Public Health Sciences 310
Epidemiologic Methods

Lecture 8
Interaction

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Effect Modification/Interaction

- **Interaction:** refers to a situation whereby the effects of the risk factor (on the disease outcome) and that of a third factor strengthen (synergism) or weaken (antagonism) each other.

  ex) Smoking + Alcohol both present : Strength effect (Risk factors interact)

- **Effect modification:** refers to the situation where the effect of the risk factor differs depending on the presence or absence of a third factor (effect modifier). The third variable modifies the effect of the risk factor.

Each of the preceding definitions leads to alternative (yet equivalent) strategies to assess the presence or absence of interaction

- "**Interaction**" definition: Relates to examining whether the observed joint effect of the two risk factors in question is the same or different than the expected from their independent effects.

- "**Effect modification**" definition: Relates to examining whether the effect of the risk factor is homogeneous or heterogeneous when stratified according to the suspected effect modifier.

How are we measuring “effect”?

- + If effect is measured on an additive scale (e.g., measuring attributable risks), we are assessing the presence or absence of **additive interaction** (*Attributable Risk model*).

- x If effect is measured on an relative scale (e.g., measuring relative risks, odds ratios), we are assessing the presence or absence of **multiplicative interaction** (*Relative Risk model*).

Additive and Relative can both exist/absent in an association

Strategies to Evaluate Interaction

- **Homogeneity vs. Heterogeneity of Effects**: Interaction occurs when the effect of a risk factor (A) on the risk of disease (Y) is not homogeneous across strata of a third variable (Z).
  - Homogeneous across strata: confounding
  - Heterogenous across strata: Interaction (EM)

- **Observed vs. Expected**:

  Comparing observed vs. expected joint effects of risk factor (A) and a third variable (Z). Interaction occurs when the observed joint effect of A and Z differs from that expected based on their independent effects.

Evaluating Homogeneity of Effects: ADDITIVE

- Additive Interactions
  Present when the attributable risk in those exposed to factor A varies (heterogeneous) as a function of a third variable (Z).

	3rd Factor **Z**	Factor **A**	Incidence Rate (per 1,000)	Attributable Risk (per 1,000)
NO Additive Interaction	No	No	5	5-5 0 (reference)
		Yes	Presence of 3rd factor 10	10-5 + 5
	Yes	No	20	20-20 reference
		Yes	Presence of 3rd factor 25	25-20 + 5

• AR remains constant across presence of A modified by Z.

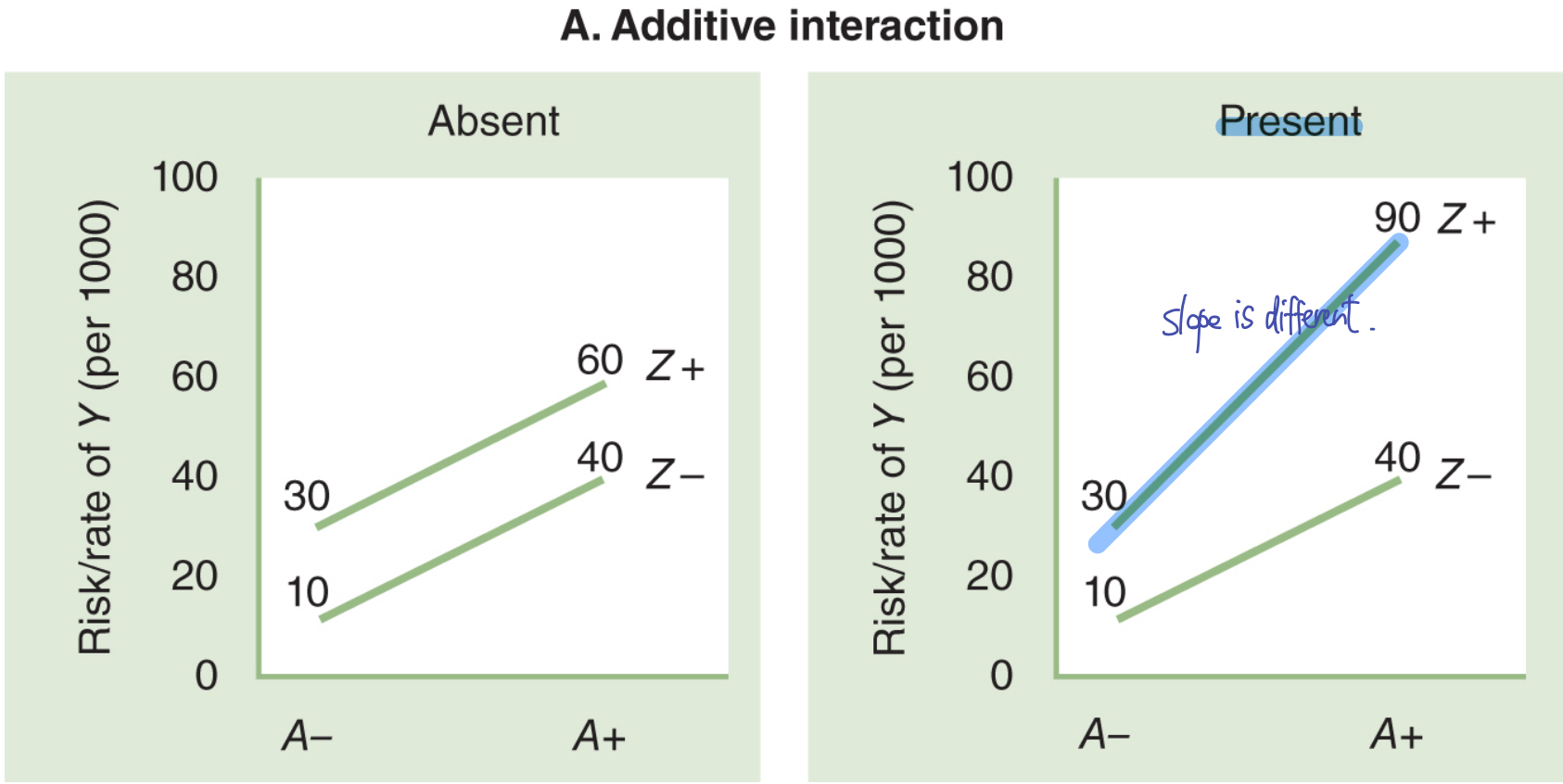
Conclusion: Because the AR's associated with A are not modified by exposure to Z, there is no additive interaction.

