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Types of effect measure modification

PHW250B

Effect measure modification topics

- **Types of interaction**
  - Statistical interaction
  - Effect measure modification
  - Biologic / causal interaction

  Focus of this video

    - Sufficient component cause model
    - Potential outcomes / counterfactual model
- **Detecting interaction**
  - Assess homogeneity of effects across levels of a potential modifier
  - Test for statistical interaction using a chi square test of homogeneity
  - Detect additive scale interaction using either additive or relative scale measures

Pearl, Glymour & Jewell 2016

Multitudes of terms

- The term “interaction” is used across different disciplines to describe statistical, biologic, and public health concepts.
- We often say “effect modification” but the technical term is “effect measure modification” since in many cases we are not estimating a causal effect and are merely observing differences in our estimated measure of association by a third variable.
- The goal of this video is to help clarify what these terms mean.
- We will do our best to be clear about what we are referring to in this class.

Comparing terms

Common to each term: The effect of two exposures together is different from the sum of their two independent effects.

Statistical interaction

Definition based on effect estimate in a study, including bias

Depends on the scale of the measure.

Corresponds to effect measure modification when no bias is present.

Effect measure modification

Definition based on unbiased effect estimate in a study

Depends on the scale of the measure (additive vs. relative).

Corresponds to statistical interaction when no bias is present.

Biologic / causal interaction

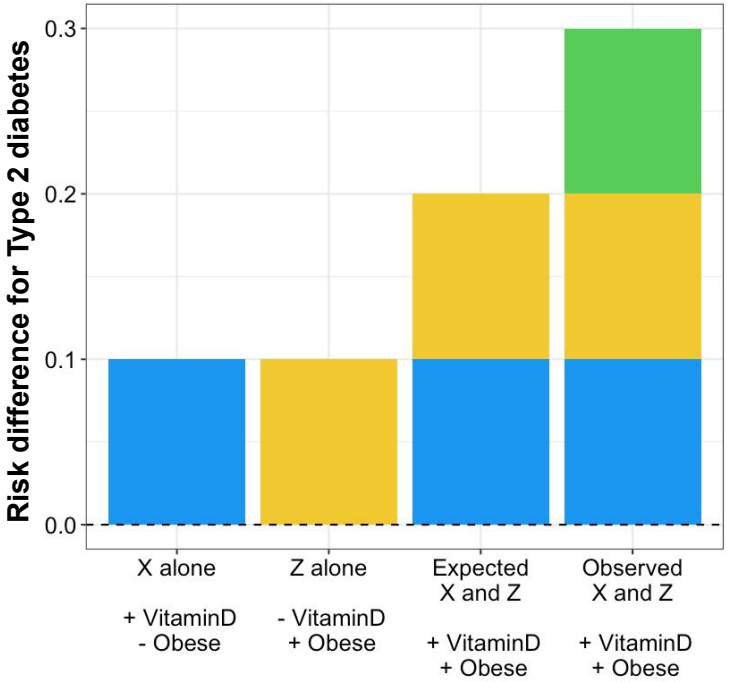
Definition based on true relationship in the population

If we do not see interaction in a study, it does not imply that there is no biologic interaction in all people.

Rothman et al, *Modern Epidemiology*. 3rd Ed.

Statistical interaction & Effect measure modification

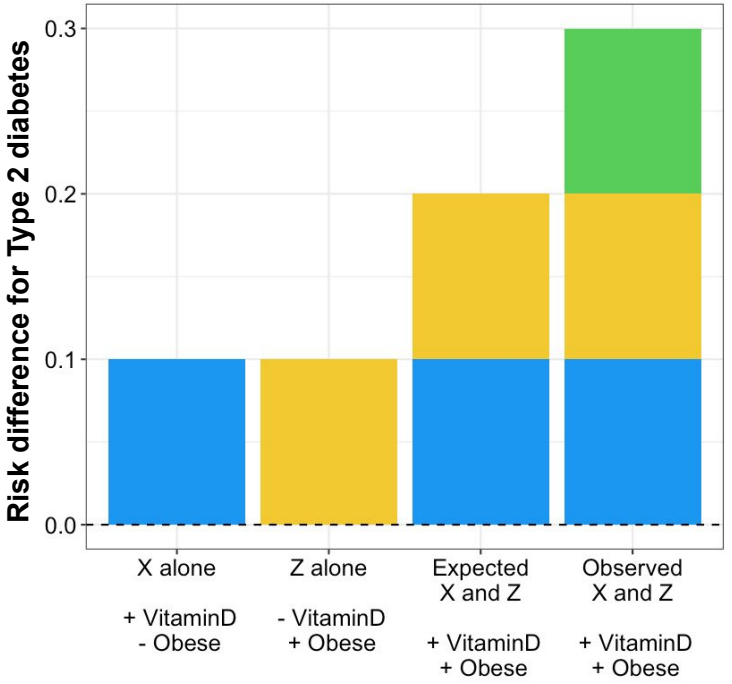
- **Statistical interaction:** Departure from additivity of estimated effects on the chosen outcome scale.
- **Effect measure modification:** Departure from additivity of the effects in the study population on the chosen outcome scale
- The green bar in the graph to the right indicates the “departure from additivity” since it implies risk above and beyond the total risk for each exposure on its own.
- Methods for assessing statistical interaction can also be used to assess effect measure modification if we assume that there is no bias in our effect estimates.



Rothman et al, *Modern Epidemiology*. 3rd Ed.

What does it mean if we find statistical interaction?

