# Confounding and Interaction

## Why did you do clinical research?

- To find a better diagnosis tool
- To determine risk factor of disease
- To identify prognosis factor
- To evaluate effectiveness of therapy
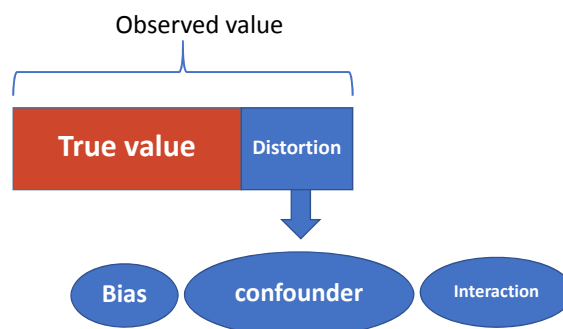- To decide better choice of treatment

"For well-being of your PATIENTS"

# Do you believe in this statement?

- Male has higher risk of liver cancer than female by 4 times. (Alc. Drinker?)
- Lack of physical activity increased risk of CHD by 10 times. (Obese?)

**It would be probably true if the study has validity or NO BIAS and NO CONFOUNDER.**

# Observed and True value

# Precision and Validity in biomedical research

- Precision (Random error)
- Validity (Systematic error)
  - External validity (Generalization; how to generalize the study result to general population)
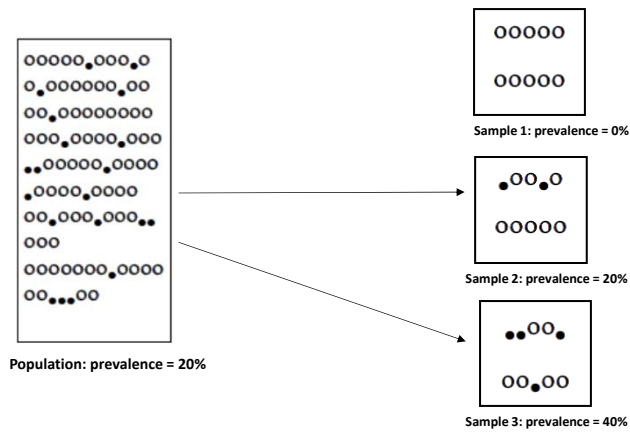  - Internal validity (how close study findings are to the TRUTH )

# Random error

- Measurements are based on a sample.
- Number of selected samples is important for the precision of the measurements

**Number of sample** == **Precision**

# Random error: Sampling



Population: prevalence = 20%

Sample 1: prevalence = 0%

Sample 2: prevalence = 20%

Sample 3: prevalence = 40%
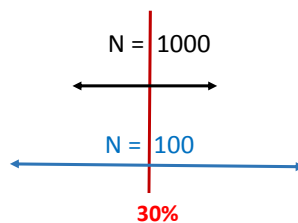
# Random error: Precision of CI

- Larger sample size provides more narrow interval
- N=1000 : 30% (95%CI 25 -36%)
- N=100 : 30% (95% CI 9 -58 %)



N = 1000

N = 100

**30%**

You should consider cost-effectiveness

# Random error: P-value

- For comparison of 2 or more
- Tell the probability (percentage) of a wrong conclusion of study result
- Association between
    - Number coffee drinking per day
    - Developing CA stomach
    - RR = 3.6
    - $X^2$ ,P value = 0.35

# To identify association sex and lung cancer



- Male
- Covariate
    - Age
    - Smoking
    - Exposed to air pollutant
    - Tuberculosis

- Lung cancer

# Threats to Validity

- External validity of Generalization
- Internal validity
  - *Bias*
    - Selection bias
    - Measurement bias
  - *Confounder*

# Bias

**BIAS** Systematic deviation of results or inferences from truth.

Processes leading to such deviation. An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from truth.

