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The Impact of Other Factors: Confounding, Mediation, and Effect Modification

Amy Yang

Senior Statistical Analyst
Biostatistics Collaboration Center

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Biostatistics Collaboration Center | 680 N. Lake Shore Drive, Suite 1400 | Chicago, IL 60611

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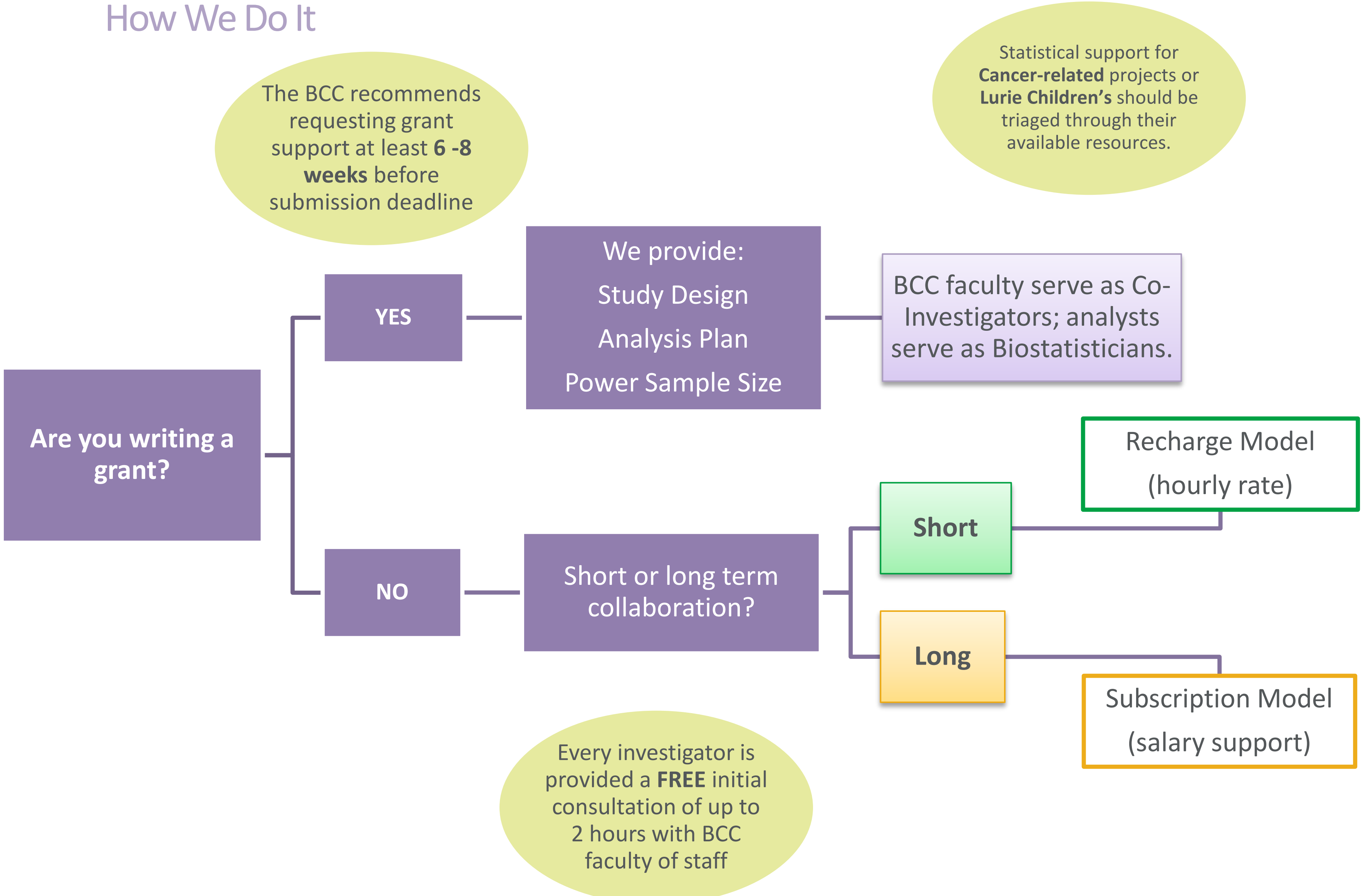