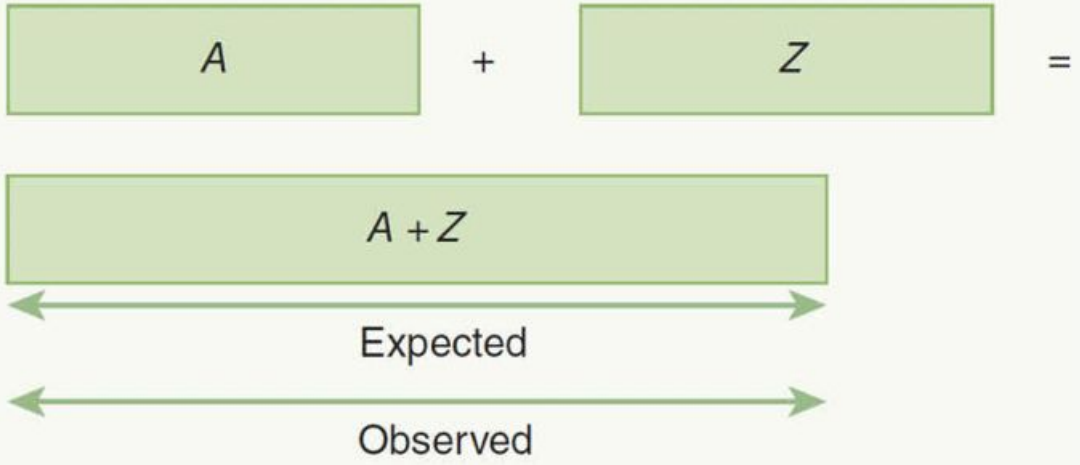
- The presence of additive or relative scale statistical interaction describe patterns on that scale in the population subgroups with the specific combination of exposure.
- Statistical interaction does not necessarily imply biologic or causal interaction.
- In the example to the right, the results imply that on the additive scale, there is a greater risk of type 2 diabetes among population subgroups who are obese and take vitamin D supplements than among other population subgroups.



Rothman et al, *Modern Epidemiology*. 3rd Ed.

Assessing interaction by comparing observed vs. expected joint effects

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



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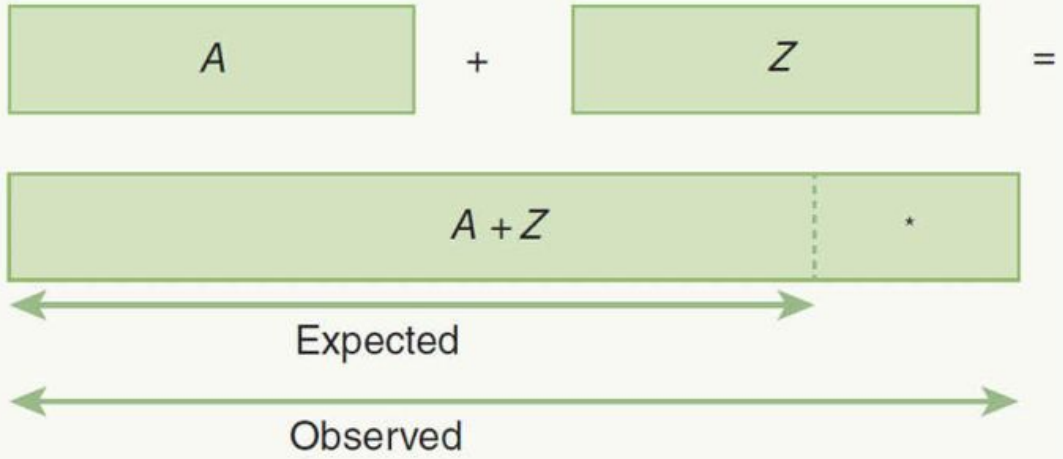
Synergism

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



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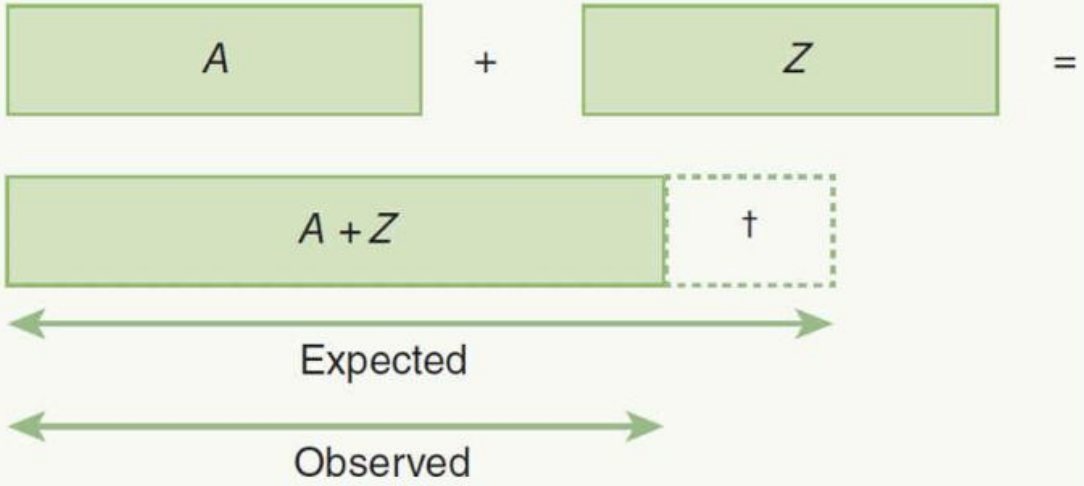
Antagonism

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



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Biologic interaction

- Two models exist describing how biological or causal interaction occurs
- **Mechanistic model:** the notion of direct physical or chemical reactions among exposures that cause disease.
  - Example: quenching of free radicals in tissues by miscellaneous antioxidants
  - It is rare for a mechanism to account for all observed cases of disease.
  - A relationship between exposure and disease can be predicted from numerous different mechanisms of disease development, even when no bias is present.
- **Potential outcome** or **counterfactual causal model** or **sufficient component cause model:** general causal models that do not depend on specific mechanistic models (see two upcoming videos on these topics)

Rothman et al, *Modern Epidemiology*. 3rd Ed.

