mean percentage of damaged trees by region

<u>Region</u>	<u>n</u>	<u>Mean</u> <u>Tree Damage(%)</u>	<u>SD</u>
South	8	14.6	9.5
North	56	40.8	20.3

Continued

Example: Tree Damage and Elevation

Results from a t-test

```
. ttest damage, by( region) unequal
```

```
Two-sample t test with unequal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
South	8	14.625	3.343103	9.455724	6.719817	22.53018
North	56	40.80357	2.71018	20.28113	35.37225	46.23489
combined	64	37.53125	2.637392	21.09914	32.26084	42.80166
diff		-26.17857	4.303652		-35.2123	-17.14484

```
Satterthwaite's degrees of freedom: 18.2225
```

```
Ho: mean(South) - mean(North) = diff = 0
```

```
Ha: diff < 0  
t = -6.0829  
P < t = 0.0000
```

```
Ha: diff != 0  
t = -6.0829  
P > |t| = 0.0000
```

```
Ha: diff > 0  
t = -6.0829  
P > t = 1.0000
```

Continued

Example: Tree Damage and Elevation

So sites in the South have less damage on average: i.e., not only is the percentage of damaged trees related to elevation, but it is also related to region

If region is related to elevation, then it's possible that part of the relationship we saw (or didn't see) between damage and elevation is because of the region-damage-elevation relationship

Example: Tree Damage and Elevation

Two-by-two table of elevation group by region