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Outline

- Confounding
  - Concept and definition
  - Identifying confounding
  - Quantifying confounding
  - Controlling confounding

- Mediation

- Effect Modification
  - Definition and examples
  - Confounding vs Effect Modification

Confounding--Example

- Cohort study -- Smoking and heart disease (HD)

- Suppose that the incidence of HD for smokers is twice that of non-smokers (Risk Ratio=2.0)

Confounding--Example

Smoking doubles your risk of getting heart disease

Before we can make a causal statement…

Rule out alternative explanations:

Chance, Bias, **Confounding**

Confounding--Example

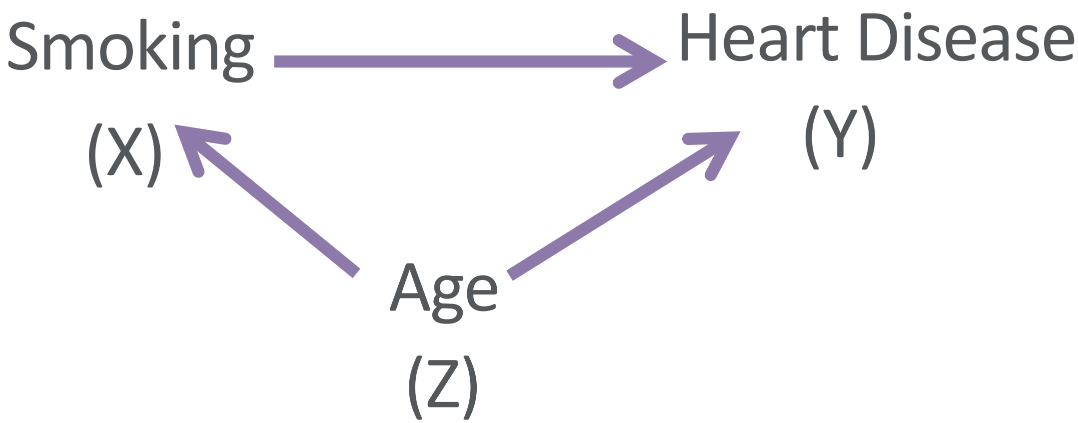
- Suppose that the smokers are much older than the non-smokers

- We know that age is a risk factor for heart disease

  - Implies the RR=2 is really reflecting the mixture of two effects (Older age and smoking)

