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PEARLS OF LABORATORY MEDICINE

Special Issues: Confounding and Effect Modification

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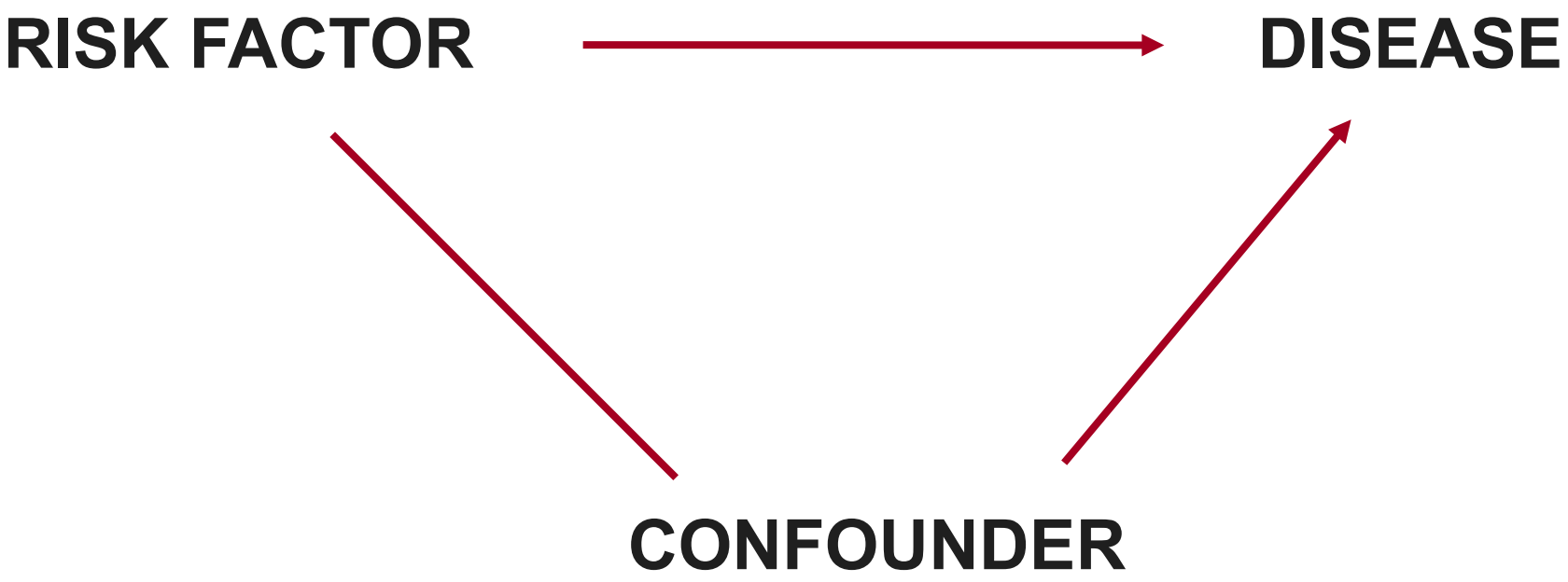
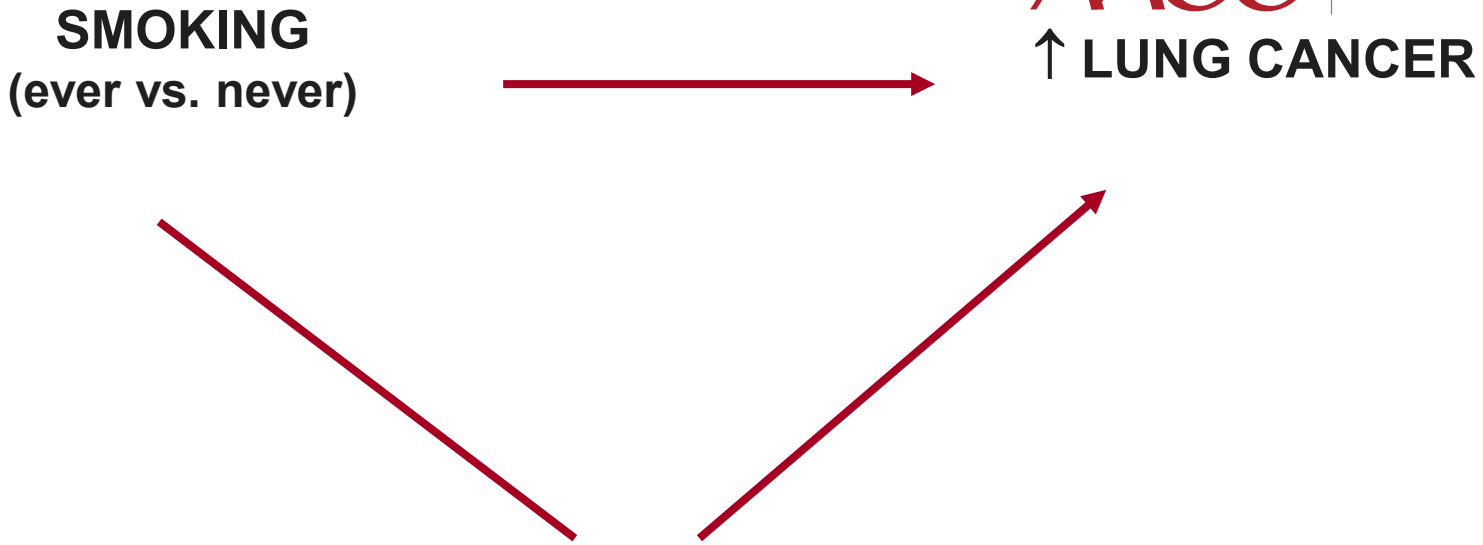
REVIEW OF CONFOUNDING

