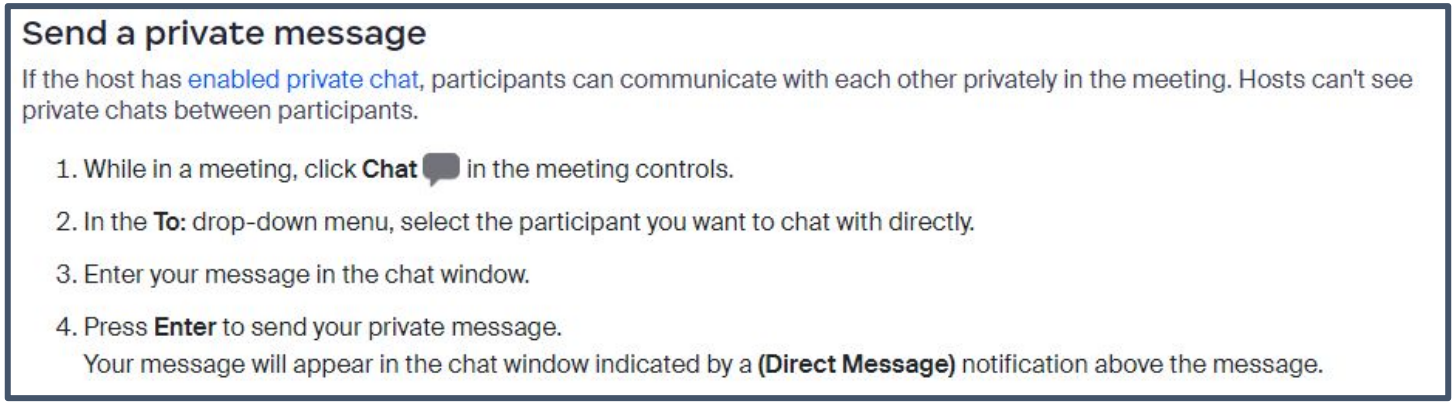
Recording sessions

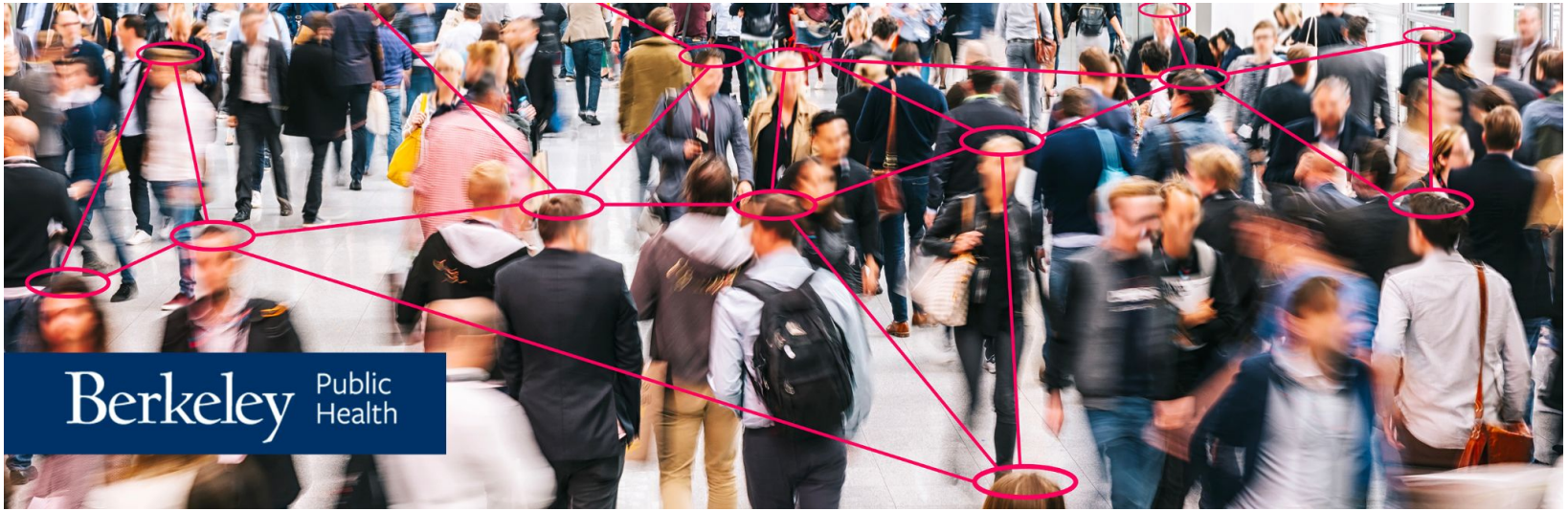
- All live sessions will be recorded and available on bCourses.
- If you want remain anonymous during the session, please send a private message to me on Zoom.