“Qualitative” and “extreme” interaction

- **Qualitative** interaction is present when the effects of an exposure on an outcome are in the opposite direction (i.e., one is protective and one increases risk) or when the there is an association in one stratum and a no association in the other.
    - *(This term is used in Szklo & Nieto)*
- **Extreme** interaction is another term for when the effects of an exposure on an outcome are in the opposite direction
    - *(This term is used in Jewell)*

Jewell. *Statistics for Epidemiology.* 2004.

Szklo & Nieto 4th Ed.

If what we care about is biologic interaction, why bother with statistical interaction?

- Statistical interaction is still important to assess in epidemiologic studies.
- Statistical interaction may provide insight into potential biologic interaction and into how a combination of risk factors affect disease risk.
- If statistical interaction is present and we ignore it, we may make an incorrect assessment of the magnitude of a measure of association, even when there is no confounding.
    - This is because ignoring interaction means we pool over the effects in strata of a variable, which could mask important associations with that variable.
    - This is especially important when there is “extreme interaction”, i.e. when the direction of the association differs and the magnitude of the association is not small when stratifying by a variable.

Example of extreme statistical interaction

- Trial of two drugs (A and B) to reduce the risk of high blood pressure. In this example, the combination of the two drugs leads to an increase in the risk of blood pressure.
  - RD for Drug A alone: -0.50
  - RD for Drug B alone: -0.25
  - Observed RD for Drug A & B: 2.00
- This is different from antagonistic interaction because the direction of the effect changes. This is what antagonistic interaction might look like on the additive scale.
  - RD for Drug A alone: -0.50
  - RD for Drug B alone: -0.25
  - Expected RD for Drug A & B: -0.50 + -0.25 = -0.75
  - Observed RD for Drug A & B: -0.10

Jewell. *Statistics for Epidemiology.* 2004.

Summary of key points

- The technical definitions for statistical interaction, effect measure modification, and biologic/causal interaction make important distinctions between these terms.
- Using only epidemiologic data, it is difficult to confidently conclude whether biologic interaction exists. We would need information on the true biological model or mechanism to do so.
- Most of the time, we can only assess statistical interaction. We hope to assess effect measure modification, but it's difficult to know if our estimates are truly unbiased.

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Detecting and Interpreting Statistical Interactions

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Effect measure modification topics

- **Types of interaction**
  - Statistical interaction
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  - Biologic / causal interaction
    - Sufficient component cause model
    - Potential outcomes / counterfactual model
- **Detecting interaction**
  - Assess homogeneity of effects across levels of a potential modifier
  - Test for statistical interaction using a chi square test of homogeneity
  - Assess whether the observed effect of two exposures differs from the expected effect of two exposures

Focus of this video

Pearl, Glymour & Jewell 2016

Interpreting interactions

An observed interaction in a dataset could reflect any of the following:

- A true biologic, causal interaction
- Heterogeneity due to random variability
- Heterogeneity due to confounding
- Heterogeneity due to bias
- Heterogeneity due to differential intensity of exposure

Szklo & Nieto 4th Ed.

Heterogeneity due to random variability

- Random variability can be produced by the stratification of a potential effect modifier
- This is most likely to occur when an investigator obtains null results in a study and wonders whether a result occurs in certain subpopulations, so he carries out a stratified analysis (e.g., estimate the association by gender or education level).
- The sample size is smaller to estimate the same measure of association in subgroup analyses.
- As a result, precision is lower, increasing the probability of finding heterogeneous measures of association due to chance rather than a true causal interaction.
- This is why it is best to pre-specify potential effect modifiers.

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Heterogeneity due to confounding

- Differential confounding across strata may explain observed heterogeneity in the measure of association.
- Confounding could either exaggerate or decrease heterogeneity.
- For this reason, adjusting for confounders while assessing effect modification is important. This can be done using multivariate statistical models (more on this later in the course).

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Example: Heterogeneity due to confounding

Gender/smoking	Coffee intake	Cases	Controls	Odds ratio
Female/ nonsmoker	Yes	10	10	1.0
	No	90	90	
	Total	100	100	
Male/total	Yes	38	22	2.2
	No	62	78	
	Total	100	100	
Male/smoker	Yes	35	15	1.0
	No	35	15	
	Total	70	30	
Male/ nonsmoker	Yes	3	7	1.0
	No	27	63	
	Total	30	70	

Assume that smoking causes cancer *Y*, 50% of smokers but only 10% of nonsmokers drink coffee, coffee intake is not independently related to cancer *Y*, all females are nonsmokers, and 70% of male cases and 30% of male controls are smokers.

- Comparing the stratified to pooled ORs for males, we see that smoking is a confounder in males.
- This causes apparent heterogeneity in the ORs for males vs. females (OR=2.2 vs. 1.0).
- If the OR for males were adjusted for confounding, the apparent heterogeneity would disappear.

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Heterogeneity due to bias

- Apparent heterogeneity may be due to differential bias between strata
- Bias could either exaggerate or decrease heterogeneity.
- Example: study of race, education, and miscarriage

	White		Black		
	Number	Risk/100	Number	Risk/100	Black/white ratio
Total	325	7.7	93	5.5	0.7
Mother's years of education					
< 9	12	10.4	0	–	–
10–11	52	8.0	15	4.5	0.6
12	111	6.3	44	4.7	0.7
≥ 13	150	9.2	33	9.5	1.0

- Only looking at the "Total" row, black women had a lower risk of miscarriage than white women.
- The authors believe this was due to underascertainment of miscarriage among blacks.
- Stratifying by education level, the absence of data among women with <9 years of education suggests that there may have been systematic underreporting in this category.