- **Age** is a confounder in the study of association between smoking and HD

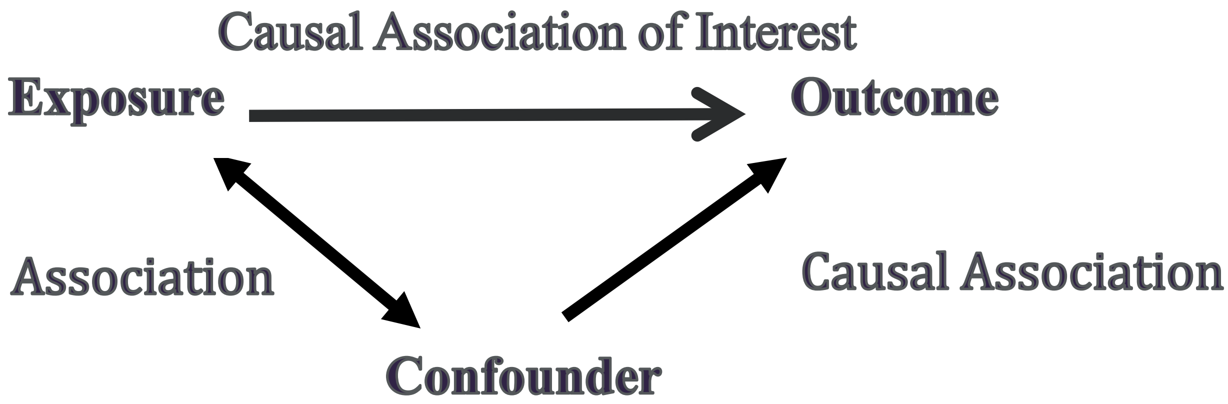
Confounding--Example



- Two pathways
  - Direct effect of smoking
  - Backdoor pathway through age → non-comparability

- **Confounding = Existence of backdoor pathway**

Confounding



Three properties of confounder:

- Should related to the exposure
- Should be an **independent** determinant of the outcome
- Should **not** be part of causal pathway from exposure to outcome
- Often taken as a **definition of a confounder**

Identifying Confounding

- **Not Recommended**
  - Approaches that are based *only* on statistical associations observed in study data

  e.g. Automated procedures (stepwise regression)

- **Recommended**
  - Three properties + knowledge/assumptions about causal relationships among variables
  - Study data are used to quantify confounding

What is not a Confounder--Example

Chemical X → Cognitive disability

- It turns out there are more blondes in the chemical X exposed group

Exposed

Non-Exposed

- **Question**: Is **hair color** a confounder?(Are blondes really…dumber?)
- Hair color is not a confounder, because hair color is not a risk factor for cognitive disability

Quantifying and Controlling Confounding in the Analysis

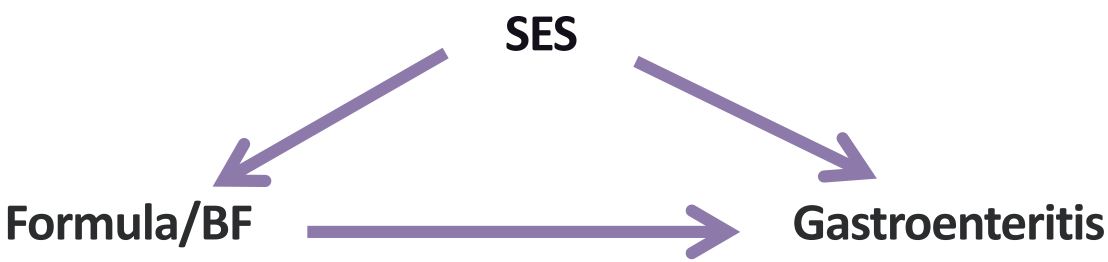
- Comparing the “crude” measure of association with the “adjusted” measures of association
- Stratification
  - Pooling (Weighted Averaging)
- Modeling

Example:

- Hypothetical case-control study examining the association between **formula vs. breastfeeding** and **gastroenteritis** among infants

Example:

- Concern about socioeconomic status (SES) as a confounder



- **Check the three properties:**

  1. SES affects whether people formula or breastfeed
  2. SES affects the outcome through the degree of crowding and hygiene issues
  3. SES is not in the pathway between feeding methods and Gastroenteritis

Quantifying and Controlling Confounding in the Analysis

- 1. Crude association -- OR=(261*296)/(645*54)=2.22

Gastroenteritis

	Yes	No
Formula	261	645
Breastfeedin g	54	296

- 2. Stratify by confounder –SES

Low SES	Yes	No
Formula	219	447
Breastfeedin g	33	118

High SES	Yes	No
Formula	42	198
Breastfeedin g	21	178

- Positive confounder because crude OR 2.2 was larger than the stratified ORs 1.75 and 1.80

Quantifying and Controlling Confounding in the Analysis

- 3. Pooling (weighted averaging) –adjusted association
  - **If appropriate**, pool information over all strata by calculating (weighted) average of stratum specific measures
  - Assumption: constant effect across strata