(Portal, 2008 A dictionary of Epidemology5[th]ed)

*Note: There is no way to correct for bias later!*

# Bias

Systematic error is caused by 2 main steps:

- **I.    Selection of study sample (Selection bias)**
- **II.   Inaccuracy of exposure or outcome measurements (Measurement bias)**

# Bias

- Wrong selection of comparison groups
- Selecting in different ways
- Give you the wrong answer for the association
- A mistaken estimate of an exposure's effect on the risk of a disease

**Selection Bias: Unrepresentative nature of sample**

**Cancer of the pancreas VS Coffee consumption**

**Example:**

**Cases: Histological confirmed diagnosis of pancreatic cancer**

**Controls: Hospitalized patients admitted during the same time as cases**

**OR of drinking coffee > 5 cups/day = 2.6**

**Do you agree with the results? Why?**

# Selecting Controls

- **Coffee and pancreatic cancer,** MacMahonB et al. NEJM 1981
  - Coffee consumption was associated with pancreatic cancer
  - Controls were selected from other patients admitted to the hospital by the same physician as the case, often gastroenterologist
  - This specialist would admit patients with other diseases (gastritis or esophagitis) for which he or the patient would reduce coffee intake
  - Controls intake of coffee not representative of population at risk

|  | Case | Control |
|---|---|---|
| **Exposed** | A | B |
| **Not Exposed** | C | D |

| Pancreatic CA | Non Pancreatic CA |
|---|---|
| Coffee Consume | ↓ ↓ ↓ |
| No Coffee Consume | |

## Unrealistically ↑ Odds Ratio (BIAS)

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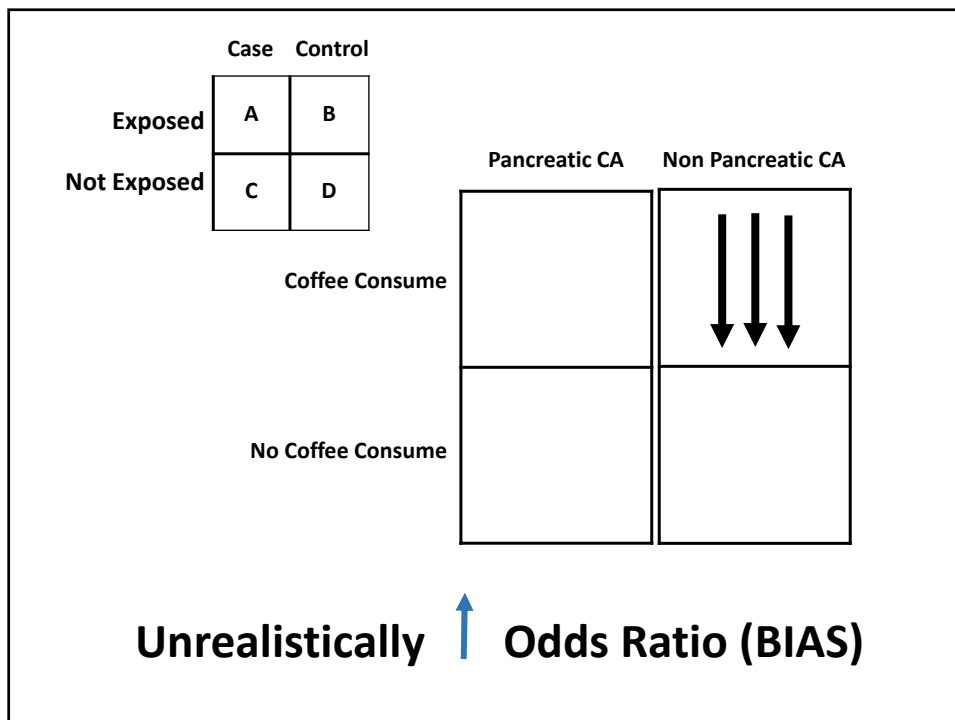
# Measurement Bias