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Heterogeneity due to differential intensity of exposure

- Heterogeneity can occur when the level of exposure to a risk factor is associated with the potential effect modifier's levels.
- Example: study of asthma and airborne soy dust
  - RR = 4.4 when wind speed was <12 miles per hour
  - RR = 1.7 when wind speed was ≥ 12 miles per hour
  - Slow wind speed may have caused heavier exposure to soy dust
  - If so, this does not reflect a true biological interaction between soy dust and wind speed.
  - This does not mean that this information is not useful — it can inform public health intervention to reduce exposure to soy dust.

Szklo & Nieto 4th Ed.

Detecting statistical interaction / effect measure modification

Three methods covered in this course:

1. Assess homogeneity of effects across levels of a potential modifier
2. Test for statistical interaction using a chi square test of homogeneity
3. Assess whether the observed effect of two exposures differs from the expected effect of two exposures
    - Modern causal approaches to assessing effect modification use this method

Rothman et al, *Modern Epidemiology*. 3rd Ed.

Summary of key points

- Random error, confounding, bias, and other factors besides true biologic / causal interaction may be responsible for observed heterogeneity of effects.

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Chi square test for homogeneity

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Focus of this video

Pearl, Glymour & Jewell 2016

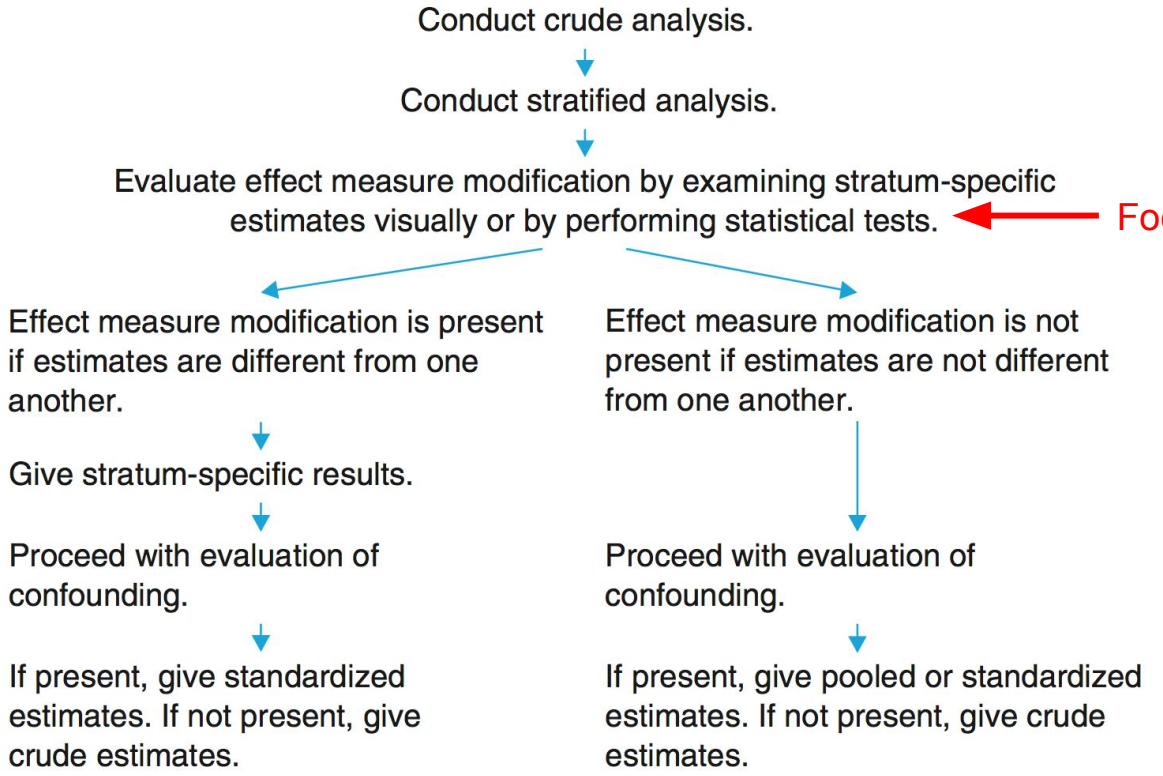

FIGURE 13–1 Decision Tree for Evaluating and Presenting Data with Effect Measure Modification and Confounding

Aschengrau & Seague. 2014. *Essentials of Epidemiology.*

Chi-square test for homogeneity

- This test allows us use “observed data stratified over levels of one or more extraneous variables to assess whether we can plausibly assume that a measure of association is consistent across strata”
- We assess evidence that the measure of association varies across strata to see whether a third variable other than the exposure or outcome modifies the measures of association.
- If we use a relative scale measure, this test assesses relative scale interaction. If we use an additive scale measure, this test assesses additive scale interaction.

Chi-square test for homogeneity

- **Purpose**: to assess whether stratum specific estimates are heterogeneous
- **Null hypothesis**: Stratum-specific measure of association are equal to each other
- **Alternative hypothesis**: At least two of the stratum-specific measure of association are not equal to each other

Chi-square test for homogeneity

- Calculate the test statistic:

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

I indexes the strata of the effect modifier

k is the total number of strata

Chi-square test for homogeneity

- Calculate the test statistic:

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$$W_i = [1/a_i + 1/b_i + 1/c_i + 1/d_i]^{-1}$$

W_i is a weight that is inversely proportional to the variance of ln OR_i

Chi-square test for homogeneity

- Calculate the test statistic:

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$$W_i = [1/a_i + 1/b_i + 1/c_i + 1/d_i]^{-1}$$

OR_i is the stratum-specific odds ratio

Chi-square test for homogeneity

- Calculate the test statistic:

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$$W_i = [1/a_i + 1/b_i + 1/c_i + 1/d_i]^{-1}$$

$$\ln OR = \frac{\sum_{I=1 \text{ to } k} w_i \ln OR_i}{\sum_{I=1 \text{ to } k} w_i}$$

Can be:

1) the Mantel-Haenszel OR or

2) a weighted OR
(focus of this video)

Chi-square test for homogeneity

- Calculate the test statistic:

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

- The **test-statistic** follows a chi-square distribution.
- Obtain a **p-value** for the test using a chi-square table or statistical software, such as R.
  - R command: `dchisq(#,df=#)`
  - df = degrees of freedom = k-1

Example

TABLE 13–3 Data from a Hypothetical Case–Control Study of DDE Exposure and Breast Cancer Stratified According to Lactation History

	Never breastfed		*Breastfed*	
DDE level	*Cases*	*Controls*	*Cases*	*Controls*
High	140	300	360	300
Low	550	2,600	950	800
Total	690	2,900	1,310	1,100
	Stratum-specific odds ratio = 2.2		Stratum-specific odds ratio = 1.0	

Null hypothesis: The OR for DDE level and breast cancer among women who breastfed and the OR for women who never breastfed are equal.

Alternative hypothesis: The OR for DDE level and breast cancer among women who breastfed and the OR for women who never breastfed are different.

Aschengrau & Seague. 2014. *Essentials of Epidemiology.*

TABLE 13–3 Data from a Hypothetical Case–Control Study of DDE Exposure and Breast Cancer Stratified According to Lactation History

	Never breastfed i=1		*Breastfed* i=2	
DDE level	*Cases*	*Controls*	*Cases*	*Controls*
High	140	300	360	300
Low	550	2,600	950	800
Total	690	2,900	1,310	1,100
	Stratum-specific odds ratio = 2.2		Stratum-specific odds ratio = 1.0	

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2 \qquad W_i = [1/a_i + 1/b_i + 1/c_i + 1/d_i]^{-1}$$

$W_1 = (1/140 + 1/300 + 1/550 + 1/2600)^{-1} = 78.87$
$W_2 = (1/360 + 1/300 + 1/950 + 1/800)^{-1} = 118.85$

Aschengrau & Seague. 2014. *Essentials of Epidemiology.*

TABLE 13–3 Data from a Hypothetical Case–Control Study of DDE Exposure and Breast Cancer Stratified According to Lactation History

	Never breastfed i=1		*Breastfed* i=2	
DDE level	*Cases*	*Controls*	*Cases*	*Controls*
High	140	300	360	300
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Total	690	2,900	1,310	1,100
	Stratum-specific odds ratio = 2.2		Stratum-specific odds ratio = 1.0	

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$\ln OR_1 = \ln (140 \times 2600 / 300 \times 550) = 0.791$
$\ln OR_2 = \ln (360 \times 800 / 950 \times 300) = 0.010$

Aschengrau & Seague. 2014. *Essentials of Epidemiology.*

TABLE 13–3 Data from a Hypothetical Case–Control Study of DDE Exposure and Breast Cancer Stratified According to Lactation History

	Never breastfed i=1		*Breastfed* i=2	
DDE level	*Cases*	*Controls*	*Cases*	*Controls*
High	140	300	360	300
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Total	690	2,900	1,310	1,100
	Stratum-specific odds ratio = 2.2		Stratum-specific odds ratio = 1.0	

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2 \qquad \ln OR = \frac{\sum_{I=1 \text{ to } k} w_i \ln OR_i}{\sum_{I=1 \text{ to } k} w_i}$$

$W_1 = 78.87$
$W_2 = 118.85$
$\ln OR_1 = 0.791$
$\ln OR_2 = 0.010$

ln OR = [(78.87 x 0.791)+(118.85 x 0.010)] / (78.87+118.85) = 0.322

Aschengrau & Seague. 2014. *Essentials of Epidemiology.*

TABLE 13–3 Data from a Hypothetical Case–Control Study of DDE Exposure and Breast Cancer Stratified According to Lactation History

	Never breastfed i=1		*Breastfed* i=2	
DDE level	*Cases*	*Controls*	*Cases*	*Controls*
High	140	300	360	300
Low	550	2,600	950	800
Total	690	2,900	1,310	1,100
	Stratum-specific odds ratio = 2.2		Stratum-specific odds ratio = 1.0	

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2 \qquad \ln OR = \frac{\sum_{I=1 \text{ to } k} w_i \ln OR_i}{\sum_{I=1 \text{ to } k} w_i}$$

$W_1 = 78.87$
$W_2 = 118.85$
$\ln OR_1 = 0.791$
$\ln OR_2 = 0.010$
$\ln OR = 0.322$

$X^2_{HOM} = 78.87 \times (0.791-0.322)^2 + 118.85 \times (0.010-0.322)^2 = 28.918$

Aschengrau & Seague. 2014. *Essentials of Epidemiology.*

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

X^2_{HOM} = 28.918

Degrees of freedom (df) = 2-1 = 1
Get the p-value in R: **`dchisq`**(28.918, **`df`**=1) = <0.001

Conclusion: We can reject the null hypothesis that the ORs are the same across strata of breastfeeding status. Effect modification on the relative scale is present.

- For the chi-square test of homogeneity, we use a p-value cutoff for statistical significance of 0.2
  - (i.e., p-value <0.2 is statistically significant).
- This is because the statistical test of homogeneity has limited statistical power
- We err on the side of concluding that interaction is present

Formula for a risk ratio

$$\mathrm{X}^2_{\mathrm{HOM}} = \sum_{\mathrm{I}=1 \text{ to } k} W_i(\ln \mathrm{OR}_i - \ln \mathrm{OR})^2$$

This is the formula we just learned.