Send a private message

If the host has enabled private chat, participants can communicate with each other privately in the meeting. Hosts can't see private chats between participants.

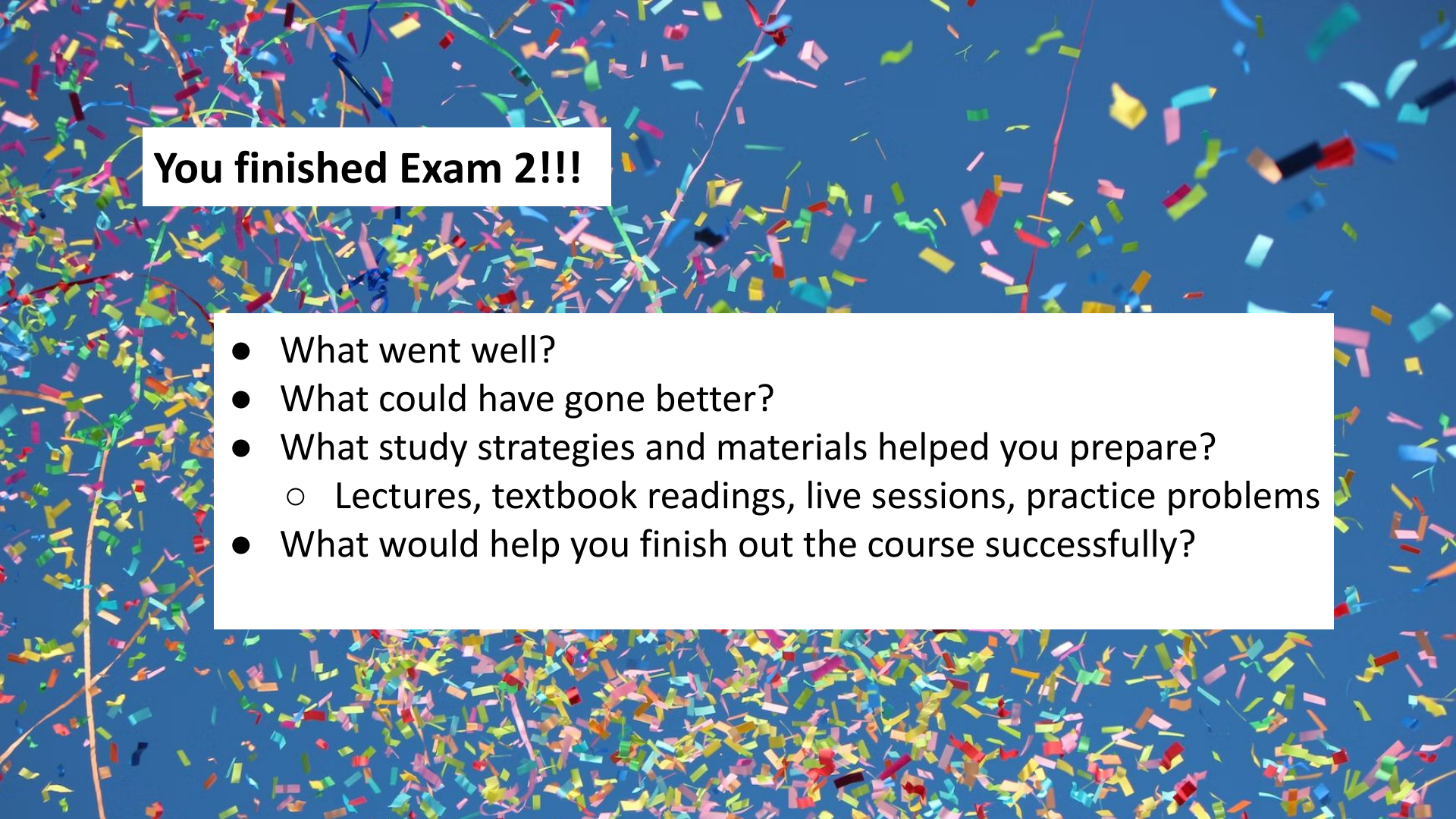
1. While in a meeting, click **Chat** in the meeting controls.
2. In the **To:** drop-down menu, select the participant you want to chat with directly.
3. Enter your message in the chat window.
4. Press **Enter** to send your private message.
   Your message will appear in the chat window indicated by a **(Direct Message)** notification above the message.



