Mental Health and Sex-based Research

Week 10

Objectives

1. Comprehend effect modification and calculate unbiased estimates

2. Distinguish between confounding and effect modification

3. Describe issues surrounding gender and mental health

4. Understand basic tenants of sex-based research

Confounding Review

Criteria

1. Correlated with your exposure of interest

2. A risk factor for the disease (outcome)

3. Not an intermediate in the causal pathway

How to control

- By design: Randomization, Restriction, Matching

- In analysis: Matched, Stratification, Multivariate regression

How to assess

- Compare CRUDE and ADJUSTED relative risks (weighted from STRATUM-SPECIFIC relative risks)

How to present

- Show adjusted results or both

Crude Analysis

Disease

Exposure

	Yes	**No**	
Yes	a	b	a+b
No	c	d	c+d
	a+c	b+d	

RR_{crude}

Stratified Analysis by Level of Confounding Factor(s)

Stratum 1
Disease

Exposure

	Yes	**No**	
Yes	a	b	a+b
No	c	d	c+d
	a+c	b+d	

$RR_{stratum1}$

Stratum 2
Disease

Exposure

	Yes	**No**	
Yes	a	b	a+b
No	c	d	c+d
	a+c	b+d	

$RR_{stratum2}$

$RR_{adjusted}$

Confounding: RR_{crude} vs $RR_{adjusted}$

Effect Modification

- Does the magnitude of the overall association observed apply to everyone? Does the magnitude of the effect "depend" on what type of people you are referring to? If so, this is effect modification.

- When the overall magnitude of the relationship between the exposure and disease depends (differs, is modified) in size or even direction by the level of a third variable (called the effect modifier).

OC Effect Modification Example

"Do not use YAZ if you smoke and are over age 35. Smoking increases your risk of serious side effects from the Pill, which can be life-threatening, including blood clots, stroke or heart attack. This risk increases with age and number of cigarettes smoked."

Effect Modification vs Confounding

Effect modifier is a factor that modifies (alters) the relationship between the exposure and disease.

- Not a nuisance/not a threat to validity

- Provides insight into the nature of the biologic relationship between exposure and disease

- Do not want to control for effect modification – want to explore and report

Effect Modification vs Confounding

Confounder is a factor which because of its relationship with the exposure and disease of interest in the population under study will distort the RR relating exposure to disease.

- Will depend on the relationships of the factors in your study

- Confounding is a nuisance factor, not some biologic insight into the relationship/threat to validity of study

- You need to remove the effect of the confounder to understand the exposure/disease relationship – want to control for confounding

Effect Modification vs Confounding

Confounding and effect modification are independent concepts.

But in an analysis of an exposure-disease relationship, the same third variable can be:

- A confounder

- An effect modifier

- Both

- Neither

Detecting Effect Modification and Confounding

- To assess/control confounding, compare crude to adjusted estimate, report adjusted.

- To assess effect modification, compare stratum-specific estimates of the measure of effect, and if different, report and discuss.

Crude Analysis

Disease

	Yes	**No**	
Exposure **Yes**	a	b	a+b
No	c	d	c+d
	a+c	b+d	

RR_{crude}

Stratified Analysis by Level of Confounding Factor(s)

Stratum 1
Disease

	Yes	**No**	
Exposure **Yes**	a	b	a+b
No	c	d	c+d
	a+c	b+d	

$RR_{stratum1}$

Stratum 2
Disease

	Yes	**No**	
Exposure **Yes**	a	b	a+b
No	c	d	c+d
	a+c	b+d	

$RR_{stratum2}$

$RR_{adjusted}$

Confounding: RR_{crude} vs $RR_{adjusted}$

Effect Modification: Compare stratum-specific RRs (RR_1 vs RR_2 vs . . . RR_n)

OC Effect Modification Examples

If told that OCs may be associated with having a myocardial infarction…

Crude (Overall) RR = 2.0

RR adjusted for smoking and drinking = 2.0

Conclude: No confounding by smoking or drinking status

$RR_{drinkers}$ = 2.0

$RR_{non-drinkers}$ = 2.0

Conclude: No effect modification by drinking status

$RR_{smokers}$ = 41.0

$RR_{non-smokers}$ = 1.9

Conclude: Effect modification by smoking status

How different is different?