Formula for a risk ratio

$$X^2_{\text{HOM}} = \sum_{\text{I}=1 \text{ to } k} W_i(\ln \text{OR}_i - \ln \text{OR})^2$$

$$X^2_{\text{HOM}} = \sum_{i=1}^{k} \frac{(\ln \text{OR}_i - \ln \text{OR})^2}{W_i}$$

It can be rewritten like this.

Formula for a risk ratio

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln OR_i - \ln OR)^2}{W_i}$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln OR_i - \ln OR)^2}{\text{var}(\ln(OR_i))}$$

The weights in the denominator of the formula are actually the variance of the ln(OR) in each stratum.

Formula for a risk ratio

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln OR_i - \ln OR)^2}{W_i}$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln OR_i - \ln OR)^2}{\text{var}(\ln(OR_i))}$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln RR_i - \ln RR)^2}{\text{var}(\ln(RR_i))}$$

When we write the formula this way, we can swap in the RR (CIR or IDR) for the OR.

Formula for a risk difference

$$X^2_{HOM} = \sum_{I=1 \text{ to } k} W_i(\ln OR_i - \ln OR)^2$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln OR_i - \ln OR)^2}{W_i}$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(\ln OR_i - \ln OR)^2}{\text{var}(\ln(OR_i))}$$

$$X^2_{HOM} = \sum_{i=1}^{k} \frac{(RD_i - RD)^2}{\text{var}((RD_i))}$$

When we write the formula this way, we can swap in the RD for the OR. If we use the RD, we don't need to take the log

Table of formulas

General formulation: $X^2_{HOM} = \sum_{i=1}^{k} \frac{(MA_i - MA)^2}{var((MA_i))}$

Measure of association (MA)	MA_i	$var(MA_i)$
(ln) Odds Ratio	$\ln\left(\frac{a_i \times d_i}{b_i \times c_i}\right)$	$\frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}$
(ln) Relative risk	$\ln\left(\frac{a_i/(a_i+b_i)}{c_i/(c_i+d_i)}\right)$	$\frac{b_i}{a_i(a_i+b_i)} + \frac{d_i}{c_i(c_i+d_i)}$
Risk difference	$\frac{a_i}{(a_i+b_i)} - \frac{c_i}{(c_i+d_i)}$	$\frac{a_i b_i}{(a_i+b_i)^3} + \frac{c_i d_i}{(c_i+d_i)^3}$

Limitations

- We cannot fully evaluate interaction using this test.
- If the sample size is large, small heterogeneity of no meaningful value may be statistically significant.
- There may be measures of association that vary substantially across a third variable, but the test may not show statistical significance.
- In practice, most epidemiologists assess statistical interaction using regression models (we'll discuss this later in the course).

Summary

- We can use the **chi-square test of homogeneity** to assess whether stratified measures of association are statistically different from each other.
- We learned the **Woolf method** for this test but there are also other methods.
- We went over an example of how to assess this for an odds ratio, but you can also conduct this test for a **relative risk** or **risk difference**.
- This method does not allow you to simultaneously adjust for confounding, which is a drawback. For this reason, epidemiologists usually use multivariate regression models to assess interaction (more on this later in the course).

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The sufficient component cause model & causal interaction

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  - Statistical interaction
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    - Sufficient component cause model
    - Potential outcomes / counterfactual model

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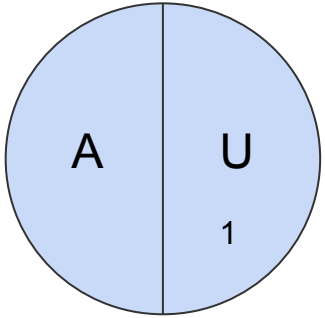
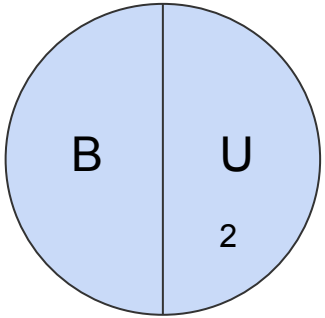
Pearl, Glymour & Jewell 2016

Calculate the prevalence

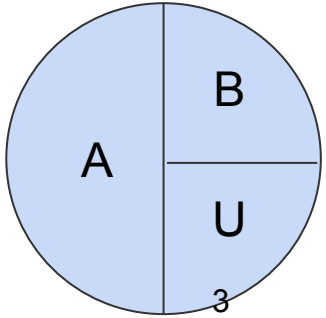
Example: Population of 1,000 people. The number below each pie indicates the number who would develop the disease if they had the combination of risk factors in the pie. The U's indicate



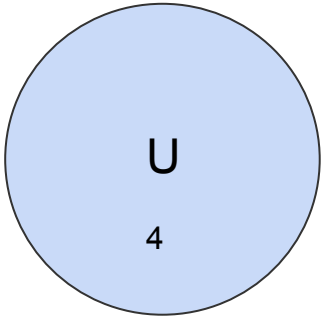
100 People



50 People



50 People



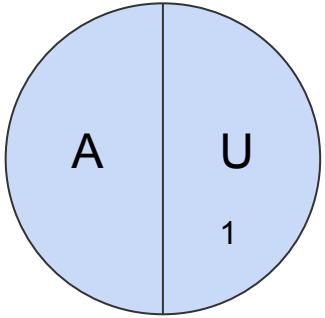
100 People

Estimate the prevalence if:

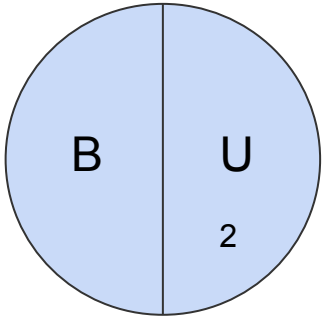
1) A and B were absent.
2) A was present and B was absent.
3) B was present and A was absent.
4) A and B were present.