Homogeneity of Effects: ADDITIVE (cont)

- Additive Interactions
  Present when the attributable risk in those exposed to factor A varies (heterogeneous) as a function of a third variable (Z).

	Z	Factor A	Incidence Rate (per 1,000)	Attributable Risk (per 1,000)
NO Additive Interaction	No	No	5	0 (reference)
		Yes	10	10-5 5
	Yes	No	20	reference
		Yes	25	25-20 5
YES Additive Interaction	No	No	5	0 (reference)
		Yes	10	10-5 5
	Yes	No	20	reference
		Yes	40	40-20 + 20

Assessment of Homogeneity of Effects



For additive interaction, an arithmetic scale should be used on the ordinate (slopes represent absolute differences). Interaction is absent on the left panel because the absolute difference between *A*+ and *A*– is the same regardless of the presence of *Z* (60 – 30 = 40 – 10 = 30 per 1000). Interaction is present on the right panel because the absolute difference between *A*+ and *A*– is greater when *Z* is present (90 – 30 = 60 per 1000) than when *Z* is absent (40 – 10 = 30 per 1000).

Homogeneity of Effects: MULTIPLICATIVE

- Multiplicative Interaction
  Present when the relative difference (ratio) in the risk of an outcome associated with a risk factor differs as a function of a third variable (Z).

	Z	Factor A	Incidence Rate (per 1,000)	Relative Risk within strata Z
NO Multiplicative Interaction	No	No	5	5/5 1
		Yes	10	10/5 + 2
	Yes	No	20	20/20 1
		Yes	40	40/20 + 2

Conclusion: Because the RR for A is the same for those exposed and those not exposed to Z, there is no multiplicative interaction.

Homogeneity of Effects: MULTIPLICATIVE (cont)

