Interaction

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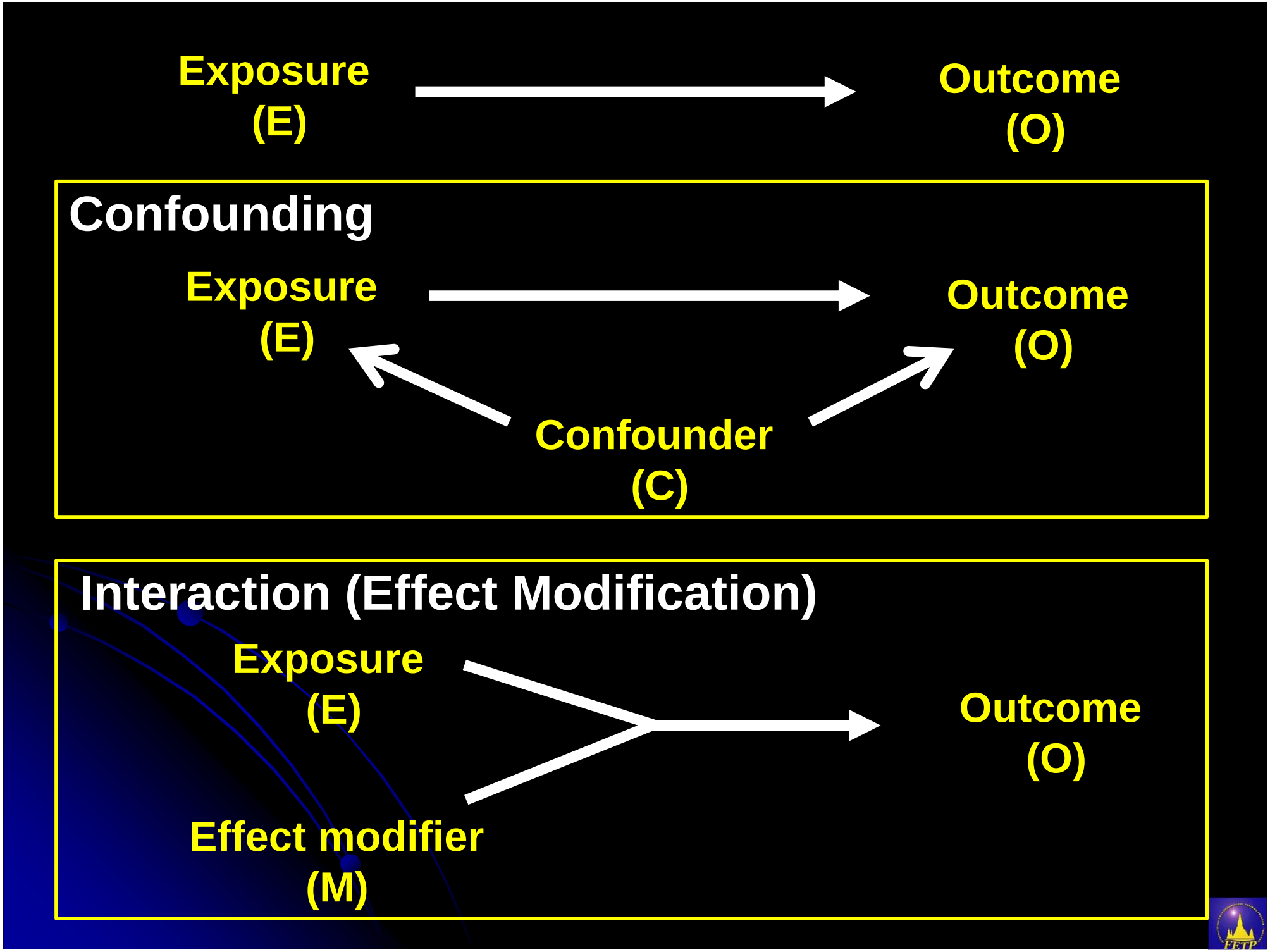
Interaction

- A situation in which two or more risk factors modify the effect of each other with regard to the occurrence or level of a given outcome
- Also known as "Effect Modification" or, more precisely, "Effect Measure Modification"
- In simplest situation, an interaction is formed when a third variable modifies the relationship between an exposure and outcome
- It is distinguished from confounding