How to calculate prevalence using causal pies

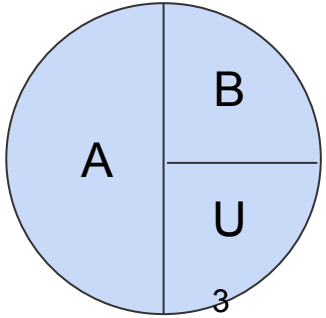
The number of people in each pie only is included in the prevalence if all non-U variables were present.



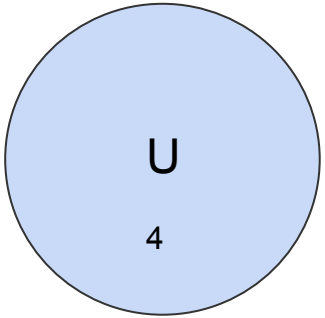
100 People



50 People



50 People



100 People

Estimate the prevalence if:

1) A and B were absent.
2) A was present and B was absent.
3) B was present and A was absent.
4) A and B were present.

Which pies should be included?

Pie 4 (not pies 1, 2, 3 since A & B were absent

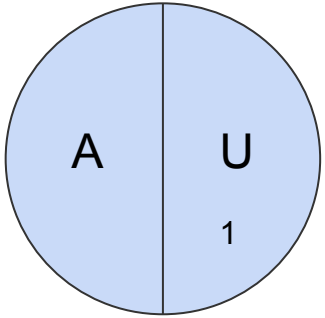
Pies 1, 4 (not pies 2 or 3 since B was absent)

Pies 2, 4 (not pies 1 or 3 since A was absent)

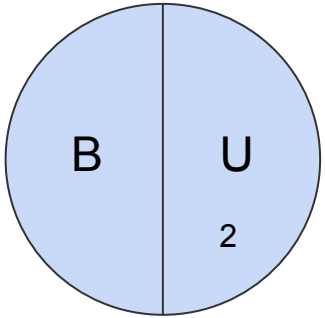
Pies 1, 2, 3, 4

Calculate the prevalence

Example: Population of 1,000 people. The number below each pie indicates the number who would develop the disease if they had the combination of risk factors in the pie. The U's indicate



100 People



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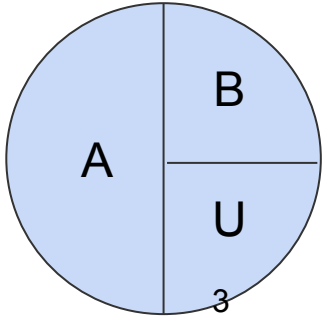
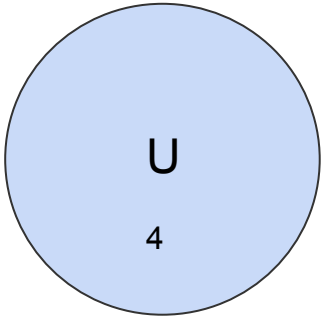


50 People



100 People

Estimate the prevalence if:

1) A and B were absent. **100/1000**
2) A was present and B was absent. **100/1000+100/1000 = 200/1000**
3) B was present and A was absent. **50/1000+100/1000 = 150/1000**
4) A and B were present. **100/1000+50/1000+50/1000+100/1000 = 300/1000**

Assess effect modification: additive scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+50/1000+100/1000 = 300/1000**

Using the prevalence estimates above, calculate prevalence differences for:

1) A without B
2) B without A
3) The expected combination of A & B
4) The observed combination of A & B

Assess effect modification: additive scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+50/1000+100/1000 = 300/1000**

Using the prevalence estimates above, calculate prevalence differences for:

1) A without B **= (200/1000) - (100/1000) = 100/1000**
2) B without A **= (150/1000) - (100/1000) = 50/1000**
3) The expected combination of A & B **= 100/1000 + 50/1000 = 150/1000**
4) The observed combination of A & B **= (300/1000) - (100/1000) = 200/1000**

Assess effect modification: additive scale

Prevalence if:

1) A and B were absent. **100/1000**
2) A was present and B was absent. **100/1000+100/1000 = 200/1000**
3) B was present and A was absent. **50/1000+100/1000 = 150/1000**
4) A and B were present. **100/1000+50/1000+50/1000+100/1000 = 300/1000**

Using the prevalence estimates above, calculate prevalence differences for:

1) A without B **= (200/1000) - (100/1000) = 100/1000**
2) B without A **= (150/1000) - (100/1000) = 50/1000**
3) The expected combination of A & B **= 100/1000 + 50/1000 = 150/1000**
4) The observed combination of A & B **= (300/1000) - (100/1000) = 200/1000**

Because the expected prevalence difference differs from the observed difference, we conclude effect modification was present on the additive scale.