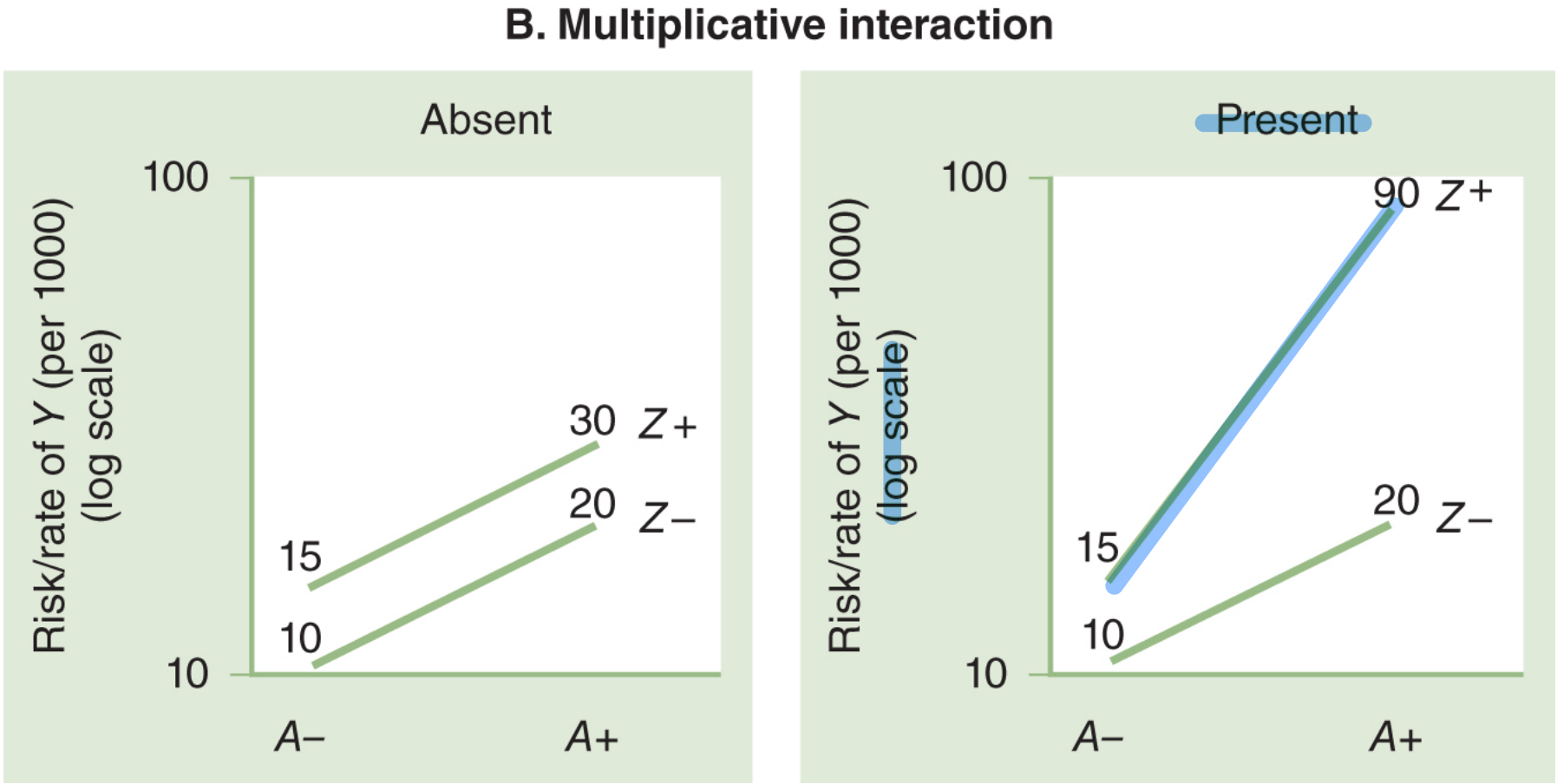
- Multiplicative Interaction

	Z	Factor A	Incidence Rate (per 1,000)	Relative Risk within strata Z
NO Multiplicative Interaction	No	No	5	1
		Yes	10	2
	Yes	No	20	1
		Yes	40	2
YES Multiplicative Interaction	No	No	5	1
		Yes	10	2
	Yes	No	20	1
		Yes	80	4

80/20 = 4

Conclusion: Because RR's associated with A are modified by exposure to Z, multiplicative interaction is present.

Assessment of Homogeneity of Effects



For multiplicative interaction, a logarithmic scale should be used on the ordinate (slopes represent relative differences). Interaction is absent on the left panel because the relative difference between *A*+ and *A*– is the same regardless of the presence of *Z* (30/15 = 20/10 = 2). Interaction is present on the right panel because the relative difference between *A*+ and *A*– is higher when *Z* is present (90/15 = 6) than when *Z* is absent (20/10 = 2).

Strategies to Evaluate Interaction

- **Homogeneity vs. Heterogeneity of Effects**: Interaction occurs when the effect of a risk factor (A) on the risk of disease (Y) is not homogeneous across strata of a third variable (Z).

- **Observed vs. Expected**:

  Comparing observed vs. expected joint effects of risk factor (A) and a third variable (Z). Interaction occurs when the observed joint effect of A and Z differs from that expected based on their independent effects.

Conceptual Framework for Observed vs. Expected

- When the observed joint effects of A and Z differs from the expected joint effects.
- Expected joint effect can be estimated by assuming the effects of A and Z are independent.