- Interview mothers about the history of x-ray exposure comparing between 2 groups
- A mother who had a child with a birth defect often tries to identify some unusual event that occurred during her pregnancy with that child.
- While a mother with a normal child do not try that much.

|  | Case | Control |
|---|---|---|
| **Exposed** | A | B |
| **Not Exposed** | C | D |

|  | Malformation+ | No Malformation |
|---|---|---|
| Hx of Radiation | ↑↑↑ |  |
| No Hx of Radiation |  | ↑↑↑ |

# Unrealistically ↑ Odds Ratio (BIAS)

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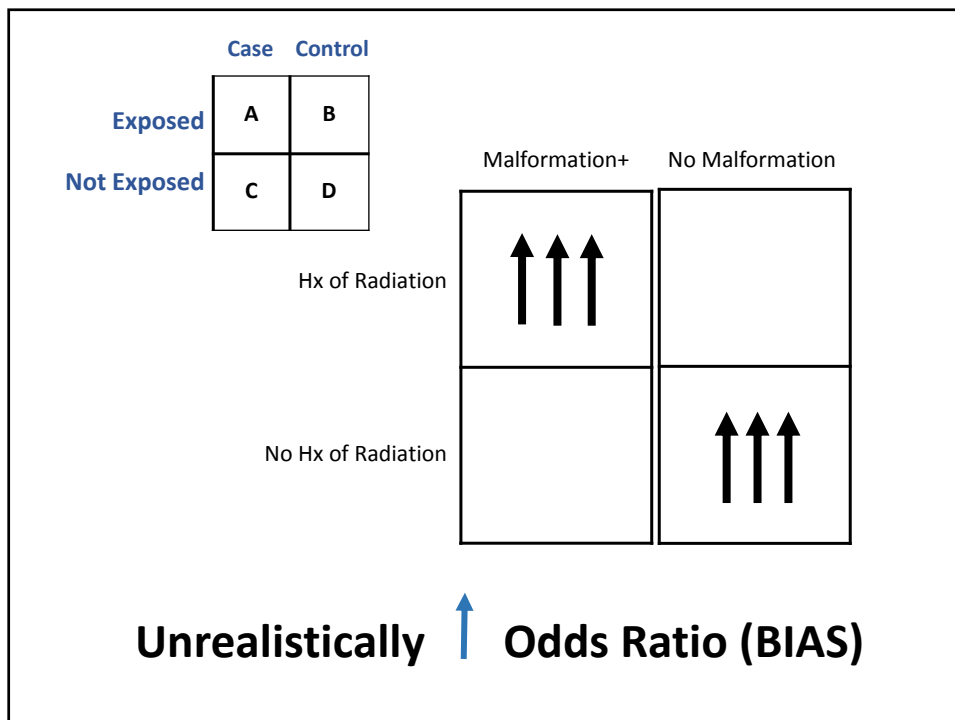
# Measurement Bias

- Misclassification
  - Recall bias

|  | Case | Control |
|---|---|---|
| **Exposed** | 24 | 24 |
| **Not Exposed** | 20 | 60 |

OR = 3.0

|  | Case | Control |
|---|---|---|
| **Exposed** | 19 | 19 |
| **Not Exposed** | 25 | 65 |

OR = 2.6

# Confounder

- An observed significant association may be attributable to **another unconsidered factor**.

- Smoking VS CHD

- The third variable ➜ Gender

# Confounder

- The third factors affected the association;

    –Confounder

    –Effect modifier or Interaction

# Confounder

- Association between CHD and Smoking

|  | CHD | No CHD |  |
| --- | --- | --- | --- |
| Smoker | 305 | 345 | 650 |
| Non smoker | 58 | 292 | 350 |
|  | 363 | 637 | 1000 |

- RR = 2.9

- It is a true effect from the study But is it OK to report this result?