OR_{LOW} =1.75 OR_{HIGH}=1.80

$OR_{adjusted}$

- Mantel-Haenszel weights
  - Reflect amount of "information" within each stratum
  - Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease JNCI 22: 719-748, 1959

Mantel-Haenszel Estimation

- Case control data:

Low SES	Yes	No
Formula	219	447
Breastfeedin g	33	118

High SES	Yes	No
Formula	42	198
Breastfeedin g	21	178

$$OR_{MH} = \frac{\sum w_i OR_i}{\sum w_i} = \frac{\sum_{i=1}^{k} (ad / Total)_i}{\sum_{i=1}^{k} (bc / Total)_i} = \frac{\frac{291*118}{817} + \frac{42*178}{439}}{\frac{447*33}{817} + \frac{198*21}{439}} = 1.77$$

$OR_{LOW} = 1.75$ $OR_{HIGH} = 1.8$

$OR_{adjusted} = 1.77$

Modeling

- Stratification and MH estimation are equivalent to…
  - Calculating an unadjusted measure of association from a model

    Gastroenteritis ~ **b1***Formula/BF

  - Examining the measure of association after including the confounder in the model

    Gastroenteritis ~ **b1'***Formula/BF + b2*SES

Preventing Confounding in Study Design

- Confounding is a **bias**
- We want to **prevent** in the conduct of the study and **remove** once we determine that it is present
- Study design strategies:
  - Randomization
  - Matching
  - Restriction

Preventing Confounding in Study Design

Randomization

- Subjects are allocated to exposure groups by a random method

- Gives subject **equal chance** of being in any exposure group

- Exposure groups will have similar distribution of
  - Age, gender, behavior …

- This includes both measured and unmeasured confounders
- Depending on the trial, confounders may still need to be considered in analysis (especially when n is small)

Preventing Confounding in Study Design

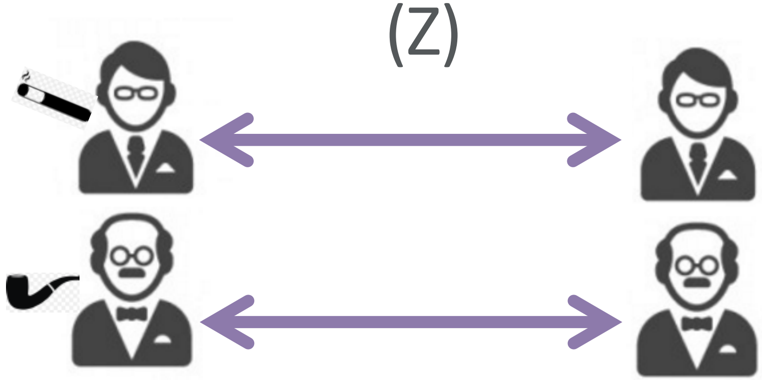
Matching

- On important potential confounders

Smoking (X) → Heart Disease (Y)

Age (Z) → Smoking (X)

Age (Z) → Heart Disease (Y)