Epidemiologic Methods II

PHW250B

Week 11: Effect Measure Modification and Interaction



You finished Exam 2!!!

- What went well?
- What could have gone better?
- What study strategies and materials helped you prepare?
  - Lectures, textbook readings, live sessions, practice problems
- What would help you finish out the course successfully?

Agenda

- **Effect measure modification and interaction overview**
- **Practice problems**
- **Q & A**

Terminology Review

Interaction: The effect of two things together is different than the sum (additive) or product (multiplicative) of its parts.

Interaction in epidemiology:

- Statistical interaction: refers to association whether causal or not
    - Equivalent to effect measure modification with no bias
    - Oftentimes you will see effect modification and interaction used interchangeably, but they are not always the same!
- Effect measure modification: valid estimate of effect measure of interest
- Biologic/causal interaction: true biologic process in the population

Quantifying and testing EM

1. Calculate a crude measure of association between the exposure and outcome (e.g., AR, RR)

↓

2. Stratify the data by the potential confounder/effect modifier

↓

3. Calculate stratified measures of association (e.g., AR, RR)

↓

4. Compare the stratified associations using the test for homogeneity (X^2_H)

↓

5. Are the associations homogeneous (H0: association the same across strata)?

Yes

(i.e., did not reject H0 for X^2_H)

↓

6. Calculate an adjusted measure of association (e.g., Mantel-Haenszel)

↓

7. Compare adjusted association with crude (step 1) to describe direction and magnitude of the confounding

No

(i.e., rejected H0 for X^2_H)

↓

6. Present measures of association stratified by the effect modifier

Confounding

Confounding vs. Effect modification

- Confounding is a nuisance.
  We want to minimize confounding.

- Effect modification is of interest.
  We want to celebrate effect modification and present it (via stratified estimates)!

Chi-square test for homogeneity

Purpose
To assess whether stratum-specific measures of association are the same (homogeneous) or different (heterogeneous).

Null Hypothesis (H_0)
All stratum-specific measures of association are equal to each other.
→ This means the effect is consistent across strata (homogeneous).

Alternative Hypothesis (H_1)
At least two of the stratum-specific measures of association are not equal to each other.
→ This indicates the effect differs between strata (heterogeneous).

How to Think About It

- Imagine two strata: smokers who are young and smokers who are old.
- If the measure of association (e.g., OR or RR) is the same in both groups, we fail to reject H_0 → evidence of homogeneity.
- If the measures are statistically different, we reject H_0 → evidence of heterogeneity or effect modification.

Chi-square test for homogeneity

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$X_2^{HOM} = 28.918$

Degrees of freedom (df) = 2-1 = 1
Get the p-value in R: **dchisq**(28.918, **df**=1) = <0.001

> **Conclusion**: We can reject the null hypothesis that the ORs are the same across strata of breastfeeding status. Effect modification on the relative scale is present.

- For the chi-square test of homogeneity, we use a p-value cutoff for statistical significance of 0.2
  - (i.e., p-value <0.2 is statistically significant).
- This is because the statistical test of homogeneity has limited statistical power
- We err on the side of concluding that interaction is present

Refresher Tab, Problem 1

The following table shows crude and stratum-specific odds ratios for six analyses. Indicate whether there is evidence that effect modification or confounding is present and, under the circumstances, what is the appropriate measure of association to report (options are: unadjusted, stratum-specific ORs, or adjusted OR).

OR_{crude}	OR_{men}	OR_{women}	Effect Modification? (Yes/No/Maybe)	Confounding? (Yes/No/Maybe)	Measure Reported (unadjusted, adjusted, or stratum-specific OR)
2.0	2.0	2.0	NO	NO	UNADJUSTED
3.6	1.9	1.9	NO	YES	ADJUSTED
1.0	6.0	2.0	YES	YES	STRATIFIED
3.1	5.8	4.2	YES	YES	STRATIFIED
0.5	1.3	1.4	MAYBE	MAYBE	STRATIFIED OR ADJUSTED

Tab 1, Problem 2

The following questions use data and situations adapted from: Nickson C, Mason KE, English DR, Kavanagh AM. Mammographic screening and breast cancer mortality: a case-control study and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012 Sep;21(9):1479-88.