# Smoking VS CHD

- Is it possible that the obtained association was actually due the effect of the other factor?
- In the reality smoking may not lead people to develop CHD.
- Smoking is a coincidence of the other true association!!!!
- Let's think about the effect of gender on this association

- CA

# Confounder

- Gender M/F might be a confounder of the association
- Gender ➜CHD
- Gender ➜Smoking

What is the RR among Men?
What is the RR among Women?

## Calculate stratum-specific measures of association…

**STRATUM 1: MEN**

|  | CHD | No CHD |  |
|---|---|---|---|
| Smoker | 300 | 300 | 600 |
| Non smoker | 50 | 150 | 200 |
|  | 350 | 450 | 800 |

**STRATUM 2: WOMEN**

|  | CHD | No CHD |  |
|---|---|---|---|
| Smoker | 5 | 45 | 50 |
| Non smoker | 8 | 142 | 150 |
|  | 13 | 187 | 200 |

## Calculate stratum-specific measures of association...

**STRATUM 1: MEN**

|            | CHD | No CHD |     |
|------------|-----|--------|-----|
| Smoker     | 300 | 300    | 600 |
| Non smoker | 50  | 150    | 200 |
|            | 350 | 450    | 800 |

RR = 2.0

**STRATUM 2: WOMEN**

|            | CHD | No CHD |     |
|------------|-----|--------|-----|
| Smoker     | 5   | 45     | 50  |
| Non smoker | 8   | 142    | 150 |
|            | 13  | 187    | 200 |

RR = 1.9

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## IS THERE A CONFOUNDER?

- CRUDE RR for smoking and CHD =2.8
- STRATUM-SPECIFIC RR for smoking and CHD with gender as a potential confounder...

    MEN RR = 2.0            roughly the same
    WOMEN RR = 1.9

- Do Breslow-Day tests or Mantel-Haenzel
- Gender confounds the association between smoking and CHD because the crude RR of 2.8 is NOT the same as the stratum-specific RR's of approx. 2.0

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# Smoking VS CHD

- Smoking ➔CHD : RR = 2.8 (Crude RR)

- After adjusting for gender
- Smoking   CHD : RR ~ 2 .0 (Adjusted RR)

- Gender confound the association between smoking and CHD
- Gender increases the effect of smoking

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**Confounders**

A third variable that can make it appear (sometimes incorrectly) that an observed exposure is associated with an outcome.
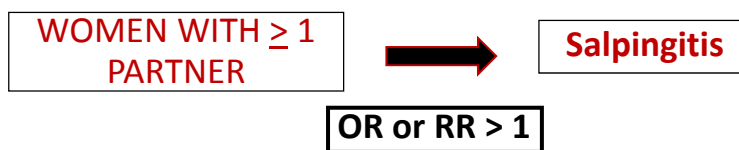


|  | | Salpingitis | | Total | Proportion with salpingitis |
|---|---|---|---|---|---|
| All women (n=2000) | | Yes | No | | |
| Use of IUD | Yes | 45 | 955 | 1000 | 4·5% |
| | No | 15 | 985 | 1000 | 1·5% |

Crude RR=$\frac{4·5\%}{1·5\%}$ =3·0 (95% CI 1·7–5·4)

|  | | Salpingitis | | Total | Proportion with salpingitis |
|---|---|---|---|---|---|
| Women with 1 sexual partner (n=1200) | | Yes | No | | |
| Use of IUD | Yes | 3 | 297 | 300 | 1·0% |
| | No | 9 | 891 | 900 | 1·0% |

RR=$\frac{1·0\%}{1·0\%}$ =1·0

|  | | Salpingitis | | Total | Proportion with salpingitis |
|---|---|---|---|---|---|
| Women with >1 sexual partner (n=800) | | Yes | No | | |
| Use of IUD | Yes | 42 | 658 | 700 | 6·0% |
| | No | 6 | 94 | 100 | 6·0% |