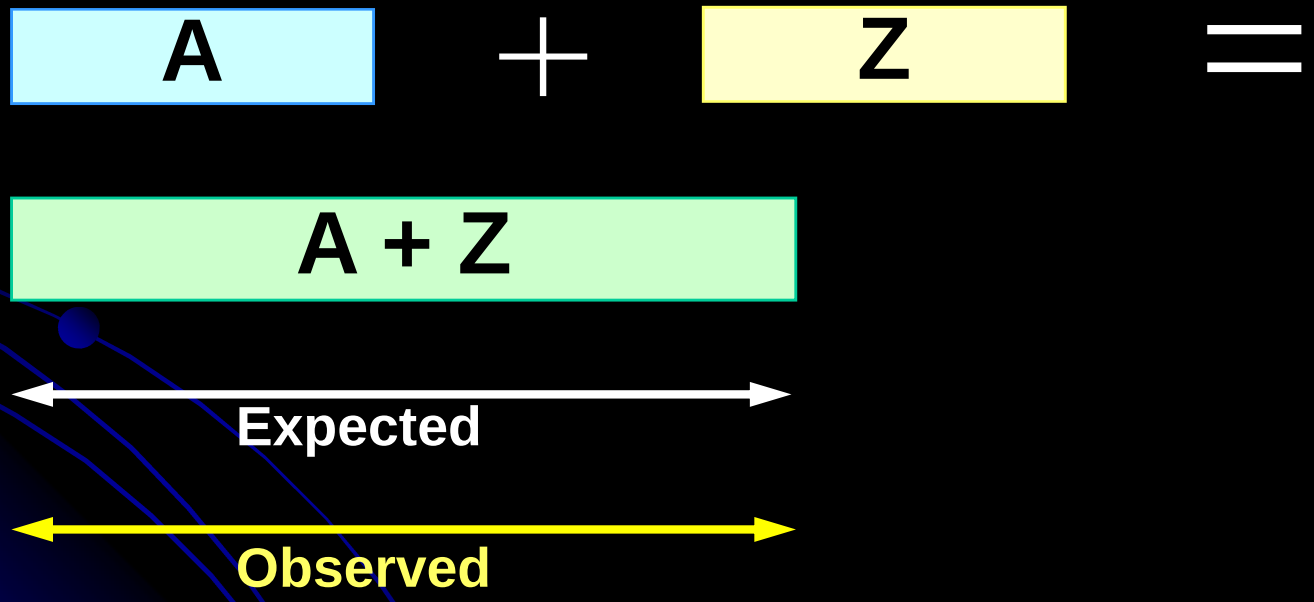

Exposure
(E)
Outcome
(O)
Confounding
Exposure
(E)
Outcome
(O)
Confounder
(C)
Interaction (Effect Modification)
Exposure
(E)
Outcome
(O)
Effect modifier
(M)

Positive vs Negative Interaction

- Interaction means having unexpected outcome
- If risk/rate is greater than expected
  - Positive interaction or Synergism
    - 2 + 3 > 5
    - 2 x 3 > 6
- If risk/rate is less than expected
  - Negative interaction or Antagonism
    - 2 + 3 < 5
    - 2 x 3 < 6

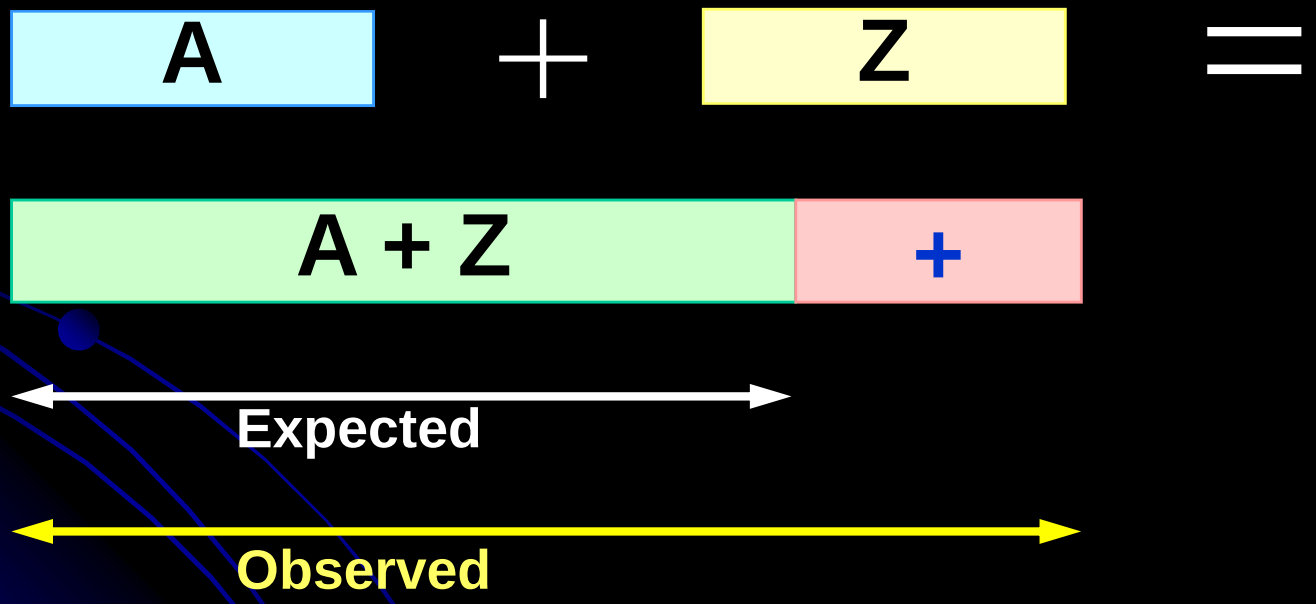
Conceptual Framework of the definition of interaction based on comparing expected and observed joint effects

