Stratified Analysis for the Control of Confounding

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Review

	Case	Control
Exposed	A	B
Not exposed	C	D

Review

Odds ratio = A D / B C

Alternative Explanations

- **Chance**
- **Bias**
- **Confounding**

See: Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston: Little, Brown and Company, 1987.

What is Confounding?

- **A mixing of the effect of the exposure under study on the disease with that of a third factor**

Confounder

- **A factor which is associated with the exposure variable, and independent of the exposure, is related to the outcome/disease (that is, it's a risk factor for the outcome)**

Example 1

- **Study finds that coffee drinkers are more likely to have a heart attack in the next year than those who don't drink coffee. But what if those coffee drinkers were more likely to be smokers than those who didn't drink coffee? Was the association between coffee consumption and the risk of heart attacks confounded by smoking?**

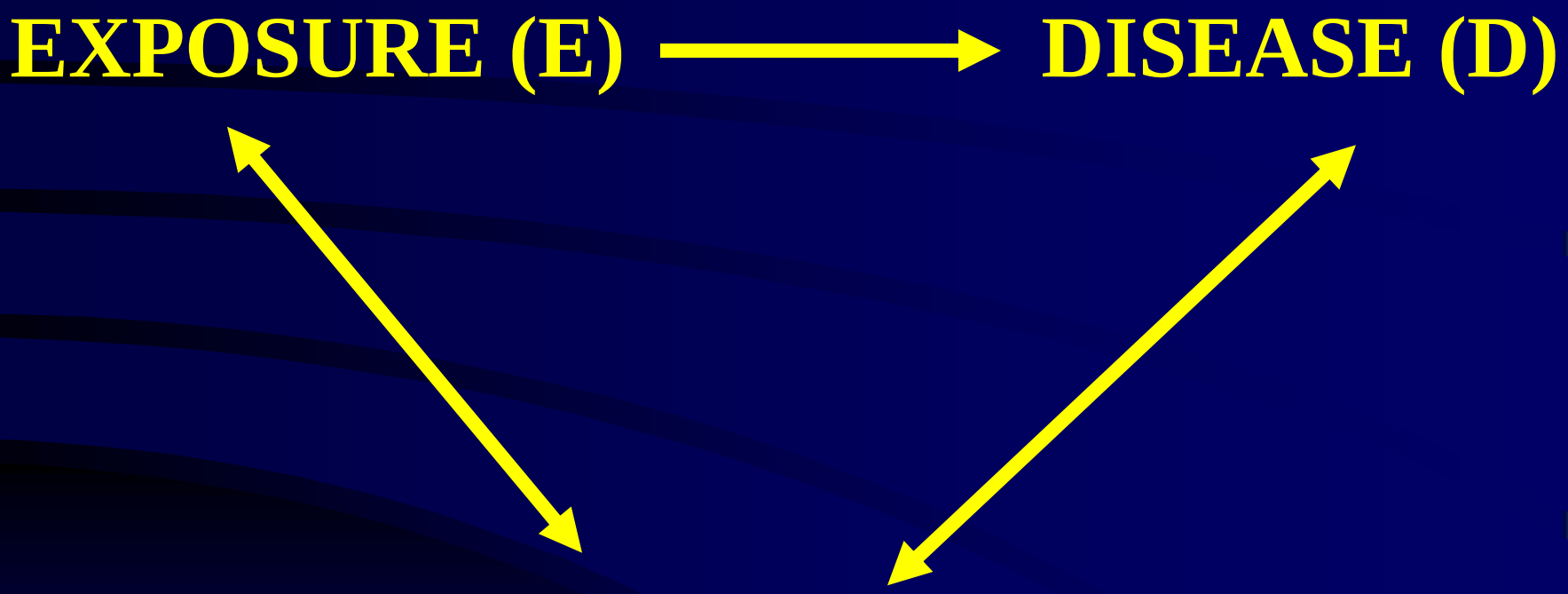
Example 2

- **Study finds that adults in Town A have a higher incidence of some cancer than adults in nearby Town B. Town A has a toxic waste dump. Can we blame the excess risk of this particular cancer in Town A on exposure to the toxic waste dump?**

- **What if Town A is a retirement town with an average age of 85 years while Town B's average age is 20 years? Older individuals have a higher risk of several malignancies versus younger individuals.**

- **Maybe the association between geographical location and cancer risk is confounded by age!**

Interrelationship



The Potential Confounder Cannot be a Variable that is on the Causal Pathway

Popular Methods to Control for Confounding

- **Randomization**
- **Matching**
- **Restriction**
- **Multivariate modeling**
- **Stratified analysis**

Stratified Analysis

- **A technique to control confounding in the analysis of a study that involves the evaluation of the association within homogeneous categories or strata of the confounding variable.**

Stratified Analysis

- **Let's say Gender was a confounder**
- **Calculate odds ratio (OR) for men and women separately**

Stratified Analysis

- **Both ORs would be unconfounded by gender since there is NO VARIABILITY of the confounding variable within each stratum**

Stratification

- **Stratify on the confounder**
- **Examine stratum-specific ORs**
- **Examine crude (overall) OR**

Stratification

- **If stratum-specific ORs are similar to one another…**
- **but different than the crude OR, then you may have confounding**

Stratification (cont.)