RR=$\frac{6·0\%}{6·0\%}$ =1·0

# Criteria of Confounder

1. Related to the disease outcome

| USE OF IDU | ➡ | **Salpingitis** |

**OR or RR > 1**

2. Related to the exposure

| WOMEN WITH $\geq$ 1 PARTNER | ➡ | **Salpingitis** |

**OR or RR > 1**

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# Criteria of Confounder

3. Not be *an intermediate* of the association between the exposure and the outcome

**High Fat Diet**          **CHD**

**Serum Cholesterol**
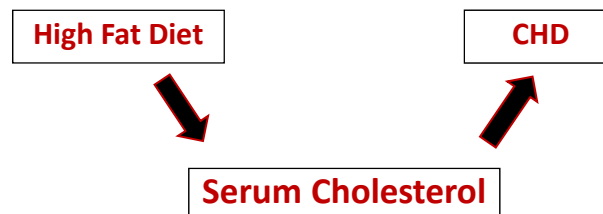
4. Not be a predisposed factor

## CONTROL FOR CONFOUNDERS

- Review for the potential confounder of the association you are going to find.
- Restriction
- **Matching (Can't calculate effect of matched variable X**
  - –Matched by Smoking status
  - –Matched by Gender
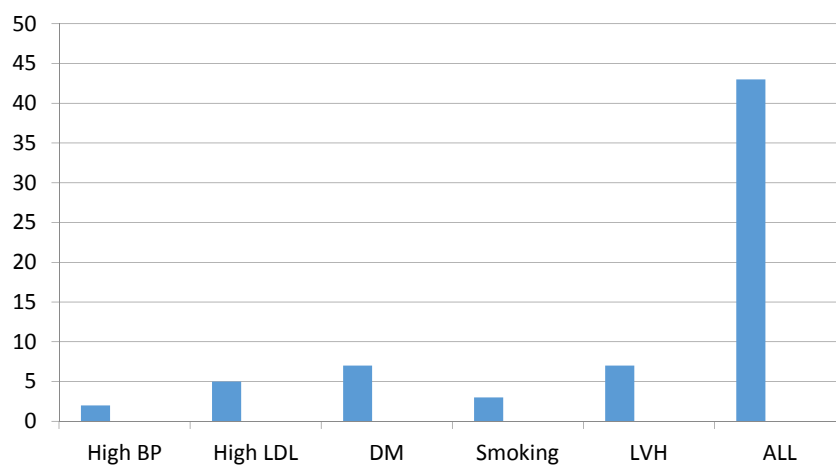- **Stratified analysis** ➔ **Mantel HaenzelMethod**
- Multivariate analysis

# Interaction and effect modification

# Interaction of multiple causes

- When more than one cause acts together, the resulting risk may be greater or less than would be expected by simply combining the effects of the separate causes.