30-40 years old

40-50 years old

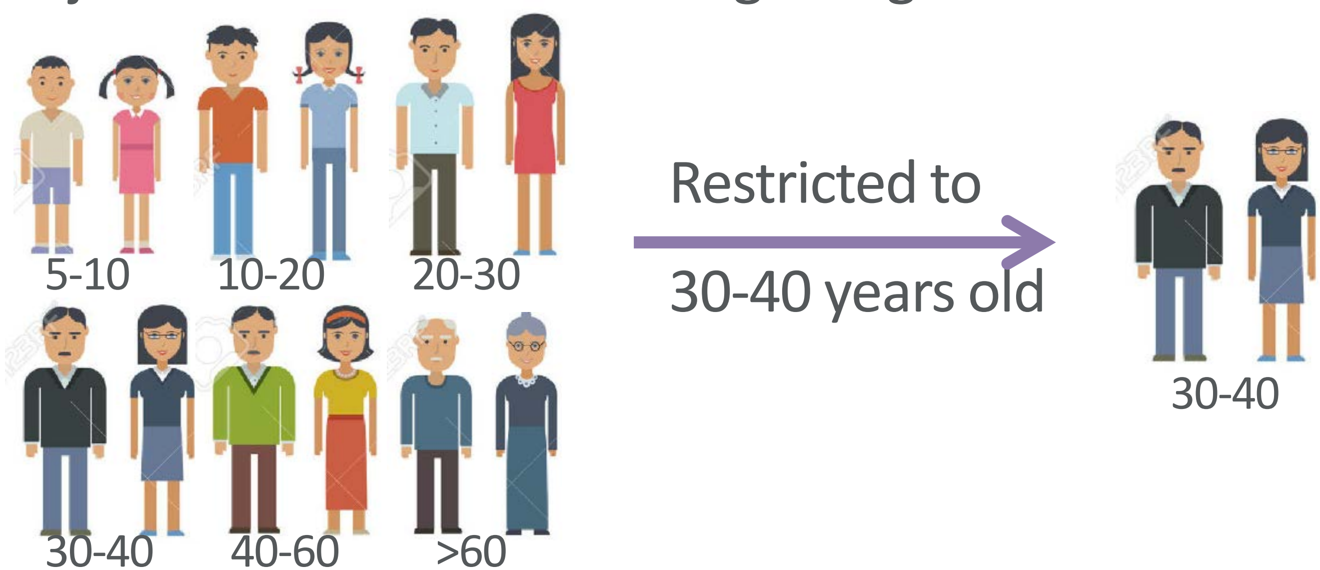
...

- Smoking and Non-Smoking groups are similar with respect to Age
- Analyses must account for matching

Preventing Confounding in Study Design

Restriction

- Restrict admission into the study to subjects who have the same level of the confounding factor
- E.g., Confounding by **Age** could be minimized by enroll subjects that are in the same age range



- **Be careful! Restriction limits generalizability**

Summary -- Confounding

- Three properties

- Control for confounding in the analysis
  - Stratification
  - MH estimation
  - Modeling

- Design strategies to prevent confounding
  - Randomization
  - Matching
  - Restriction

Mediation

- Confounder should *not* be in the pathway between the exposure and outcome
- If the other variable is in the pathway between the two, it is called a mediator

$$X \rightarrow Z \rightarrow Y$$

Mediation

Poverty

Limited access to healthy food

Diabetes

Mediation

Multiple sexual partners

Increased risk of HPV infection

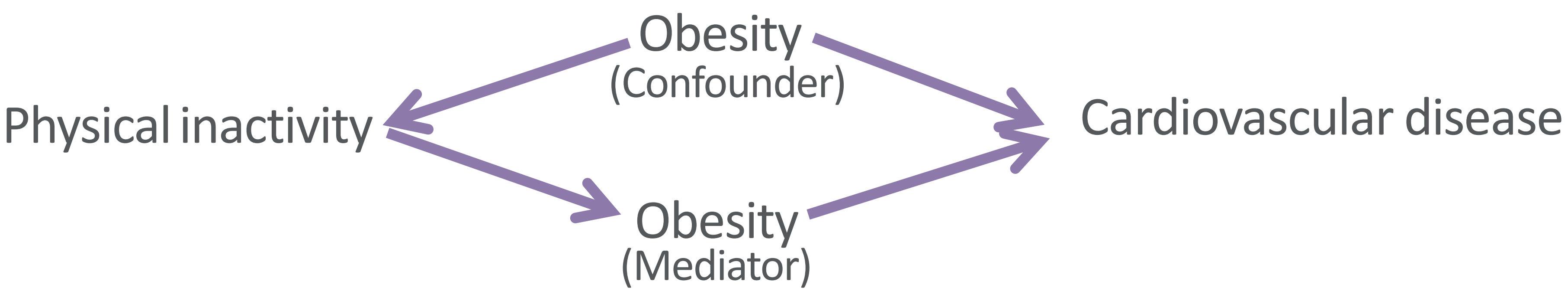
Cervical cancer

Mediation

- It is difficult to distinguish confounder and mediator **statistically**

- They should be separated from each other based on an **understanding of disease process**