- This study was designed to investigate the association between mammograms and breast cancer mortality among women over 50
- **Cases:** Breast cancer patients who had died as a result of their cancer
- **Controls:** women who were still living at the time of the study, regardless of their breast cancer diagnosis.
- Participants were categorized as "exposed" if they had received at least one mammogram any time after their 50th birthday.

	Cases	Controls
Exposed	167	2051
Unexposed	264	1599

The investigators were also concerned that socioeconomic disadvantage might be a potential confounder or effect modifier. They measured SES and found the following:

Low SES	Cases	Controls	Total
Exposed	56	1095	
Unexposed	131	1107	
Total			2389

High SES	Cases	Controls	Total
Exposed	111	956	
Unexposed	133	492	
Total			1680

Tab 1, Problem 2

	Cases	Controls
Exposed	167	2051
Unexposed	264	1599

Low SES	Cases	Controls	Total
Exposed	56	1095	
Unexposed	131	1107	
Total			2389

High SES	Cases	Controls	Total
Exposed	111	956	
Unexposed	133	492	
Total			1680

a. Calculate the crude OR and the stratum-specific ORs for those with low and high SES.

OR = AD / BC

CRUDE OR
(167*1599) / (2051*264) = 0.493.

STRATUM SPECIFIC OR (LOW SES)
(56*1107)/(131*1095)=0.432.

STRATUM SPECIFIC OR (HIGH SES)
(111*492)/(133*956)=0.430

Tab 1, Problem 2

	Cases	Controls
Exposed	167	2051
Unexposed	264	1599

$OR_{crude} = 0.493$
$OR_{low\ SES} = 0.432$
$OR_{high\ SES} = 0.430$

$$OR_{MH} = \frac{\sum_{i=1}^{k} \{ad/T\}_i}{\sum_{i=1}^{k} \{bc/T\}_i}$$

Where k = number of strata

Low SES	Cases	Controls	Total
Exposed	56	1095	
Unexposed	131	1107	
Total			2389

High SES	Cases	Controls	Total
Exposed	111	956	
Unexposed	133	492	
Total			1680

b. Calculate and interpret the adjusted OR.

Low SES strata ↓ High SES strata ↓

= [((56*1107)/2389) + ((111*492)/1680)] ÷
[((131*1095)/2389) + ((133*956)/1680)] = 0.431.

↑ Low SES strata ↑ High SES strata

Women who died of breast cancer had 0.431 times the odds of having a mammogram than those who did not die, adjusting for SES.

Tab 1, Problem 2

$OR_{crude} = 0.493$
$OR_{low\ SES} = 0.432$
$OR_{high\ SES} = 0.430$
$OR_{adj} = 0.431$

c. **The p-value on the chi-squared test for homogeneity is 0.98.**

State the null hypothesis being tested.

The null hypothesis is that the stratum-specific ORs are not different from one another.

Tab 1, Problem 2

$OR_{crude} = 0.493$
$OR_{low\ SES} = 0.432$
$OR_{high\ SES} = 0.430$
$OR_{adj} = 0.431$

c. Given these results, what do you conclude about the role of SES? Is it a confounder, effect modifier, or neither?

INTERPRETATION 1:

- Effect modification is not present because the stratum-specific ORs are not statistically different from each other (P = 0.98).
- The adjusted OR appears to be **meaningfully different** from the crude OR, which suggests confounding is present.
- We conclude that SES is a confounder.

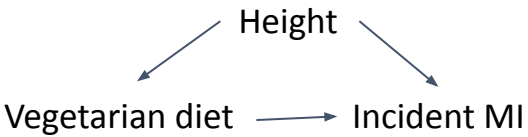
Interpretations may differ since we are visually assessing differences between the crude and adjusted OR.

INTERPRETATION 2:

- Effect modification is not present because the stratum-specific ORs are not statistically different from each other (P = 0.98).
- The adjusted OR **does not appear** to be meaningfully different from the crude OR.
- We conclude that SES is a **neither** a confounder or an effect modifier.