# Interactions

Coronary artery disease

# Interaction of multiple causes

- When more than one cause acts together, the resulting risk may be greater or less than would be expected by simply combining the effects of the separate causes.
  - **Synergism**: when the joint effect is greater than the sum of effects of the individual causes
  - **Antagonism**: when the joint effect is lesser than the sum of effects of the individual causes
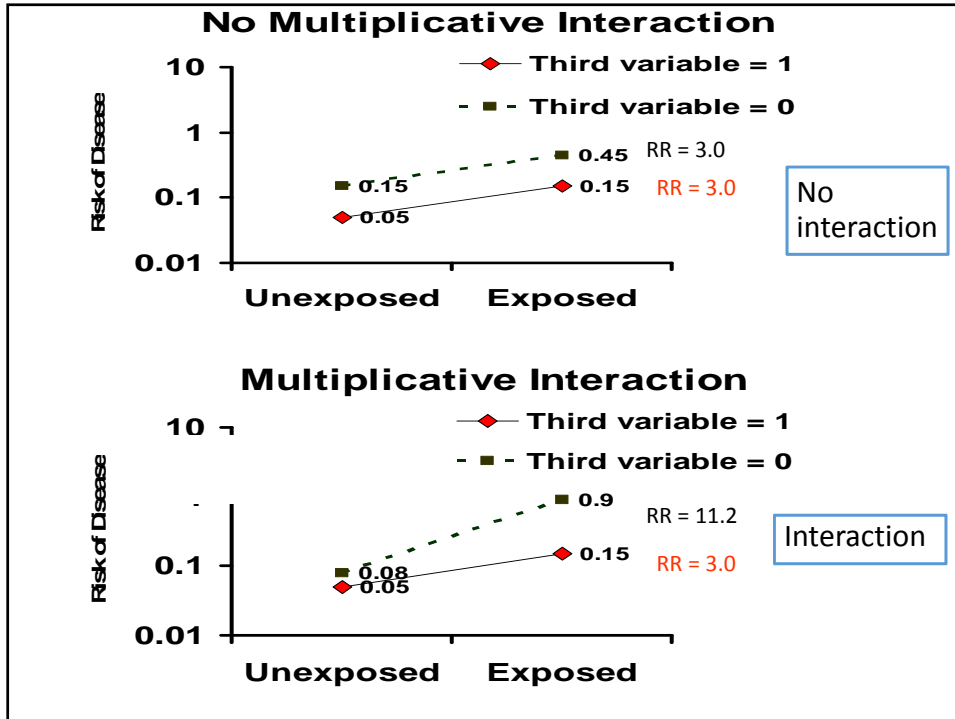
# Effect modification

- **Effect modification** occurs when a factor (an effect modifier) modifies the causal relationship between a risk factor and the outcome.

- For example, **immunization status** is a strong effect modifier of the relationship between exposure to a specific pathogen and subsequent disease from that pathogen. As an effect modifier, immunization status then modifies the biologic response of the person. The presence of effect modification supports a causal relationship because it implies a biologically plausible process.

# Interaction vs. effect modification

- Interaction:  Statistics term
  - Joint effect found from data analysis
  - Not necessary for biological/mechanism explanation
- Effect modification: Epidemiology term
  - Joint effect found in population-base analysis
  - Not necessary for biological/mechanism explanation

# Type of interaction

- When there is interaction in terms of the ratio measures of association (in this case, the risk ratio), we call this **multiplicative interaction**
- Interaction in the risk difference is called **additive interaction**

## No Multiplicative Interaction

**Risk of Disease** (y-axis): 10, 1, 0.1, 0.01

Legend:
- Third variable = 1
- Third variable = 0

0.15
0.45    RR = 3.0
0.15    RR = 3.0
0.05

Unexposed    Exposed

No interaction

## Multiplicative Interaction

**Risk of Disease** (y-axis): 10, 0.1, 0.01

Legend:
- Third variable = 1
- Third variable = 0

0.9     RR = 11.2
0.08
0.05
0.15    RR = 3.0

Unexposed    Exposed

Interaction

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### Smoking, Caffeine Use and Delayed Conception: Additive vs Multiplicative Interaction

Crude

| | Delayed | Not Delayed | |
|---|---|---|---|
| Smoking | 2 6 | 1 3 3 | RR |
| No Smoking | 6 4 | 6 0 1 | RD |

Stratified    Heavy Caffeine Use          No Caffeine Use

| | Delayed | Not Delayed |
|---|---|---|
| Smoking | 1 1 | 7 2 |
| No Smoking | 1 7 | 7 3 |

RR
RD

| | Delayed | Not Delayed |
|---|---|---|
| Smoking | 1 5 | 6 1 |
| No Smoking | 4 7 | 5 2 8 |

RR
RD

## Smoking, Caffeine Use and Delayed Conception: Additive vs Multiplicative Interaction

Crude

| | Delayed | Not Delayed |
|---|---|---|
| Smoking | 26 | 133 |
| No Smoking | 64 | 601 |