Comparing expected vs. observed joint effects

- Independent effects of A and of Z

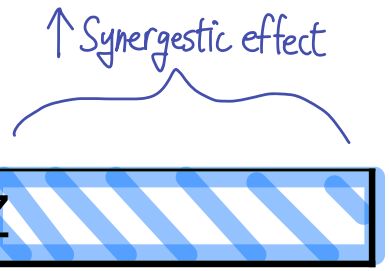
A	Z

- No interaction: joint effects of A & Z = the sum of independent effects

Expected	A + Z
Observed	A + Z

- Positive interaction: joint effects of A & Z > the sum of independent effects

Expected	A + Z
Observed	A + Z



Expected vs. Observed: ADDITIVE

ADDITIVE Interaction

ABSENT

	Observed Incidence rates/10000		Observed AR/10000	
	Factor A		Factor A	
Factor z	-	+	-	+
-	5	10	0 (reference)	10-5 5
+	20	25	20-5 15	25-5 20

different approach

Factor Z + Factor A

Expected joint AR	AR/10000	5 + 15 = 20
Observed joint AR	AR/10000	20

Conclusion: Because the observed joint AR is the same as the expected by adding the individual AR, there is no additive interaction.

Expected vs. Observed: ADDITIVE (cont.)

ADDITIVE Interaction

ABSENT

	Observed Incidence		Observed AR	
	Factor A		Factor A	
Factor z	-	+	-	+
-	5	10	0 (ref)	5
+	20	25	15	20

Expected joint AR	AR/10000	5 + 15 = 20
Observed joint AR	AR/10000	20

ADDITIVE Interaction

PRESENT

	Observed Incidence		Observed AR	
	Factor A		Factor A	
Factor z	-	+	-	+
-	5	10	0 (ref)	10-5 5
+	20	40	20-5 15	40-5 35

Indirect	Expected joint AR	AR/10000	5 + 15 = 20
Direct	Observed joint AR	AR/10000	35

Conclusion: Since the observed joint AR is different than the expected by adding the individual AR's, there is additive interaction.

Expected vs. Observed: MULTIPLICATIVE

MULTIPLICATIVE

Interaction

ABSENT

	Observed Incidence		Observed RR	
	Factor A		Factor A	
Factor z	-	+	-	+
-	5	10	$\frac{5}{5}$ 1 (ref)	$\frac{10}{5}$ 2
+	20	40	$\frac{20}{5}$ 4	$\frac{40}{5}$ 8

Expected joint RR	2 x 4 = 8
Observed joint RR	8

Conclude: Because the observed joint RR is the same as the expected by multiplying the individual RR, there is no multiplicative interaction.

Expected vs. Observed: MULTIPLICATIVE (cont)

Multiplicative Interaction

ABSENT

	Observed Incidence		Observed RR	
	Factor A		Factor A	
Factor z	-	+	-	+
-	5	10	1 (ref)	2
+	20	40	4	8

Expected joint RR	2 x 4 = 8
Observed joint RR	8

Multiplicative Interaction

PRESENT

	Observed Incidence		Observed RR	
	Factor A		Factor A	
Factor z	-	+	-	+
-	5	10	$\frac{5}{5}$ 1 (ref)	$\frac{10}{5}$ 2
+	20	80	$\frac{20}{5}$ 4	$\frac{80}{5}$ 16

Expected joint RR	2 x 4 = 8
Observed joint RR	16

Conclusion: Since the observed joint RR is different than the expected by multiplying the individual RR's, there is multiplicative interaction.

How can we assess interaction in case-control studies?

RR from cohort; but can be use to estimate OR.

- In a case-control study, the homogeneity strategy can be used only to assess the multiplicative interaction because incidence cannot be measured (and thus additive interaction cannot be assessed).

Incidence can't be determined from c.c. study.

- However, you can compare observed to expected to get additive interactions or to get multiplicative effects.

Case-Control Study: Homogeneity of Effects

	Z	Factor A	Cases	Controls	Odds Ratio
NO Multiplicative Interaction	No	No	a	b	1.0 (ref)
		Yes	c	d	X
	Yes	No	a’	b’	1.0
		Yes	c’	d’	~X
YES Multiplicative Interaction	No	No	a	b	1.0
		Yes	c	d	X
	Yes	No	a’	b’	1.0
		Yes	c’	d’	≠ X

Case-control

Age at Menarche and Endometrial Cancer Risk

Several factors are associated with a higher risk of endometrial cancer (e.g., nulliparity, late age at menopause, increased obesity, use of HRT). There is some evidence that the strength of these association differ by menopausal status. The following data are from a paper by La Vecchia et al (JNCI 1984) in which the focus was the association between age at menarche and risk of endometrial cancer.