Tab 1, Problem 3

Investigators of a cohort study examining the relation between vegetarian diet and incident myocardial infarction (MI) drew a DAG at the beginning of their study, consulted the existing literature, and identified height as a confounder and also potentially an effect modifier of this relation.



The investigators calculated an overall CIR of 0.45 for the relation between vegetarian diet and incident MI. They then stratified by ***height***, and found a **CIR=0.82 for people less than 5'6"** and a **CIR=0.83 for people 5'6" and taller**.

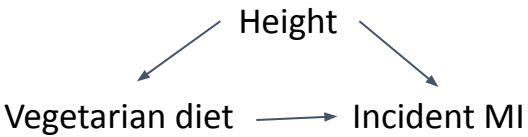
A. In the relationship between vegetarian diet and incident MI, is ***height*** a confounder, effect modifier, both, or neither?

a confounder but not an effect modifier.

- Stratified CIR are visually very similar to each other (not an effect modifier)
- Stratified CIR are pretty different from the overall CIR (confounder)

Tab 1, Problem 3

Investigators of a cohort study examining the relation between vegetarian diet and incident myocardial infarction (MI) drew a DAG at the beginning of their study, consulted the existing literature, and identified height as a confounder and also potentially an effect modifier of this relation.



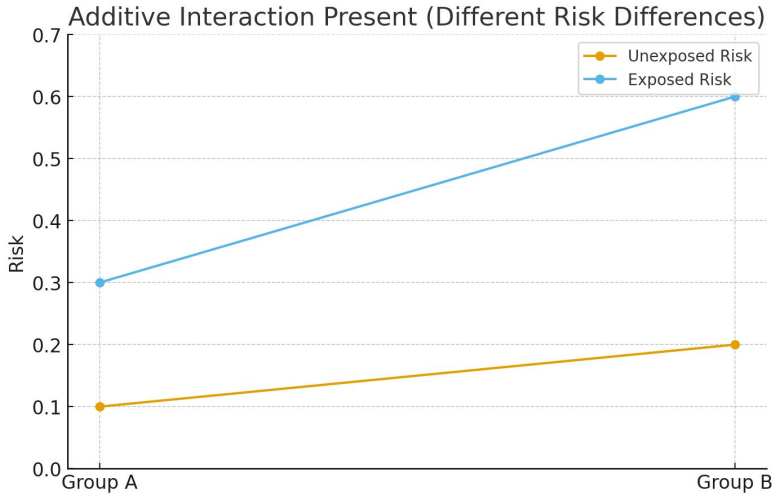
The investigators calculated an overall CIR of 0.45 for the relation between vegetarian diet and incident MI. They then stratified by ***height***, and found a **CIR=0.82 for people less than 5'6"** and a **CIR=0.83 for people 5'6" and taller**.

B. What measure(s) of association would you recommend that the investigators report given the role of ***height*** you identified in A) in the relation between vegetarian diet and MI, and why?

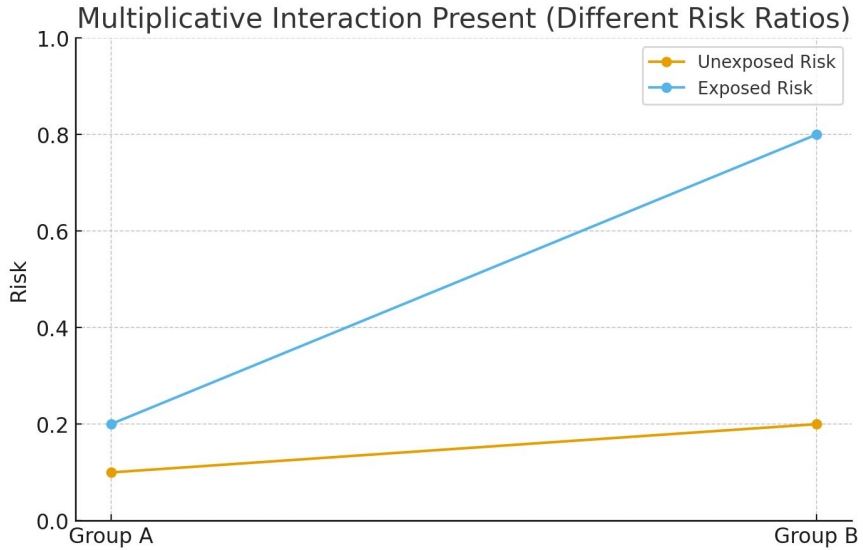
Confounding by height appears to be present, so the investigators should calculate the MH CIR (or CIR adjusted some other way – e.g., regression model) and present the results for the relationship between vegetarian diet and incident MI adjusted for height.