- A mixture of effects between the association under study and a third variable.
- This third factor (the confounder) must be BOTH associated with the exposure under study and, independently of the exposure, be a risk factor or correlate of the risk factor for the disease.
- The confounder may be responsible in part or totally for the association seen in the data.



NOTE: A confounder of an association in one population may not be so in another population.



POTENTIAL CONFOUNDERS:

- **Age (ever smoker, ↑ age → ↑ lung cancer, overestimate harm)**
- **Gender (ever, ↑ male → ↑ lung cancer, overestimate harm)**
- **Pollution (urban,rural)**
- **Occupational asbestos exposure**

NOT POTENTIAL CONFOUNDERS:

- **Exercise (associated with smoking, but not associated with lung cancer)**
- **Any variable intermediate factor, link in causal chain**

WHAT ARE POTENTIAL CONFOUNDERS?

- **Factors known to be related to the exposure of interest and disease of interest, but are not part of the mechanisms by which the exposure is postulated to affect the disease of interest.**
- **If all this is unknown, then suspect all known risk factors for the outcome to be potential confounders, and collect information on them in the design of the study.**

METHODS FOR CONTROLLING POTENTIAL CONFOUNDERS

1. **IN THE DESIGN OF THE STUDY:**
   - **Restriction: restrict study subjects to one stratum of the confounding factor**
   - **Matching: match study groups so identical levels of the confounding factor**
   - **Randomization: only if trial**

METHODS FOR CONTROLLING POTENTIAL CONFOUNDERS

2. IN THE ANALYSIS OF THE STUDY:

- **Matched analysis:** if matched in design
- **Stratification:** analyze association separately for each level of the confounding factor
- **Multivariable analysis:** mathematical modeling to control for many confounders simultaneously

HOW DO YOU KNOW IF A POTENTIAL CONFOUNDER WAS A REAL CONFOUNDER?

- Compare the overall (crude) RR and the adjusted RR's: the difference between these values is due to confounding. Report and use the adjusted RR.

Example:

- Low fat diet and CHD, RR = 0.60 compared to usual fat diet.
- Adjusted for BMI, RR of low fat diet vs. usual fat diet = 0.80.
- Difference due to effects of confounding by BMI. Only controls for effects of BMI.