Can use statistical testing, such as Breslow-Day test.

- Interaction terms in multivariate modeling

- $y = intercept + b1(X1) + b2(X2) + b3(X1X2)$

Compare stratum-specific estimates and determine if the public health message would differ between stratum.

Presenting Effect Modification Results

- Best option: Present stratum-specific results, in addition to overall association – not just overall association alone.

- Single RR cannot reflect different effects in different stratum

Effect Modification Review

Definition

- Effect is different depending on the level of third variable

    - e.g. sex being male or female

- Often implies a biologic interaction

How to assess

- Compare the STRATUM-SPECIFIC relative risks

How to present

- Show stratified results

    - e.g. separate effect for men and effect for women

Applying Confounding and Effect Modification

For variable 1-3 in the table below, select the best answer from the following (answers can be used more than once):

A) Confounding

B) Effect modification

C) Combination of two of the above

D) No apparent confounding or effect modification

	Variable 1	Variable 2	Variable 3
Crude OR	4.0	4.0	4.0
OR$_{stratum\ 1}$	3.0	1.0	1.0
OR$_{stratum\ 2}$	3.0	6.0	6.0
Adjusted OR	3.0	2.3	4.0
Illustrates:	?	?	?

Applying Confounding and Effect Modification

Variable 1: A—Confounding

No effect modification, Adjusted OR is greater than 10% different than the crude (confounding)

Variable 2: C—Both effect modification and confounding

As with variable 2, ORs of 1.0 and 6.0 are quite different (effect modification)

Additionally, the crude and adjusted ORs are more than 10% different (confounding)

Variable 3: B—Effect modification

An OR of 1.0 (null) in stratum 1 is different from the large OR of 6.0 in stratum in 2.

Adjusted OR is a plausible weighted average of the stratum-specific OR (no obvious calculation error) and it is the same as the crude OR (so no confounding…)

	Variable 1	Variable 2	Variable 3
Crude OR	4.0	4.0	4.0
OR$_{stratum\ 1}$	3.0	1.0	1.0
OR$_{stratum\ 2}$	3.0	6.0	6.0
Adjusted OR	3.0	2.3	4.0
Illustrates:	?	?	?

Confounding and Effect Modification Exercise

Question 1

Age < 40
OC Use

	Case	Control	
User	17	121	
Non-User	47	944	
Total	64	1065	1129

Age 40 - 44
OC Use

	Case	Control	
User	6	9	
Non-User	65	362	
Total	71	371	442

Age 45-49
OC Use

	Case	Control	
User	6	5	
Non-User	93	301	
Total	99	306	405

1a. Calculate and Interpret Stratum-Specific

Calculate and interpret the appropriate stratum-specific measures of association.

$$OR_{age<40} = (17*944)/(121*47) = 2.82$$

Among women who are younger than 40, women who are OC users have 2.82 times the odds of having a MI compared to women who are not OC users.

$$OR_{age\ 40\text{-}44} = (6*362)/(9*65) = 3.71$$

Among women between the ages of 40 and 44, women who are OC users have 3.71 times the odds of having a MI compared to women who are not OC users.

$$OR_{age\ 45\text{-}49} = (6*301)/(5*93) = 3.88$$

Among women between the ages of 45 and 49, women who are OC users have 3.88 times the odds of having a MI compared to women who are not OC users.

1b. Calculate and Interpret Crude

Combine the data into a single table and calculate and interpret the crude odds ratio from that table.

Crude Data

OC Use	Case	Control
User	29	135
Non-User	205	1607
Total	234	1742

OR = (29*1607)/ (135*205) = 1.68

Women who are OC users have 1.68 times the odds of having a MI compared to women who are not OC users.

1c. Calculate and Interpret Age-Adjusted

Using the Mantel-Haenszel weighting formula, calculate and interpret the age-adjusted odds ratio.

$$OR_{MH} = \frac{\sum a_i d_i / T_i}{\sum b_i c_i / T_i} = \frac{\left(\frac{(17*944)}{1129}\right) + \left(\frac{(6*362)}{442}\right) + \left(\frac{(6*301)}{405}\right)}{\left(\frac{(47*121)}{1129}\right) + \left(\frac{(65*9)}{442}\right) + \left(\frac{(93*5)}{405}\right)} = 3.14$$

After adjusting for age, women who are OC users have 3.14 times the odds of having a MI compared to women who are not OC users.