A. When there is no interaction, the joint effect of risk factors A and Z equals the sum of their independent effects :



Conceptual Framework of the definition of interaction based on comparing expected and observed joint effects

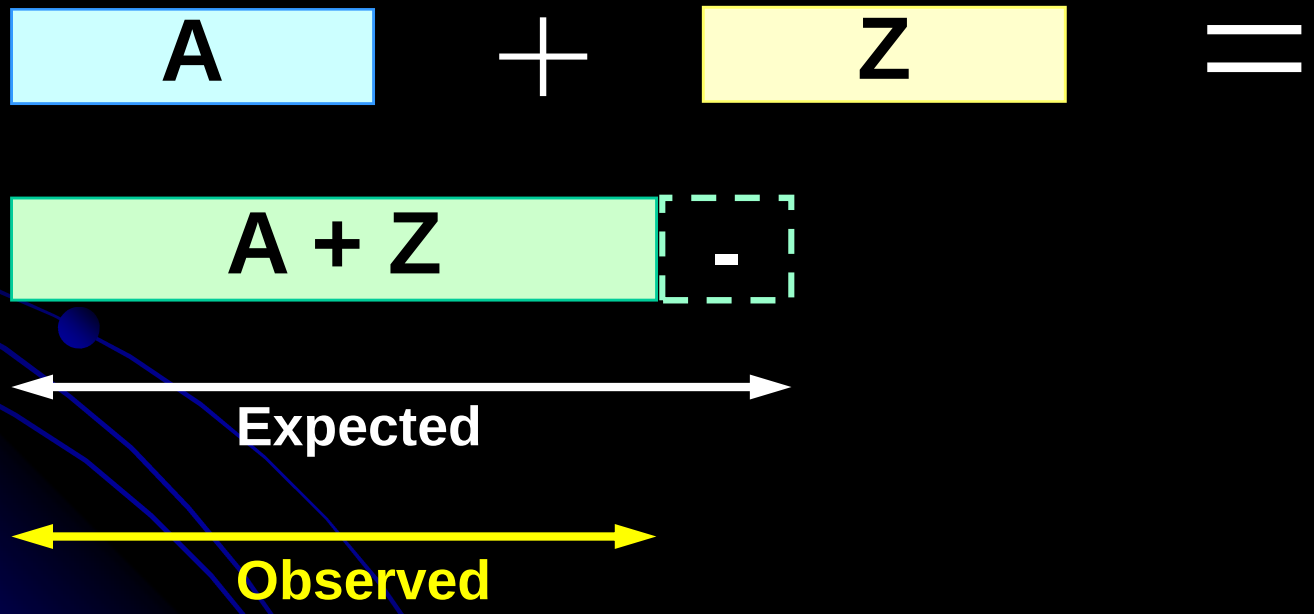
B. When there is positive interaction (synergism). The observed joint effect of risk factors A and Z is greater than that expected on the basis of summing the independent effects of A and Z :



+ = Excess due to positive interaction

Conceptual Framework of the definition of interaction based on comparing expected and observed joint effects

C. When there is negative interaction (antagonism), the observed joint effect of risk factors A and Z is smaller than that expected on the basis of summing the independent effects of A and Z :



- = Deficit due to negative interaction

Interaction (Miettinen, 1974)