CONFOUNDER

- **Confounder is a factor which because of its relationship with the exposure and disease of interest, will distort the RR relating exposure to disease.**
  - **Will depend on the relationships of the factors in your population.**
  - **Confounding is a nuisance factor, not some biologic insight into the relationship.**
  - **You need to remove the effect of the confounder to understand the exposure/disease relationship - want to control for confounding.**

EFFECT MODIFICATION

- When the overall magnitude of the relationship between the exposure and disease for the entire population differs in size (is modified) by the level of a third variable (called the effect modifier).
- Does the magnitude of the overall association observed apply to everyone? Does the magnitude of the effect "depend" in size or even direction on what type of people you are referring to? If so, this is effect modification.

Indications and Usage

What is YAZ® prescribed for?
For women who choose the Pill for birth control, YAZ is approved to:

Prevent pregnancy - 99% effective when taken as directed
Treat premenstrual dysphoric disorder (PMDD)
YAZ is not approved to treat Premenstrual Syndrome (PMS), a less serious set of symptoms occurring before your period
Treat moderate acne in women at least 14 years of age

Who should not take YAZ?

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.

DIFFERENCE BETWEEN CONFOUNDER AND EFFECT MODIFIER

- **Effect modifier is a factor that modifies (alters) the relationship between the exposure and disease.**
  - **Not a nuisance.**
  - **Provides insight into the nature of the biologic relationship between exposure and disease.**
  - **Do not want to control effect modification – you want to explore and report.**

Detecting Confounding and Effect Modification

- 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.

Approach for the Assessment of Confounding and Effect Modification

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Crude Analysis:

Exposure	Disease +	Disease -	
+	a	b	a+b
-	c	d	c+d
	a+c	b+d	

RR_{crude}

Stratified Analysis by level of the factor(s):

Exposure	Stratum 1 D+	Stratum 1 D-	Stratum 2 D+	Stratum 2 D-	Stratum n D+	Stratum n D-
+	a_1	b_1	a_2	b_2	a_n	b_n
-	c_1	d_1	c_2	d_2	c_n	d_n
	RR_1		RR_2	. . .	RR_n	

$RR_{adjusted}$

Confounding: compares RR_{crude} to $RR_{adjusted}$

Effect Modification: compares stratum-specific RRs (RR_1 to RR_2 to . . . RR_n)

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Confounding and Effect Modification

- 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

Example: Oral Contraceptives (OC) and Myocardial Infarction (MI) in Women of Childbearing Age

Crude (Overall) RR = 2.0

RR adjusted for smoking and ETOH = 2.0

RR (for OCs and MI, among non-drinkers) = 2.0

RR (for OCs and MI, among drinkers) = 2.0

RR (for OCs and MI, among non-smokers) = 1.9

RR (for OCs and MI, among smokers) = 41.0

PMH and CHD

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Current use of postmenopausal hormones (PMH) and CHD

- Crude RR (PMH/CHD) = 0.4
- RR (PMH/CHD, adjusted*) = 0.5
  * adjusted for age, BMI, diabetes, hypertension, smoking, OC use, parental history of MI
- Over 60 yrs of age: adjusted RR = 0.95
- Under 60 years of age: adjusted RR = 0.35

Low-Dose Aspirin in CVD Primary Prevention Meta-Analysis

	Myocardial Infarction	Stroke
All Participants (N=95,456)	0.76 (0.62–0.95)	0.97 (0.83–1.13)
Men (N=44,114)	0.68 (0.54–0.86)	1.13 (0.96–1.33)
Women (N=51,342)	0.99 (0.83–1.19)	0.81 (0.69–0.96)

How Different is Different Enough for EM?

- Can use statistical testing, such as Breslow-Day test.
- Interaction terms in multivariate modeling
  - y = intercept + b1(X1) + b2(X2) + b3(X1X2)
- OR…Compare stratum-specific estimates and determine if the public health message would differ between stratum.

Presenting Results in the Presence of Effect Modification

- **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.**

Presenting Final Results

- Report crude (overall) measure of effect.
- Report adjusted measure of effect (to assess confounding).
- If large amount of confounding present, be cautious in interpretation of findings because of unknown or unmeasured confounding.
- If effect modification is present, report stratum specific estimates and discuss (biology).

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