1d-f. Interpretation

Is age a confounder? Why or why not?

Is age an effect modifier? Why or why not?

Summarize your overall findings in a few sentences.

1d-f. Interpretation

Is age a confounder? Why or why not?

- Yes. The odds of developing an MI increases with age among the non-users of OC (Age <40: Odds=47/944=0.05, Age 40-44: Odds=65/362=0.18, Age 45-49: Odds=93/301=0.31). The odds of OC use decreases with age among the controls (Age <40: Odds=121/944=0.128, Age 40-44: Odds=9/362=0.025, Age 45-49: Odds=5/301=0.010). Therefore, age is associated with the exposure and age is associated with the outcome.

- Moreover, the crude odds ratio (1.68) is substantially different from the age-adjusted odds ratio (3.14).

Is age an effect modifier? Why or why not?

Summarize your overall findings in a few sentences.

1d-f. Interpretation

Is age a confounder? Why or why not?

- Yes.

Is age an effect modifier? Why or why not?

- Yes, age is an effect modifier.

- While the stratum-specific odds ratios for women 40-44 years of age and 45-49 years of age appear similar (OR=3.71 and 3.88 respectively), they are different from the odds ratio for women less than 40 years of age (OR=2.82).

- Since the effect of OC user on the odds of developing an MI differs for women less than 40 years of age versus those over 40 years of age, we do have effect modification by age.

Summarize your overall findings in a few sentences.

1d-f. Interpretation

Is age a confounder? Why or why not?

- Yes.

Is age an effect modifier? Why or why not?

- Yes.

Summarize your overall findings in a few sentences.

- The crude odds ratio shows that women who use OCs have 1.68 times the odds of having an MI compared to women who do not use OCs.

- Since there was evidence of confounding by age, we also performed an age-adjusted analysis and found that after adjusting for age, women who use OCs have 3.14 times the odds of having an MI compared to non-users.

- Finally, we assessed whether or not there was effect modification by age. We did find evidence of effect modification by age. Among women 40 years of age or older, OC users have over 3.7 times the odds of having an MI compared to non-users. In contrast, among women aged <40, OCs users only have 2.82 times the odds of having an MI compared to non-users.

Question 2

- In a cohort study of the association between obstructive sleep apnea (OSA) and the incidence of stroke among men, the crude incidence rate ratio was 5.1.

- In these data, obese men are more likely to have OSA than non-obese men and obesity is a cause of stroke even in the absence of OSA.

- After stratifying on obesity, the incidence rate ratio for the OSA-stroke association was 7.5 among obese men and 3.7 among non-obese men.

2a. Confounder

Is obesity a confounder of the association between OSA and stroke? Why or why not?

- Yes, obesity is associated with our exposure (OSA) and obesity is a risk factor for our outcome (stroke) even in the absence of our exposure (OSA).

- Additionally, obesity is not on the causal pathway between OSA and stroke.

2b. Effect Modification

Is obesity an effect modifier of the association between OSA and stroke? Why or why not?

- Yes, the RR among obese men is different from the RR among non-obese men.

2c. Presenting Results

If effect modification is present, how should we present our results?

- Report stratum-specific incidence rate ratios (within strata of obese and non-obese).

Question 3

- We conducted a study to investigate if **swimming in the upper deck** of a cruise ship swimming pool increases the risk of developing **Norwalk virus** gastroenteritis compared to those who did not swim in the upper deck pool.

- We found that those who swam in the upper deck pool at a **two-fold increased** risk of developing Norwalk virus gastroenteritis compared to those who did not swim in the pool.

- However, the cruise ship owners said that the results were **invalid** because of the age differences between the people who swam in the upper deck pool and those who did not. Those who swam in the upper deck pool were younger than those who did not swim in the upper deck pool.

Question 3

Given that younger age is associated with swimming in the upper deck pool, what other characteristic(s) does age need to have, in order to be a confounder of the association between swimming in the upper deck pool and gastroenteritis?

- Age would also need to be a risk factor for Norwalk virus gastroenteritis.

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