Age at menarche	Case	Control
< 12	37	72
≥ 12	57	137
Total	94	209

$$\text{OR (crude)} = \frac{(37 \times 137)}{(72 \times 57)} = 1.24$$

"The odds of endometrial cancer is 1.24 times greater in women whose menarche occurred before age 12"

Age at Menarche and Endometrial Cancer Risk by Menopausal Status: Homogeneity of Effects

Stratification

Premenopausal		
Age at menarche	Case	Control
< 12	6	5
≥ 12	7	23

$$OR = \frac{(6/7)}{(5/23)} = 3.95$$

Different Statum ORs: Interaction
Modified by menopausal status.

Postmenopausal		
Age at menarche	Case (+)	Control (−)
(+) < 12	31	67
(−) ≥ 12	50	114

$$OR = \frac{(31/50)}{(67/114)} = 1.05$$

A+ 2−

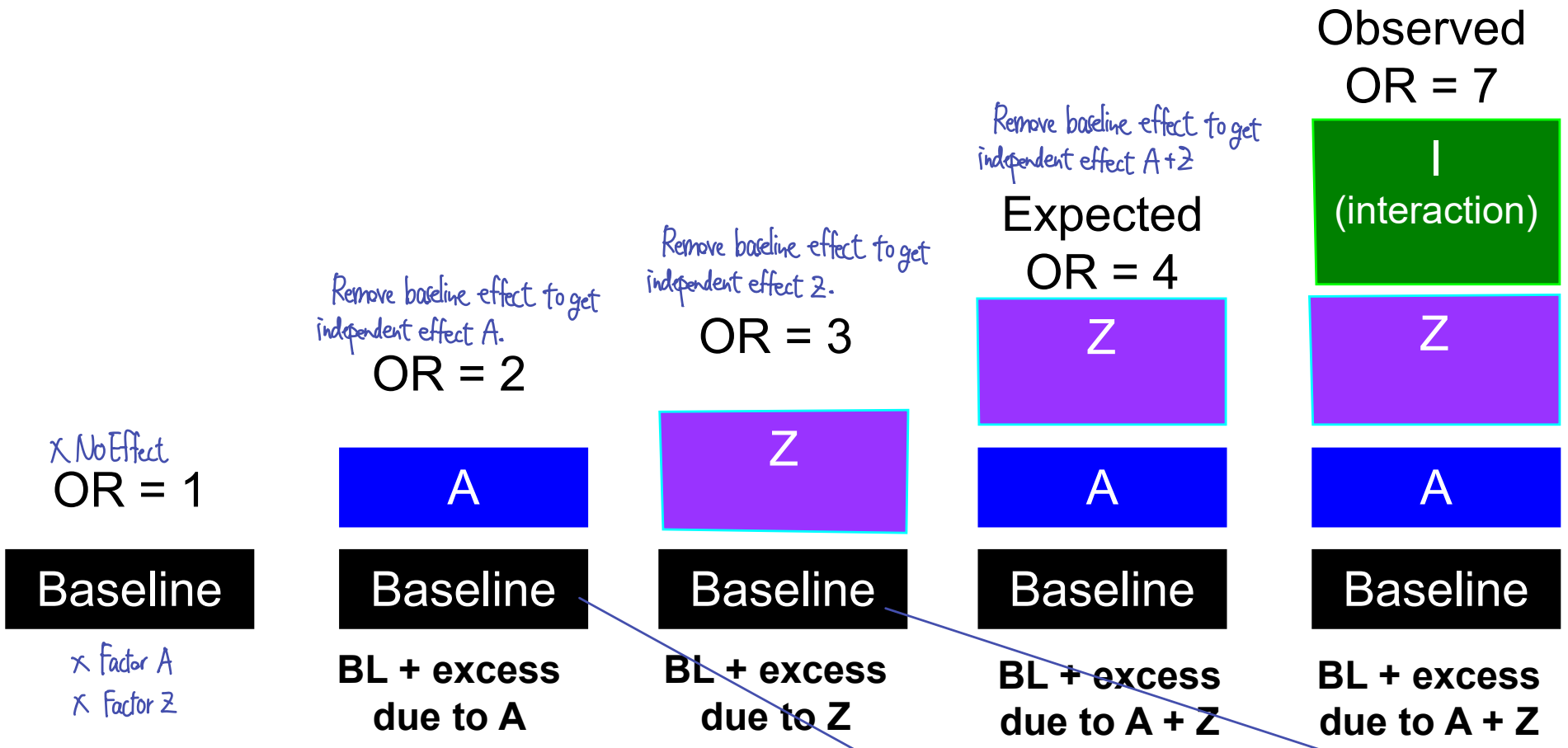
Age at Menarche and Endometrial Cancer Risk by Menopausal Status: Observed vs. Expected

TABLE 13 Outline of table to assess both additive and multiplicative interaction in case-control studies using the strategy of comparing expected and observed joint effects.