SAMPLE BASED

- **Statistical Interaction**

POPULATION BASED

- **Effect Modification**
- **Biological Interaction**

Statistical Interaction

- Interaction is “model dependent”
- = Depends on deviation from statistical model (not biologic)
- There are two models (or two ways of expectation)

2 Models

Additive Model

Difference measure:
Risk Difference (RD)
Rate Difference

Multiplicative Model

Ratio measure:
Risk Ratio (RR)
Incidence Rate Ratio (IRR)
Odds Ratio (OR)

Evaluation of Interaction

- Homogeneity of Effects
- Comparison of observed and expected joint effects
- Multivariate modeling

Note: The assessment of interaction should also be based on knowledge from previous studies or a biological basis

Evaluation of Interaction

- **Homogeneity of Effects**
- **Comparison of observed and expected joint effects**
- **Multivariate modeling**

Homogeneity of Effects

- Between individual (measured by the group) heterogeneity of the effect of the risk factor
- Does the magnitude or direction of the effect of exposure (E) on outcome (O) vary according to the occurrence of some other variable (M) ?
- Example:
  - If diabetes is a stronger risk factor for CHD in women than in men
  - If diabetes is a stronger risk factor for CHD in women than in men only among older subjects
  - Both variables (gender and age) are needed to modify the effect of diabetes

Homogeneity of Effects – Additive Model

Additive interaction is present when the RD (risk difference) varies across strata of the effect modifier (M)

Homogeneity of Effects – Additive Model

- Example - Additive Interaction:

Modifier (M)	Exposure (E)	Incidence Rate (per 1000)	RD (per 1000)
No	No	10.0	Ref.
	Yes	20.0	10.0
Yes	No	30.0	Ref.
	Yes	40.0	10.0

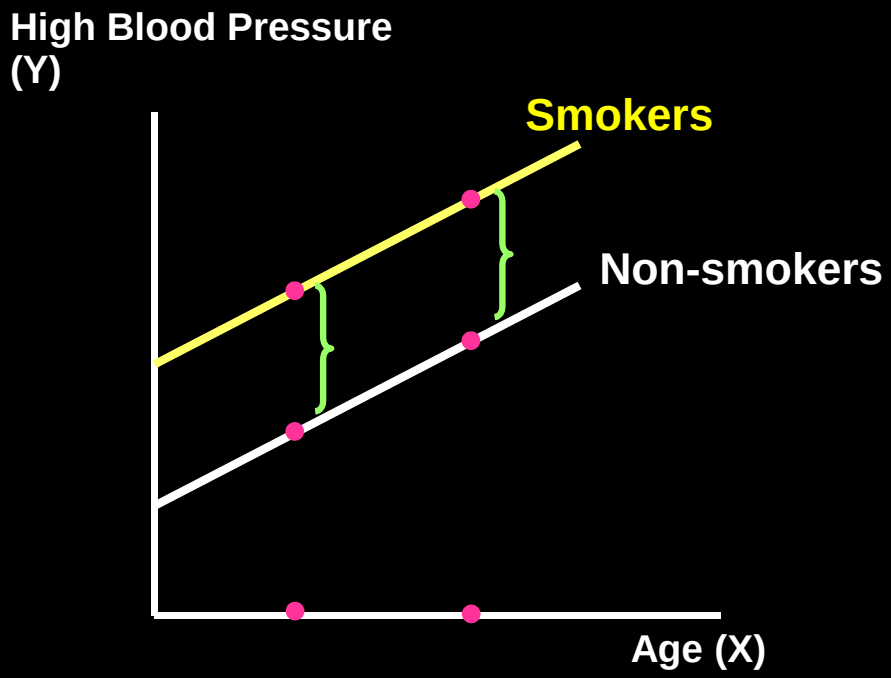
No additive interaction ; RD does not vary according to M

Homogeneity of Effects – Additive Model

- Example - Additive Interaction:

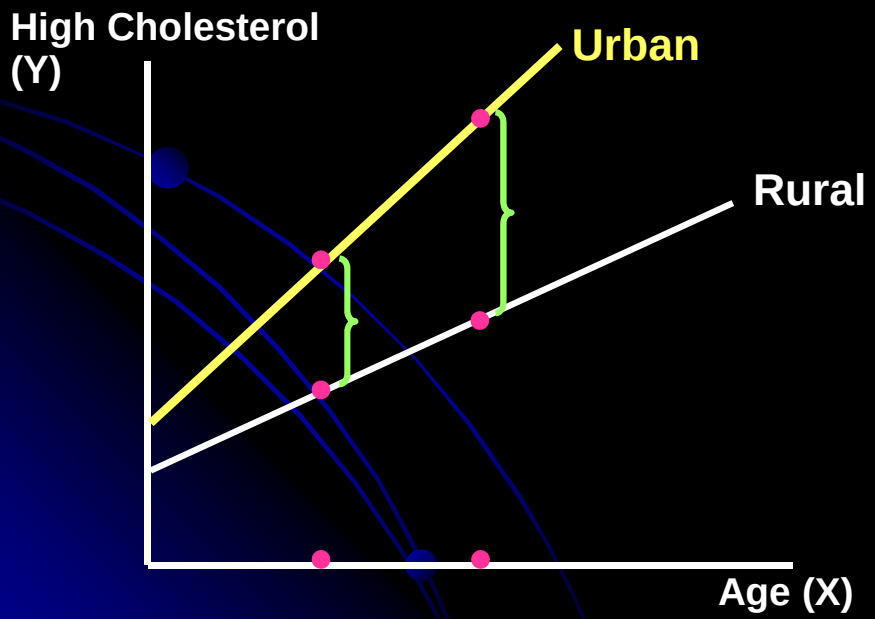
Modifier (M)	Exposure (E)	Incidence Rate (per 1000)	RD (per 1000)
No	No	5.0	Ref.
	Yes	10.0	5.0
Yes	No	10.0	Ref.
	Yes	30.0	20.0

Additive interaction ; RD does vary according to M



Additive Model (No interaction)

Only change in intercepts no change in slope irrespective of the value of Xi which is being held constant



Additive Interactive Model

There is change in both intercepts and slope as the level of Xi which is held constant and varied

Homogeneity of Effects – Multiplicative Model

Multiplicative interaction is present when the RR, IRR or OR varies across strata of the effect modifier (M)

Homogeneity of Effects – Multiplicative Model

- Example – Multiplicative Interaction

Modifier (M)	Exposure (A)	Incidence Rate (per 1000)	IRR
No	No	10.0	Ref.
	Yes	20.0	2
Yes	No	25.0	Ref.
	Yes	50.0	2

No multiplicative interaction; IRR does not vary according to M

Homogeneity of Effects – Multiplicative Model

- Example – Multiplicative Interaction

Modifier (M)	Exposure (A)	Incidence Rate (per 1000)	IRR
No	No	10.0	Ref.
	Yes	20.0	2
Yes	No	25.0	Ref.
	Yes	125.0	5

Multiplicative interaction; IRR does vary according to M

Evaluation of Interaction

- Homogeneity of Effects
- Comparison of observed and expected joint effects
- Multivariate modeling

Comparison Observed and Expected Joint Effects

- The expected joint effect can be estimated by assuming that the effects of E and M are independent
- Interaction is present when the observed joint effect of E and M differs from the expected joint effect
- So, to compare the observed and expected joint effects of E and M, we need to estimate their independent effects

Comparison Observed and Expected Joint Effects: Additive Interaction

- The joint effect of exposure (E) and modifier (M) is estimated as the arithmetic sum of the independent effects measured by the RD
- Additive interaction <u>is not present</u> when:

$$RD_{E+M+} = RD_{E+M-} + RD_{E-M+}$$

or

$$(RR_{E+M+} - 1) = (RR_{E+M-} - 1) + (RR_{E-M+} - 1)$$

$$(IRR_{E+M+} - 1) = (IRR_{E+M-} - 1) + (IRR_{E-M+} - 1)$$

$$(OR_{E+M+} - 1) = (OR_{E+M-} - 1) + (OR_{E-M+} - 1)$$

Comparison Observed and Expected Joint Effects: Additive Interaction

- Example – Absence of Additive Interaction

Strata	Observed Incidence Rate (per 1000)	Observed RD (per 1000)
E- M-	10.0	Ref.
E- M+	20.0	10.0
E+ M-	30.0	20.0
E+ M+	40.0	30.0

Joint Expected RD = Obs RD $_{E+M-}$ + Obs RD $_{E-M+}$ = 10.0 + 20.0 = 30.0

Joint Observed RD = 30.0

Comparison Observed and Expected Joint Effects: Additive Interaction

- Example – Presence of Additive Interaction

Strata	Observed Incidence Rate (per 1000)	Observed RD (per 1000)
E- M-	10.0	Ref.
E- M+	20.0	10.0
E+ M-	30.0	20.0
E+ M+	60.0	50.0