Interaction on additive scale

Group	Unexposed Risk	Exposed Risk	Risk Difference (RD)	Risk Ratio (RR)
A	0.10	0.30	**+0.20**	3.0
B	0.20	0.60	**+0.40**	3.0



Interaction on additive and multiplicative scale



Group	Unexposed Risk	Exposed Risk	Risk Difference (RD)	Risk Ratio (RR)
A	0.10	0.20	+0.10	**2.0**
B	0.20	0.80	+0.60	**4.0**

Tab 3, Problem 1

A cohort study estimates the risk of asthma among teens associated with E-cigarette smoking and type of neighborhood of residence.

Risk of asthma (Y) stratified by E-cigarette use and neighborhood type

	Urban neighborhood (Z=1)	Suburban / rural neighborhood (Z=0)
E-cigarette Smoker (X=1)	0.08	0.04
E-cigarette Non-smoker (X=0)	0.02	0.01

a. Fill in the risk of asthma in each of the categories of exposure below:

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

Tab 3, Problem 1

	Urban neighborhood (Z=1)	Suburban / rural neighborhood (Z=0)
E-cigarette Smoker (X=1)	0.08	0.04
E-cigarette Non-smoker (X=0)	0.02	0.01

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

b. Calculate the risk differences below:

RD for X alone (Z=0): P(Y|X = 1, Z = 0) - P(Y|X = 0, Z = 0) = 0.04-0.01 = 0.03

RD for Z alone (X=0): P(Y|X = 0, Z = 1) - P(Y|X = 0, Z = 0) = 0.02-0.01 = 0.01

Observed RD for X and Z: P(Y|X = 1, Z = 1) - P(Y|X = 0, Z = 0) = 0.08-0.01 = 0.07

Expected RD for X and Z: RD for X alone + RD for Z alone = 0.03 + 0.01 = 0.04

Tab 3, Problem 1

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

RD for X alone (Z=0): 0.03
RD for Z alone (X=0): 0.01
Observed RD for X and Z: 0.07
Expected RD for X and Z: 0.04

c. What do you conclude about the presence of statistical interaction on the additive scale?

The observed joint RD differs from the expected RD for both X and Z, suggesting that there is an additive scale interaction.

Tab 3, Problem 1

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

RD for X alone (Z=0): 0.03
RD for Z alone (X=0): 0.01
Observed RD for X and Z: 0.07
Expected RD for X and Z: 0.04

d. Calculate $p_{11} - p_{10} - p_{01} + p_{00}$. Interpret the resulting value. If interaction is present, what kind? Be as specific as possible.

Because the exposure is harmful….
0.08 - 0.04 - 0.02 + 0.01 = 0.03 > 0
Therefore, the interaction is present and positive/synergistic.

Defining a measure of interaction on the additive scale

If the **exposures are harmful** (increase risk of disease):

- If $p_{11} - p_{10} - p_{01} + p_{00} > 0$ interaction is positive or synergistic
- If $p_{11} - p_{10} - p_{01} + p_{00} = 0$ no interaction is present
- If $p_{11} - p_{10} - p_{01} + p_{00} < 0$ interaction is negative or antagonistic

Tab 3, Problem 1

	Urban neighborhood (Z=1)	Suburban / rural neighborhood (Z=0)
E-cigarette Smoker (X=1)	0.08	0.04
E-cigarette Non-smoker (X=0)	0.02	0.01

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

e. Calculate the risk ratios below:

RR for X alone (Z=0): $P(Y|X = 1, Z = 0) / P(Y|X = 0, Z = 0) = 0.04/0.01 = 4$

RR for Z alone (X=0): $P(Y|X = 0, Z = 1) / P(Y|X = 0, Z = 0) = 0.02/0.01 = 2$

Observed RR for X and Z: $P(Y|X = 1, Z = 1) / P(Y|X = 0, Z = 0) = 0.08/0.01 = 8$

Expected RR for X and Z: RR for X alone x RR for Z alone = 4 X 2 = 8

Tab 3, Problem 1

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

RD for X alone (Z=0): 0.03
RD for Z alone (X=0): 0.01
Observed RD for X and Z: 0.07
Expected RD for X and Z: 0.04

RR for X alone (Z=0): 4
RR for Z alone (X=0): 2
Observed RR for X and Z: 8
Expected RR for X and Z: 8

f. What do you conclude about the presence of statistical interaction on the relative scale?