- A variable can act partially as a confounder and partially as a mediator



Mediation

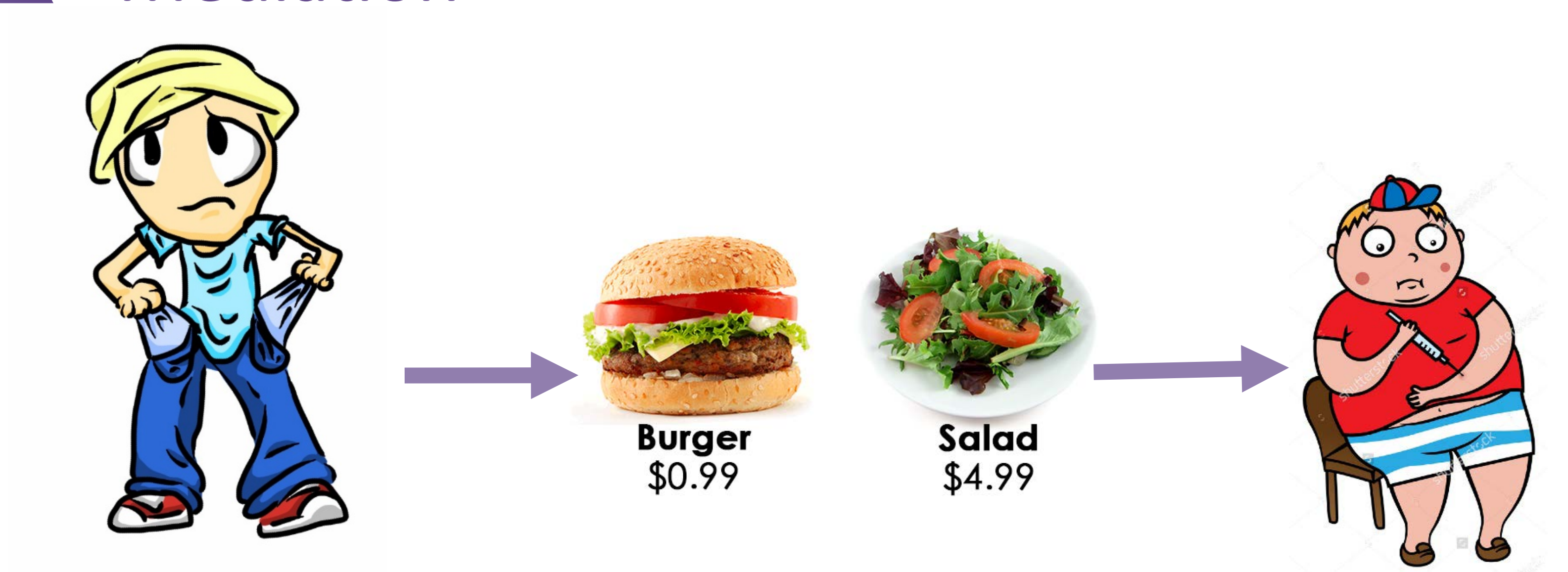
- **Question** : Should we adjust for mediators, as we do for confounders?
- We can, but the meaning of this adjustment is different

- Before adjustment, we have the **total effect** of the potential risk factor on the outcome

- After adjustment, we have the **remaining effect** of the risk factor after the partial effect of that mediator is considered