```
. tab region elev_group
```

region	elev_group		Total
	< 1,100 m	>=1,100 m	
South	2	6	8
North	49	7	56
Total	51	13	64

Continued

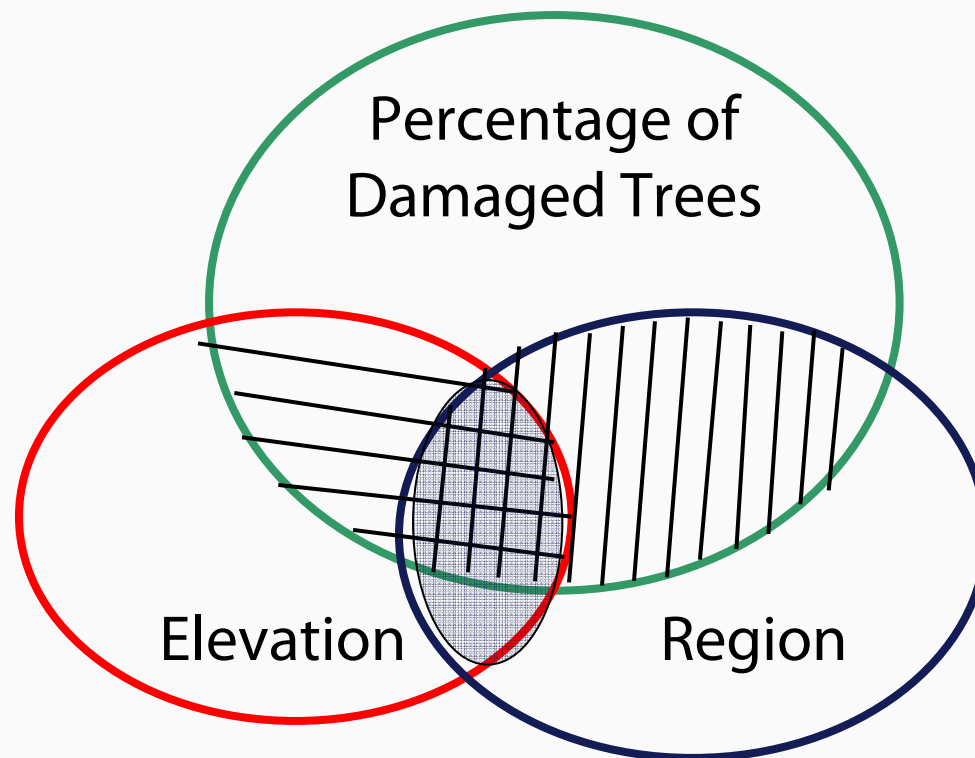
Example: Tree Damage and Elevation

75% of the sites in the south are at higher elevation as compared to 13% of the northern sites (difference = 62%, 95% CI 31%–94%)

So it appears that region is also related to elevation

Example: Tree Damage and Elevation

Possible diagram of this scenario



Continued

Example: Tree Damage and Elevation

Recall the original finding—sites with lower elevation had a marginally lower percentage of damaged trees on average: 0.2% less damaged than sites at higher elevation

To adjust for regional differences in the elevation groups, and the damage/region relationship, let's stratify by region, and estimate the damage/elevation association in each region

Example: Tree Damage and Elevation

Mean percentage of damage tree by elevation stratified by region

★ *South*

<u>Elevation Group</u>	<u>n</u>	<u>Mean</u> <u>Tree Damage(%)</u>	<u>SD</u>
< 1,100 m	2	25.5	7.7
≥ 1,100 m	6	11.0	7.1

★ *Southern sites at lower elevation have 14.5% more damaged trees on average than Southern sites at high elevation (95% CI: 19.7 % lower—48.7 % higher)*

Continued

Example: Tree Damage and Elevation

Mean percentage of damage tree by elevation stratified by region

★ *North*

<u>Elevation Group</u>	<u>n</u>	<u>Mean</u> <u>Tree Damage(%)</u>	<u>SD</u>
<i>< 1,100 m</i>	<i>49</i>	<i>38.0</i>	<i>18.5</i>
<i>≥ 1,100 m</i>	<i>7</i>	<i>60.6</i>	<i>22.6</i>

★ *Northern sites at lower elevation have 22.6% less damaged trees on average than Northern sites at high elevation (95% CI: 1.5% lower—43.6 % lower)*

Continued

Example: Tree Damage and Elevation

A recap

- ★ *Ignoring region, sites with lower PCV sites with lower elevation had marginally lower percentage of damaged trees on average—0.2 % less damaged than sites at higher elevation*

When stratified by region

- ★ *Northern sites showed positive, significant association between damage and elevation*
- ★ *Southern sites showed negative, non-significant association between damage and elevation*

Example: Tree Damage and Elevation

So, it appears as though the association between tree damage and elevation is different, both in magnitude and direction depending on region

We have a small dataset, so lack of statistical significance of negative damage/elevation associations in the South may be because of low power

Example: Tree Damage and Elevation

One approach—take a weighted average of the average damage differences between sites at low and high elevations within each region, weighted by number of observations in each region

However, does not necessarily make sense here—why combine estimates that differ in direction into one overall estimate?

Example: Tree Damage and Elevation

Better approach—to report two mean differences in damage between low and high elevation sites (one estimate for Northern sites, one estimate for Southern sites)

Better approach—multiple regression methods (forthcoming!)



JOHNS HOPKINS
BLOOMBERG
SCHOOL *of* PUBLIC HEALTH

Section B

Practice Problems

1. Explain the difference between **confounding** and **statistical interaction**.
2. Can you envision a design situation where there is no **confounding** but there is **interaction**?



JOHNS HOPKINS
BLOOMBERG
SCHOOL *of* PUBLIC HEALTH

Section B

Practice Problem Solutions

1. Explain the difference between **confounding** and **statistical interaction**.

- ★ *A lot of people have trouble with these two concepts, as they are difficult. **Confounding** occurs when the relationship between two factors (exposure and outcome) is obscured by a third, hidden factor.*

1. Explain the difference between **confounding** and **statistical interaction**.

- ★ *Statistical interaction* occurs when the relationship between two factors (exposure and outcome) is different across different levels of a third factor. It is possible to uncover both confounding and statistical interaction at the same time.

2. Can you envision a design situation where there is no confounding, but there is interaction?

★ *We will discuss this further in LiveTalk—but feel free to add your thoughts on this to a BBS topic.*