What is measured	Exposed to *Z*?	Exposed to *A*?	Cases	Controls	Odds ratio
Reference category	No	No			$OR_{A-Z-} = 1.0$
Independent effect of *A*	No	Yes			OR_{A+Z-}
Independent effect of *Z*	Yes	No			OR_{A-Z+}
Observed joint effect	Yes	Yes			OR_{A+Z+}

Menopausal Status Z	Age at menarche A	Case	Control	OR
− Post	− ≥ 12	50	114	A^-Z^- 1.0 (ref)
	+ < 12	31	67	A^+Z^- 1.05
+ Pre	− ≥ 12	7	23	A^-Z^+ 0.69
	+ < 12	6	5	A^+Z^+ 2.74

Expected OR for an Additive Interaction in a Case-Control Study: Observed vs. Expected



$$\text{Exp OR}_{A+Z+} = 1.0 + (\text{Obs OR}_{A+Z-} - 1.0) + (\text{Obs OR}_{A-Z+} - 1.0)$$

$$= \text{Obs OR}_{A+Z-} + \text{Obs OR}_{A-Z+} - 1.0$$

Extra BL from 2 sets of OR.

Expected OR for an Multiplicative Interaction in a Case-Control Study: Observed vs. Expected

$$\text{Exp OR}_{A+Z+} = \text{Obs OR}_{A+Z-} \times \text{Obs OR}_{A-Z+}$$

Age at Menarche and Endometrial Cancer Risk by Menopausal Status: Observed vs. Expected

Menopausal Status	Age at menarche	Case	Control	OR
− Post	− ≥ 12	50	114	A^-Z^- 1.0
	+ < 12	31	67	A^+Z^- 1.05
+ Pre	− ≥ 12	7	23	A^-Z^+ 0.69
	+ < 12	6	5	A^+Z^+ 2.74

A^+Z^- A^-Z^+

EXPECTED	OR additive	(1.05 + 0.69) - 1	0.74
A^+Z^+	OR multiplicative	(1.05 x 0.69)	0.72
OBSERVED	OR	-	2.74

Another Example

TABLE 14 Example of how to assess interaction on both scales in a case-control study using the formulas Expd $OR_{A+Z+} = Obs\ OR_{A+Z-} + Obs\ OR_{A-Z+} - 1.0$ (additive) and Expd $OR_{A+Z+} = Obs\ OR_{A+Z-} \times Obs\ OR_{A-Z+}$ (multiplicative): the relationship of heavy smoking and oral contraceptive (OC) use to the odds of myocardial infarction in women.

Heavy smoking (Z)*	OC use (A)	Odds ratio
No	No	1.0
No	Yes	4.5
Yes	No	7.0
Yes	Yes	39.0

Observed OR_{A+Z+}: 39.0
Expected OR_{A+Z+}:
Additive model: 4.5 + 7.0 – 1.0 = 10.5
Multiplicative model: 4.5 × 7.0 = 31.5

* ≥ 25 cigarettes/day.

Data from Shapiro S, Slone D, Rosenberg L, Kaufman DW, Stolley PD, Miettinen OS. Oral-contraceptive use in relation to myocardial infarction. *Lancet*. 1979;1:743-747.[10]

Interaction vs. Confounding

- Biases and confounding effects distort true causal associations. Remove
  - A variable may confound in one population and not another population
  - Strategies: avoid, eliminate, reduce, control
- Effect Modification is informative Detect
  - Provides insight into the nature of the relationship between exposure and outcome.
  - May be the most important result of a study.
  - It should be reported and understood.
- The purpose of the analysis is to **remove** confounding but **detect** interaction

Detecting Interaction

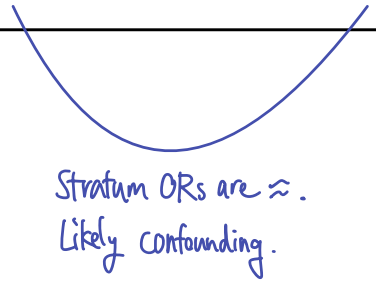
1. Look at the effect estimates in strata formed by levels of the third factor

   When interaction is present, these stratum-specific risk estimates will be different.

2. Look at the test for homogeneity p-value.

What if the Strata Specific ORs Appear to be Different but not sure Adjustment is Appropriate?