The observed joint RR is the same as the expected RR for both X and Z, suggesting that there is no relative scale interaction.

Tab 3, Problem 1

P(Y|X=1, Z=1) = 0.08
P(Y|X=1, Z=0) = 0.04
P(Y|X=0, Z=1) = 0.02
P(Y|X=0, Z=0) = 0.01

RD for X alone (Z=0): 0.03
RD for Z alone (X=0): 0.01
Observed RD for X and Z: 0.07
Expected RD for X and Z: 0.04

RR for X alone (Z=0): 4
RR for Z alone (X=0): 2
Observed RR for X and Z: 8
Expected RR for X and Z: 8

g. Calculate $RR_{11} / (RR_{10} \times RR_{01})$. Interpret the resulting value. If interaction is present, what kind? Be as specific as possible.

The observed joint RR is the same as the expected RR for both X and Z, suggesting that there is no relative scale interaction.

Defining a measure of interaction on the relative scale

If the **exposures are harmful** (increase risk of disease):

- If $RR_{11} / (RR_{10} \times RR_{01}) > 1$ interaction is positive or "super-multiplicative"
- If $RR_{11} / (RR_{10} \times RR_{01}) = 1$ no interaction is present
- If $RR_{11} / (RR_{10} \times RR_{01}) < 1$ interaction is negative or "sub-multiplicative"

Tab 3, Problem 2

The study of whether prenatal zinc supplementation and vitamin A supplementation reduce the risk of low birth weight reported the following results:

RR for prenatal zinc alone: 0.75
RR for vitamin A alone: 0.50
RR for both: 0.20

a. Was interaction present on the relative scale? If so, which direction is it in?

Expected: RR for both = RR for zinc alone x RR for vitamin A alone = 0.75*0.50 = 0.375
Observed: RR for both = 0.20
$RR_{11} / (RR_{10} \times RR_{01}) = 0.20 / (0.75 \times 0.50) = 0.53$

Yes, the expected joint RR (0.375) is less (closer to the null) than the observed joint RR (0.375), so interaction is present on the relative scale.
The joint observed effect of prenatal zinc and prenatal vitamin A supplementation is greater (more beneficial, ie, less low birth weight) than the expected joint effect. Because $RR_{11} / (RR_{10} \times RR_{01}) < 1$ and **the interventions are preventive,** we conclude that there is positive interaction on the relative scale.

Tab 3, Problem 2

The study of whether prenatal zinc supplementation and vitamin A supplementation reduce the risk of low birth weight reported the following results:

RR for prenatal zinc alone: 0.75
RR for vitamin A alone: 0.50
RR for both: 0.20

b. Even though the study only reported RRs, you want to assess whether interaction occurred on the additive scale. Use the appropriate formula to assess whether interaction is present on the additive scale. If so, which direction is it in?

$RERI = RR_{11} - RR_{10} - RR_{01} + 1 = 0.20 - 0.75 - 0.50 + 1 = -0.05$

Because the **interventions are preventive** and the RERI<0, we conclude that there is positive interaction on the additive scale.

Defining a measure of interaction on the additive scale

For **harmful exposures** that increase the risk of disease:

- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 > 0$ interaction is positive or "super-additive"
- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 = 0$ no interaction is present
- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 < 0$ interaction is negative or "sub-additive"

For **preventive exposures** that decrease the risk of disease:

- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 < 0$ interaction is positive or "super-additive"
- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 = 0$ no interaction is present
- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 > 0$ interaction is negative or "sub-additive"

The Vanderweele & Knol 2014 paper includes a derivation for the odds ratio as well.

The paper also includes example code for estimating the RERI and obtaining standard errors for the RERI.

Vanderweele & Knol 2014

Agenda

- **Effect measure modification and interaction overview**
- **Practice problems**
- **Q & A**