$RR_{crude} = 1.7$
$RD_{crude} = 0.07$

Stratified        Heavy Caffeine Use          No Caffeine Use

| | Delayed | Not Delayed | | Delayed | Not Delayed |
|---|---|---|---|---|---|
| Smoking | 11 | 72 | Smoking | 15 | 61 |
| No Smoking | 17 | 73 | No Smoking | 47 | 528 |

$RR_{caffeine\ use} = 0.7$
$RD_{caffeine\ use} = -0.05$

$RR_{no\ caffeine\ use} = 2.4$
$RD_{no\ caffeine\ use} = 0.12$

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## Smoking, Caffeine Use and Delayed Conception: Additive vs Multiplicative Interaction

Crude

| | Delayed | Not Delayed |
|---|---|---|
| Smoking | 26 | 133 |
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$RR_{crude} = 1.7$
$RD_{crude} = 0.07$

Stratified        Heavy Caffeine Use          No Caffeine Use

| | Delayed | Not Delayed | | Delayed | Not Delayed |
|---|---|---|---|---|---|
| Smoking | 11 | 72 | Smoking | 15 | 61 |
| No Smoking | 17 | 73 | No Smoking | 47 | 528 |

$RR_{caffeine\ use} = 0.7$
$RD_{caffeine\ use} = -0.05$

$RR_{no\ caffeine\ use} = 2.4$
$RD_{no\ caffeine\ use} = 0.12$

$RR_{adjusted} = 1.4$ (95% CI= 0.9 to 2.1)

Is it appropriate to summarize these two stratum-specific estimates?

**Smoking, Caffeine Use**
**and Delayed Conception: Additive vs Multiplicative Interaction**

Crude

| | Delayed | Not Delayed | |
|---|---|---|---|
| Smoking | 26 | 133 | $RR_{crude} = 1.7$ |
| No Smoking | 64 | 601 | $RD_{crude} = 0.07$ |

Stratified    Heavy Caffeine Use    No Caffeine Use

| | Delayed | Not Delayed | | Delayed | Not Delayed |
|---|---|---|---|---|---|
| Smoking | 11 | 72 | Smoking | 15 | 61 |
| No Smoking | 17 | 73 | No Smoking | 47 | 528 |

$RR_{caffeine\ use} = 0.7$ ←——— Multiplicative interaction ———→ $RR_{no\ caffeine\ use} = 2.4$

$RD_{caffeine\ use} = -0.05$ ←——— Additive interaction ———→ $RD_{no\ caffeine\ use} = 0.12$

Is it appropriate to summarize these two
stratum-specific estimates?
**Here, adjustment is contraindicated**
**When interaction is present, confounding becomes irrelevant!**