- **Remaining effect will be smaller than total effect**

Mediation



Poverty | Limited access to healthy food | Diabetes

- If we do not adjust for the mediator
  - Crude OR = 2.4; **Total effect** of poverty on diabetes
- If we adjust for eating unhealthy food
  - OR_{adjust}=1.6; **Remaining** effect of poverty on diabetes

Effect Modification (Interaction)

- Effect modification is present when the measure of association between X and Y **varies** across a third variable (Z)

- **Gender** modifies the effect of **marital status** on health outcomes

J Epidemiol Community Health 2000;**54**:254-261 doi:10.1136/jech.54.4.254

Research report

Marital status and suicide in the National Longitudinal Mortality Study

Abstract

OBJECTIVES The purpose of the study was to examine the effect of marital status on the risk of suicide, using a large nationally representative sample. A related objective was to investigate the association between marital status and suicide by sex.

RESULTS For the entire sample, higher risks of suicide were found in divorced than in married persons. Divorced and separated persons were over twice as likely to commit suicide as married persons (RR=2.08, 95% confidence intervals (95% CI) 1.58, 2.72). Being single or widowed had no significant effect on suicide risk. When data were stratified by sex, it was observed that the risk of suicide among divorced men was over twice that of married men (RR=2.38, CI 1.77, 3.20). Among women, however, there were no statistically significant differentials in the risk of suicide by marital status categories.

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Effect Modification

- Conceptualization of effect modification
  - Approach one

  The "effect" of variable X on Y is not the same across levels of variable Z

  Divorced → Suicide → Men RR=2.38
  Divorced → Suicide → Women RR=1 no association

  - Approach two

  The "effect" of variables X and Z on Y combined is larger or smaller than you would expect given the "effect" of each on Y individually

  $$Y=X+Z+X*Z$$

- Mathematically these two approaches are the same

Confounding vs Effect Modification

- Stratification is a step in the process of **adjusting for confounding**
    - Bias we want to remove

- Stratification is a step in the process of **describing effect modification**
    - We want to describe effect modification

Confounding vs Effect Modification

Crude association

Stratum specific association Stratum specific association

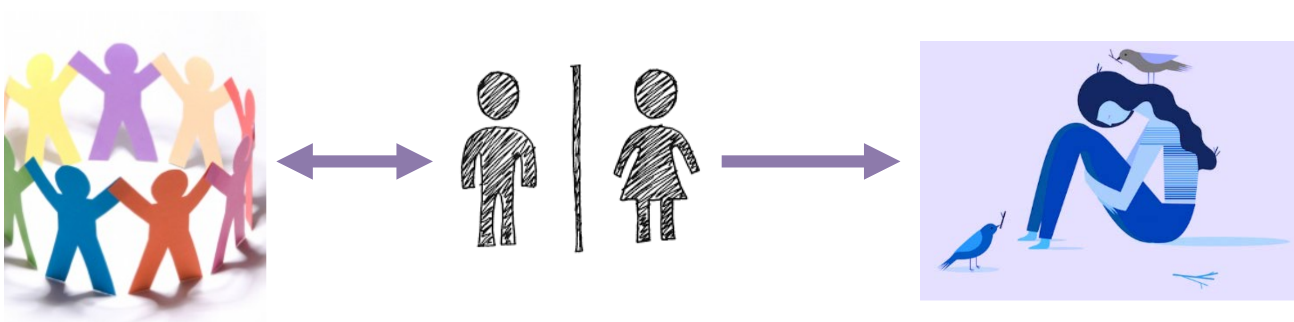
Adjusted association

- Confounding
  - Association is **similar** in different strata of Z
  - Compare the adjusted association with the crude association

- Effect modification
  - Association is **different** in different strata of Z
  - Compare associations across strata

Confounding vs Effect Modification

- A factor could be confounder and/ or modifier
- Example: Study of relation between social support and depression



Road Map

- 1. Calculate the crude measure of association
- 2. Stratify the data by the potential confounder/ effect modifier
- 3. Calculate the stratified measure of association
- 4. Compare 3 using the **Test for Homogeneity** (**Breslow-Day Test**)
- 5. Are the associations homogeneous?