Odds Ratios				
Crude OR For Watch Game and MVI	No Beer	Beer Drinker	Confounding	Effect Modification
23	8.2	9.0	✓	



Test for Homogeneity: Mantel-Haenszel

$$\chi^2_{k-1} = \sum_{i-1}^{K} \frac{(\ln OR_i - \ln OR_{MH})^2}{\text{Var}(\ln OR_i)}$$

Ho: the strength of the association is homogenous across all strata

Test for Homogeneity: The Absurd Example

$$\chi^2_{k-1} = \sum_{i-1}^{K} \frac{(\ln OR_i - \ln OR_{MH})^2}{\text{Var}(\ln OR_i)}$$

$OR_{MH}=8.5$

Strata I	OR	ln OR_i	$(\ln OR_i - \ln OR_{MH})^2$	Var ($\ln OR_i$)	
No Beer Drinking	8.2	2.104	$(2.104-2.140)^2$	(1/10+1/10+1/10+1/82)	0.00415
Beer Drinking	9.0	2.197	$(2.197-2.140)^2$	(1/81+1/9+1/9+1/9)	0.00939
				Σ	0.01355

$\chi^2_{k-1} = 0.0135$ where (k=2) so p>0.5

Fail to reject H_0: Homogenous → Confounding.

Odds Ratios				
Crude OR For watch game and MVI	No Beer	Beer Drinker	Confounding	Effect Modification
23	8.2	9.0	Yes	No

Since confounding is present, but there is no effect modification, then we can compute an adjusted estimate of association between watching football game and MVI adjusted for Beer Drinking (as we did before).

Regenerate hypothesis based on:

Article Report results based confounder/EM.

Body Mass Index and Overall Survival of Patients with Newly Diagnosed Multiple Myeloma

Patient Cohort

Bei Wang [1], Benjamin A. Derman [2], Spencer S. Langerman [1], Julie Johnson [3], Wei Zhang [4], Andrzej Jakubowiak [2] and Brian C.-H. Chiu [1,*]

		At-Risk (N)	Deaths (N)	Model 1 [a]	Model 2 [b]
				Hazard Ratio (95% confidence interval)	
At diagnosis					
				N = 508	N = 494
BMI	Normal	97	51	1.0 (Referent)	1.0 (Referent)
	Overweight	139	73	0.93 (0.64, 1.33)	0.89 (0.62, 1.29)
	Obese	122	62	0.87 (0.60, 1.28)	0.88 (0.60, 1.28)
	p Trend [d]			0.23	0.37
Adulthood maximum					
BMI	Normal	29	17	1.0 (Referent)	1.0 (Referent)
	Overweight	77	48	1.06 (0.60, 1.86)	0.93 (0.51, 1.68)
	Obese	118	69	0.88 (0.51, 1.51)	0.80 (0.45, 1.40)
	p Trend [d]			0.28	0.24

Adjust for prognostic factor/clinical variable.

Article

Body Mass Index and Overall Survival of Patients with Newly Diagnosed Multiple Myeloma

Bei Wang [1], Benjamin A. Derman [2], Spencer S. Langerman [1], Julie Johnson [3], Wei Zhang [4], Andrzej Jakubowiak [2] and Brian C.-H. Chiu [1,*]

Stratify by gender

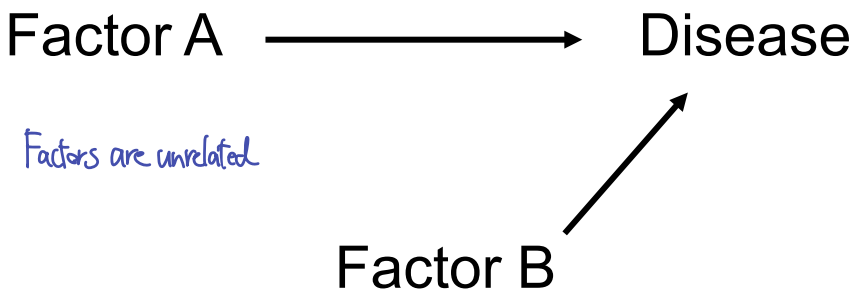
	Female (better survival)			Male			*p* Homogeneity [c]
	At-Risk (N)	Deaths (N)	HR 95% CI [a]	At-Risk (N)	Deaths (N)	HR 95% CI [a]	
							At diagnosis
			N = 215			N = 280	
Normal	47	31	1.0 (referent)	47	20	1.0 (referent)	
Overweight	44	26	0.64 (0.36, 1.12)	89	47	1.15 (0.67, 1.97)	
Obese	61	25	0.39 (0.22, 0.71)	58	37	1.57 (0.90, 2.74)	Heterogenous
p Trend [b]			<0.001			0.06	0.01
							Adulthood maximum
			N = 140			N = 190	
Normal	20	13	1.0 (referent)	9	4	1.0 (referent)	
Overweight	22	16	0.81 (0.36, 1.86)	51	32	1.45 (0.50, 4.20)	
Obese	52	25	0.45 (0.21, 0.97)	61	44	1.68 (0.59, 4.82)	
p Trend [b]			0.03			0.57	0.08

Sex: gender may modify association for obesity and BMI.