Joint Expected RD = Obs RD $_{E+M-}$ + Obs RD $_{E-M+}$ = 10.0 + 20.0 = 30.0

Joint Observed RD = 50.0

Comparison Observed and Expected Joint Effects: Multiplicative Interaction

- The joint <u>expected effect</u> of risk factor (E) and modifier (M) is estimated by multiplying the independent effects measured by the RR, IRR or OR

- Multiplicative interaction <u>is not present</u> when:

$RR_{E+M+} = RR_{E+M-} \times RR_{E-M+}$

$IRR_{E+M+} = IRR_{E+M-} \times IRR_{E-M+}$

$OR_{E+M+} = OR_{E+M-} \times OR_{E-M+}$

Comparison Observed and Expected Joint Effects: Multiplicative Interaction

- Example – Absence of Multiplicative Interaction

Strata	Observed Incidence Rate (per 1000)	Observed IRR
E- M-	10.0	Ref.
E- M+	20.0	2.0
E+ M-	30.0	3.0
E+ M+	60.0	6.0

Joint Expected IRR = $2.0 \times 3.0 = 6.0$

Joint Observed IRR = 6.0

Comparison Observed and Expected Joint Effects: Multiplicative Interaction

- Example – Presence of Multiplicative Interaction

Strata	Observed Incidence Rate (per 1000)	Observed IRR
E- M-	10.0	Ref.
E- M+	20.0	2.0
E+ M-	30.0	3.0
E+ M+	90.0	9.0

Joint Expected IRR = $2.0 \times 3.0 = 6.0$

Joint Observed IRR = 9.0

Evaluation of Interaction

- Homogeneity of Effects
- Comparison of observed and expected joint effects
- Multivariate modeling

Multivariate Modeling

- The usual approach is to fit regression models that contain cross-product terms and then to analyze regression coefficients
- In general,
  - Logistic regression models detect multiplicative interaction
  - Linear models can be used to assess both additive and multiplicative interactions

Which of the 2 models we should use :

1. **Additive model:**
   - For addressing clinical or public health concerns regarding disease risk/frequency reduction, deviation from **additivity** appears to be most relevant

2. **Multiplicative model:**
   - Able to assessing causality probability
   - More convenient statistical properties

Example

Asbestos Exposure, Smoking and Lung Cancer Risk

	Exposed to asbestos	Not exposed to asbestos
Smokers	35/1000	10/1000
Non-smokers	5/1000	1/1000
Rate difference	30/1000	9/1000
Rate ratio	7.0	10.0

Source: N. Pearce, 2005

Qualitative Vs. Quantitative Interaction

- **Quantitative:**
  - When the association between E and O is in the same direction in each stratum of M, and
  - Strength of association differs in each stratum of M
- **Qualitative:**
  - When the effects of E on O are in opposite directions (crossover) according to M, or
  - When there is an association between E and O in one strata of M, but not in the other

Interaction Vs. Confounding

- Generally, distinct phenomena
- Confounding is undesirable – make it difficult to evaluate whether a statistical association is also causal
- Interaction is part of the web of causation and may have important implications for preventive intervention
- If interaction is found to be present, it is <u>inappropriate to adjust</u> for the effect modifier

Third variable summary

Are stratum-specific OR's the same?

(Using statistical test for interaction or heterogeneity)

YES

NO

INTERACTION

Report **stratum-specific OR or RR**

Crude **OR or RR differs from adjusted?**

YES

NO

CONFOUNDING

Report adjusted OR or RR

NO CONFOUNDING or INTERACTION

Report crude OR or RR

Framework for the interpretation of an epidemiologic study

- Is there a valid statistical association?
  - Is the association likely to be due chance?
  - Is the association likely to be due bias?
  - Is the association likely to be due confounding?

  → Issue of error
- Does the association vary according to other factor?

  → Issue of effect modifier
- Can this valid statistical association be judged as cause and effect?

  → Issue of causal association

Further Readings

- Modern Epidemiology, 3rd Ed., K. Rothman et al.
- Epidemiology: Beyond the Basics, 3rd Ed., M. Szklo & J. Nieto.
- Epidemiology, 5th Ed., L. Gordis.
- Epidemiology: Concepts and Methods, 1st Ed., W. Oleckno.
- A Dictionary of Epidemiology, 6th Ed., M. Porta.

Thank you

Acknowledgements

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