# Example conclusion

- Smoking, caffeine use, and delayed conception
  - Caffeine use modifies the effect of smoking on the risk for delayed conception.
  - There is interaction between caffeine use and smoking in the risk for delayed conception.
  - Caffeine is an effect modifier in the relationship between smoking and delayed conception.
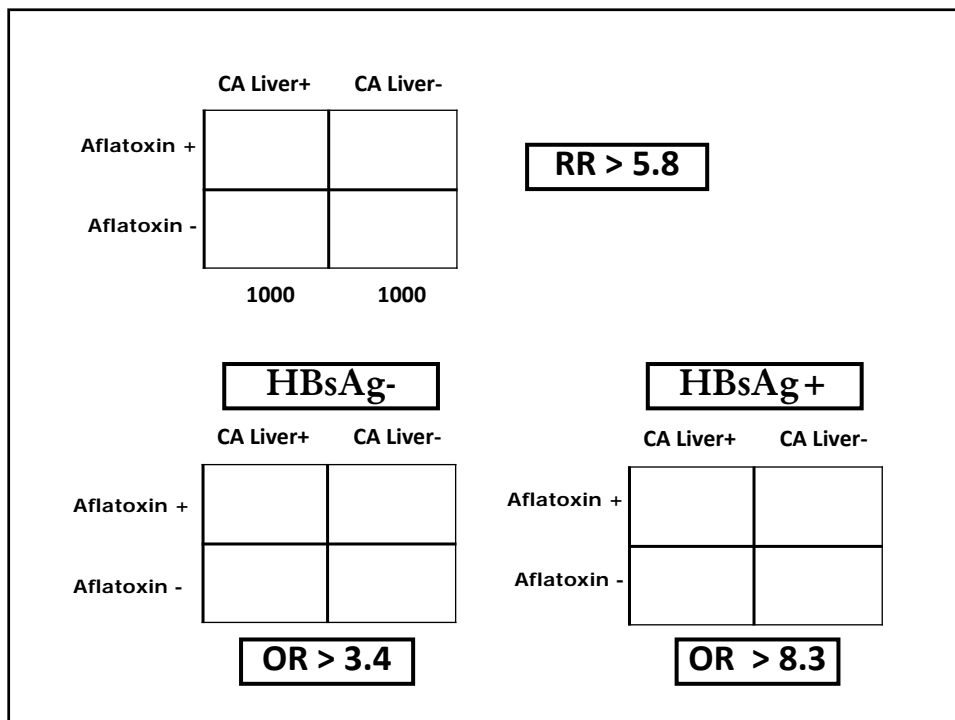
# Effect Modification

- You were going to find the association between Aflatoxin and liver cancer
- You conducted a cohort study
- Crude RR of Aflatoxin = 5.8

- You would like to know if HBsAG was a confounder for the association or not
- You performed STRATIFIED ANALYSIS

# Effect modification

Heterogeneity of Effect = the selected effect measure for the factor under study varies across levels of another factor.

In the process of stratification to look at the RR or ORin each subgroup, what is the explanation when the RRs or ORs in each subgroup are not the same?

**CA Liver+**  **CA Liver-**

**Aflatoxin +**

**Aflatoxin -**

**RR > 5.8**

**1000**  **1000**

**HBsAg-**

**CA Liver+**  **CA Liver-**

**Aflatoxin +**

**Aflatoxin -**

**OR > 3.4**

**HBsAg+**

**CA Liver+**  **CA Liver-**

**Aflatoxin +**

**Aflatoxin -**

**OR > 8.3**

# Effect Modification

- Crude RR; Aflatoxin: CA Liver = 5.8
- Stratum specific: HBs Ag +
  - RR = 3.4
- Stratum specific: HBs Ag -
  - RR = 8.3
- HBs Ag is not the confounder of the association
  - (3.4 ≠ 8.3 ; not homogeneous)
- HBs Ag is the effect modifier of the association
- No adjustment required
- Report stratum specific RR

## Effect Modification

Aflatoxin → CA Liver

Hbs Ag

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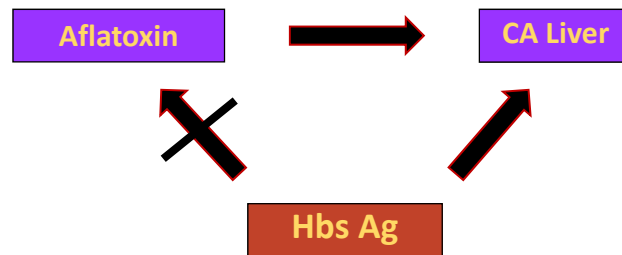
# Confounding vs. interaction

**Confounding**

- Use stratification analysis (subgroup) to identify
- Interfere the finding
- Prevent, control, role out
- Asymmetry

**Interaction**

- Use stratification analysis (subgroup) to identify
- Show real finding
- Understand, explain, report
- Symmetry

When Assessing the Association Between an Exposure and a Disease, What are the Possible Effects of a Third Variable?

Intermediate

Caffeine

C

Confounder

Smoking

E

Delayed conception

D

+
–

EM

Effect Modifier (Interaction): MODIFIES THE EFFECT OF THE EXPOSURE