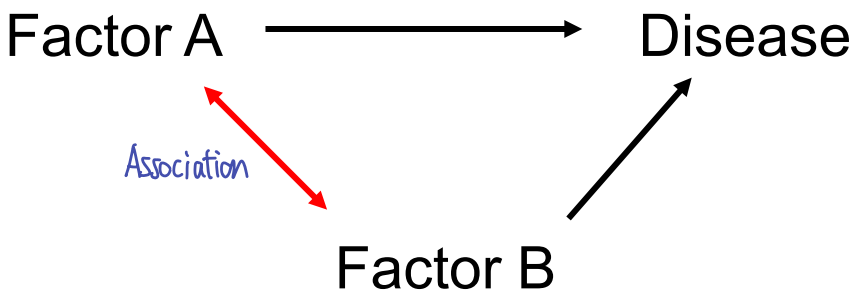
Cancers **2022**, *14*, 5331. https://doi.org/10.3390/cancers14215331

SUMMARY: Four Possible Relationships Between Two Risk Factors

- *Independent risk factors*: Factor A is a risk factor for disease and this association is not influenced by Factor B.



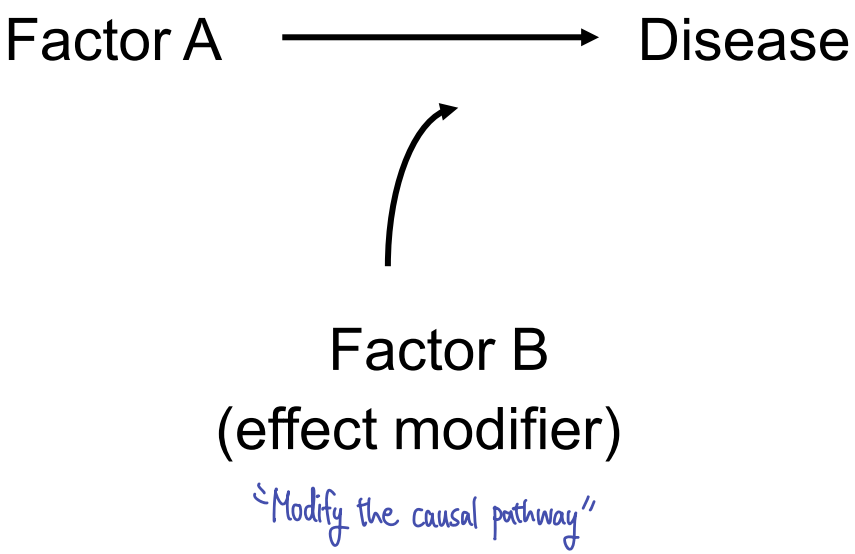
- *Confounding:* association of Factor A and disease is partially or totally explained by another risk factor, Factor B.



Four Possible Relationships (cont.)

- *Same causal pathway*: Factor A causes Factor B causes the disease.

- *Effect modification*: The strength of association between Factor A and disease depends on the level of Factor B.



Confounding or Effect Modification

Association between Factor A and Outcome.

What is effect of Factor B?

Odds Ratios					
Crude OR For A & Outcome	Factor B Stratum 1		Factor B Stratum 2	"Co-found" ≈ for stratums Confounding	Effect Modification
4	4	=	4	No	No
4	1.5	=	1.5	Yes	No
4	2.8	≈	1.0	If homogenous $p > 0.05$ Yes	If heterogenous $p < 0.05$ Yes
4	1.2		9.4	?	Yes

When to Do What?

- When it is appropriate to present stratified results?
  - When the association across strata are different (i.e., effect modification). (OR1 ≠ OR2)
  - You can conduct a statistical test for heterogeneity.
  - Be careful with sparse data (next slide)

- When it is appropriate adjust?
  - When the risk across strata is homogeneous (i.e., no effect modification). (OR crude ≠ OR1 = OR2) Confounding
  - Remember, you must be very careful in interpreting your findings if you adjust for an intermediate factor in the causal pathway.

Detecting Interaction

1. Look at the effect estimates in strata formed by levels of the third factor

   When interaction is present, these stratum-specific risk estimates will be different.

2. Look at the test for homogeneity / heterogeneous

   Confounding / EM

3. Do not over-interpret an unexpected and/or biologically implausible significant test of homogeneity. Sometimes this happens by chance and NEEDS CONFIRMATION in other populations.
4. Unexpected heterogeneity is "hypothesis-generating" based on interaction → Need to detect.
5. Interaction tests in effect split the sample, and so studies not designed to detect interactions are often too small (underpowered) to find them.

↓ Studies don't usually define many ↑↑↑ populations.