- **If confounding present, calculate a summary measure of association: Mantel-Haenszel OR**

Mantel-Haenszel Odds Ratio

- **An unconfounded measure of association**
- **It's a weighted average of the stratum-specific ORs**

History

- **Nathan Mantel and William Haenszel**
- **“Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease”**
- ***Journal of the National Cancer Institute*, 1959; 22: 719 - 748**

History

- **Very famous paper!**

- **Highly cited paper in the scientific literature**

Mantel-Haenszel (M-H) Odds Ratio

$$(\Sigma \ AD / T) / (\Sigma \ BC / T)$$

- M-H formula not affected by zero cell entries
- It will give a consistent estimate of the Common Odds Ratio even with large numbers of small strata

Mantel-Haenszel Odds Ratio

- **Is this association, after adjusting for confounding, likely due to random chance?**

- **Mantel-Haenszel chi-square & test-based CI, etc.**

Mantel-Haenszel Odds Ratio

- More on interval estimation later…

A mathematical definition of confounding

- **The crude (unadjusted) measure of association does not equal the adjusted measure of association:**

  Crude OR ≠ Adjusted OR

- **Change-in-estimate method, say 10% rule**

A mathematical definition of confounding (continued)

- **If the adjusted OR deviates from the crude OR by more than 10% then some researchers would say that confounding is present**

- **Reference: Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989; 79: 340-349.**

Change-in-Estimate Method Using a 10% Change

Crude OR = 1.50

10% of 1.50 is 0.15

1.50 + 0.15 is 1.65 and 1.50 – 0.15 is 1.35

If adjusted OR <1.35 or >1.65 then control for that variable

IMPORTANT!

- **Assessment of confounding not a statistical issue**

- **Don’t examine p-values to see if there is a statistically-significant association between E and C, or C and D**

IMPORTANT!

- **Statistical significance is a function of**
  - **Strength of the association / Difference**
  - **Sample size!!!**

(see Hennekens and Buring, *Epidemiology in Medicine*)

The presence or absence of confounding should not be assessed using a statistical test

- A large sample size can easily result in a statistically significant association between the C and E or the C and the D even though there is no confounding (see Hennekens and Buring, *Epidemiology in Medicine*)

The presence or absence of confounding should not be assessed using a statistical test

- **"On the other hand, even strong associations that could produce confounding of substantial epidemiologic importance may fail to reach statistical significance with a small sample size." – Hennekens and Buring, *Epidemiology in Medicine***

Confounding Appears to be Present

- **Stratum One: OR = 2.23**
- **Stratum Two: OR= 2.45**

- **Crude (Overall) OR = 1.20**

Confounding Not Present

- **Stratum One: OR = 2.23**
- **Stratum Two: OR= 2.45**

- **Crude (Overall) OR = 2.19**

Positive Confounding

- **Confounding away from the null value, either towards 0 or $+\infty$**
- **Crude OR = 3.00**
- **Adjusted OR = 2.00**

Possible Values of OR

Confounding away from the null: start at the adjusted measure and move your finger towards the unadjusted (crude) value.

If your finger moved away from 1 (which is the null value for ORs) then positive confounding was present. ***(The figure below isn't drawn to scale.)***

Another Example of Positive Confounding

- **Crude OR = 0.10**
- **Adjusted OR = 0.80**

Away from the Null

Negative Confounding

- **Confounding towards the null value, which is 1, the value of "no association"**

Negative Confounding

- **Crude OR = 1.50**
- **Adjusted OR = 3.00**

Negative Confounding

- **Crude OR = 0.80**
- **Adjusted OR = 0.20**

Salmonellosis Example (Adapted from the hepatitis A example from Gregg, *Field Epidemiology*, 1st edition, 1996)

- Hypothetical outbreak of *Salmonella* infections among students

- Food consumption questionnaire administered to 50 students with salmonellosis, and to 50 healthy students

Example (continued)

- **Only two food items had elevated ORs which were statistically significant**

- **Elevated ORs may indicate potential culprits**

- **The two suspects:**
  - **Milk**
  - **Donuts**

2 x2 Table for Milk: OR=3.9, p=0.0002

	Case	Control	
Had Milk	37	21	58
No Milk	13	29	42
	50	50	100

2 x2 Table for Donuts: OR=6.0, p=0.0001

	Case	Control	
Ate Donuts	40	20	60
No Donuts	10	30	40
	50	50	100

- **Donuts were often consumed with milk!**

- **How do you tease apart the effect of each food item?**

Association between Donuts and Salmonellosis Stratified by Milk: DRANK MILK stratum

	Case	Control
Ate Donut	36	18
No Donut	1	3

OR = 6.0

Association between Donuts and Salmonellosis Stratified by Milk: DID NOT DRINK MILK stratum

	Case	Control
Ate Donut	4	2
No Donut	9	27

OR = 6.0

Association between Milk and Salmonellosis Stratified by Donuts: ATE DONUT stratum

	Case	Control
Had Milk	36	18
No Milk	4	2

OR = 1.0

Association between Milk and Salmonellosis Stratified by Donuts: DID NOT EAT DONUT stratum

	Case	Control
Had Milk	1	3
No Milk	9	27

OR = 1.0

Exposure: Donut
Potential Confounder: Milk

- **Stratum One: OR = 6.0**
- **Stratum Two: OR= 6.0**

- **Crude (Overall) OR = 6.0**

- **Conclusion: No confounding by Milk**

Exposure: Milk
Potential Confounder: Donut

- **Stratum One: OR = 1.0**
- **Stratum Two: OR= 1.0**

- **Crude (Overall) OR = 3.93**

- **Conclusion: Confounding by Donut**

Culprit: Donuts

Another way to look at it...

ORs for the Outcome of Salmonellosis

- **Crude Donut OR = 6.00**
- **Mantel-Haenszel Donut OR, adjusted for Milk = 6.0**

ORs for the Outcome of Salmonellosis

- **Crude Milk OR = 3.9**
- **Mantel-Haenszel Milk OR, adjusted for Donuts = 1.0**