Yes
(i.e. did not reject H0)

- 6. Calculate the adjusted measure of association – **Mantel-Haenszel estimation**
- 7. Compare 6 and 1 to describe direction and magnitude of the confounding

No
(i.e. rejected H0)

6. Present measures of association stratified by effect modifier

Road Map Step 1

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

Incident depression

	Yes	No	Total
Low social support	191	7909	8100
High social support	50	7550	7600
Total	241	15459	15700

Risk ratio = (191/8100)/(50/7600)=3.6

Road Map Step 2 & 3

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

Incident depression

Men	Yes	No	Total
Low social support	26	2574	2600
High social support	18	3582	3600
Total	44	6156	6200

Incident depression

Women	Yes	No	Total
Low social support	165	5335	5500
High social support	32	3968	4000
Total	197	9303	9500

easure

RR_{Men}= (26/2600)/(18/3600)=2

RR_{Women}= (165/5500)/(32/4000)=3.75

Road Map Step 4

- 4. Compare the RRs using the **Test for Homogeneity** (**Breslow-Day Test**)
  - Equivalent to test statistics for interaction term in regression model
  - Null hypothesis: the measure of association is homogeneous across strata

- If the test of homogeneity is “significant”
  - Reject homogeneity
  - Evidence for heterogeneity (i.e. effect modification)

- The choice of significant level (e.g. $p<0.05$) is open to interpretation
  - One “conservative” approach is using significant level of larger than 0.05 (maybe 0.10 or 0.20)

Road Map Step 5 & 6

- In our example χ^2=3.08, DF=1, P=0.08
- 5. **Question**: Does it appear we have homogeneous association (H0: Association the same across strata)?
- Assume we used conservative 10% level of significance…
- No ($p=0.08<0.10$)
- Reject H0; we have evidence of effect modification

- 6. Present measures of association stratified by gender

$RR_{MEN}= 2$ $RR_{WOMEN}=3.75$

Exercise

- X-Y association stratified by potential confounder/EM Z

Z=0	Z=1	Crude	Adjusted	Confounding?	EM?
4	0.25	1	1		√
1	1	8.4	1	√	
4	0.25	1	2	√	√

Adjusted estimate not relevant – present stratified associations when there is effect modification

Properties of Stratification

- Pro:
  - Simple and intuitive

- Con:
  - Not practical when there are multiple factors
  - With continuous variables (e.g. age) have to create categories
  - In these situations, regression models have many strengths

Summary

- Other variables in a study can be
  - Confounders
    - Bias
    - Prevent in study design
    - Adjust for in analysis
  - Effect modifiers
    - Personalized medicine; effects in a subgroup
    - Stratify and report
  - Mediators
    - X→Z→Y

Statistically Speaking …

What's next?

Tuesday, October 18	**Statistical Power and Sample Size: What You Need and How Much** **Mary Kwasny, ScD**, Associate Professor, Division of Biostatistics, Department of Preventive Medicine
Friday, October 21	**Clinical Trials: Highlights from Design to Conduct** **Masha Kocherginsky, PhD**, Associate Professor, Division of Biostatistics, Department of Preventive Medicine
Tuesday, October 25	**Finding Signals in Big Data** **Kwang-Youn A. Kim, PhD**, Assistant Professor, Division of Biostatistics, Department of Preventive Medicine
Friday, October 28	**Enhancing Rigor and Transparency in Research: Adopting Tools that Support Reproducible Research** **Leah J. Welty, PhD,** BCC Director, Associate Professor, Division of Biostatistics, Department of Preventive Medicine

All lectures will be held from noon to 1 pm in Hughes Auditorium, Robert H. Lurie Medical Research Center, 303 E. Superior St.