Assess effect modification: relative scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+50/1000+100/1000 = 300/1000**

Using the prevalence estimates above, calculate prevalence ratios for:

1) A without B
2) B without A
3) The expected combination of A & B
4) The observed combination of A & B

Assess effect modification: relative scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+50/1000+100/1000 = 300/1000**

Using the prevalence estimates above, calculate prevalence ratios for:

1) A without B **= (200/1000) / (100/1000) = 2**
2) B without A **= (150/1000) / (100/1000) = 1.5**
3) The expected combination of A & B **= 2 * 1.5 = 3**
4) The observed combination of A & B **= (300/1000) / (100/1000) = 3**

Assess effect modification: relative scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+50/1000+100/1000 = 300/1000**

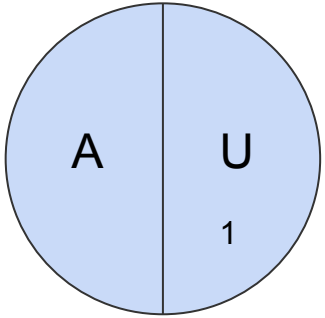
Using the prevalence estimates above, calculate prevalence ratios for:

1) A without B **= (200/1000) / (100/1000) = 2**
2) B without A **= (150/1000) / (100/1000) = 1.5**
3) The expected combination of A & B **= 2 * 1.5 = 3**
4) The observed combination of A & B **= (300/1000) / (100/1000) = 3**

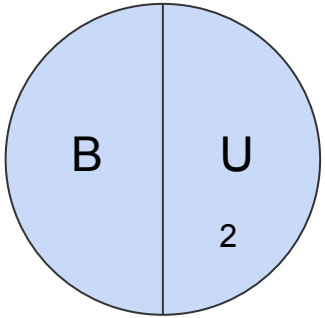
Because the expected and observed prevalence ratios were the same, we conclude effect modification was absent on the relative scale.

Calculate the prevalence

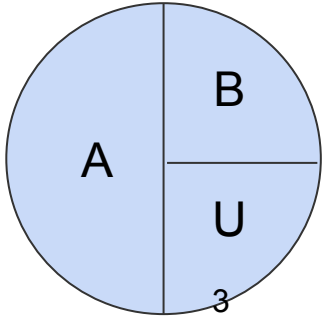
Example: Population of 1,000 people. The number below each pie indicates the number who would develop the disease if they had the combination of risk factors in the pie. The U's indicate



100 People



50 People



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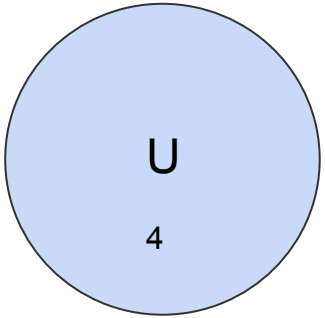
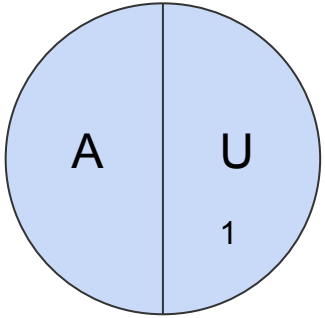


100 People

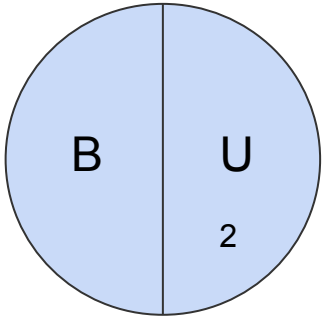
Which pie is responsible for effect modification? If we remove the third pie and repeat this exercise, what happens?

Calculate the prevalence

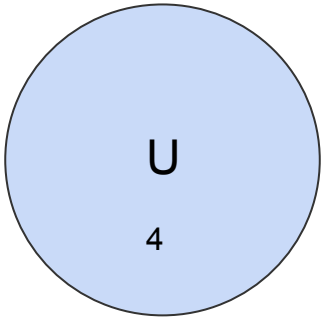
Example: Population of 1,000 people. The number below each pie indicates the number who would develop the disease if they had the combination of risk factors in the pie. The U's indicate



100 People



50 People



100 People

Estimate the prevalence if:

1) A and B were absent. **100/1000**
2) A was present and B was absent. **100/1000+100/1000 = 200/1000**
3) B was present and A was absent. **50/1000+100/1000 = 150/1000**
4) A and B were present. **100/1000+50/1000+100/1000 = 250/1000**

Assess effect modification: additive scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+100/1000 = 250/1000**

Using the prevalence estimates above, calculate prevalence differences for:

1) A without B
2) B without A
3) The expected combination of A & B
4) The observed combination of A & B

Assess effect modification: additive scale

Prevalence if:

1) A and B were absent. **100/1000**
2) A was present and B was absent. **100/1000+100/1000 = 200/1000**
3) B was present and A was absent. **50/1000+100/1000 = 150/1000**
4) A and B were present. **100/1000+50/1000+100/1000 = 250/1000**

Using the prevalence estimates above, calculate prevalence differences for:

1) A without B **= (200/1000) - (100/1000) = 100/1000**
2) B without A **= (150/1000) - (100/1000) = 50/1000**
3) The expected combination of A & B **= 100/1000 + 50/1000 = 150/1000**
4) The observed combination of A & B **= (250/1000) - (100/1000) = 150/1000**

Because the expected and observed prevalence differences were the same, we conclude effect modification was absent on the additive scale.

Assess effect modification: relative scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+100/1000 = 250/1000**

Using the prevalence estimates above, calculate prevalence ratios for:

1) A without B
2) B without A
3) The expected combination of A & B
4) The observed combination of A & B

Assess effect modification: relative scale

Prevalence if:

1)	A and B were absent.	**100/1000**
2)	A was present and B was absent.	**100/1000+100/1000 = 200/1000**
3)	B was present and A was absent.	**50/1000+100/1000 = 150/1000**
4)	A and B were present.	**100/1000+50/1000+100/1000 = 250/1000**

Using the prevalence estimates above, calculate prevalence ratios for:

1) A without B **= (200/1000) / (100/1000) = 2**
2) B without A **= (150/1000) / (100/1000) = 1.5**
3) The expected combination of A & B **= 2 * 1.5 = 3**
4) The observed combination of A & B **= (250/1000) / (100/1000) = 2.5**

Because the expected and observed prevalence ratios differ, we conclude effect modification was present on the relative scale.

Summary of key points

- In this video, you've learned how to connect the concepts of the sufficient component cause model with the concept of effect modification.
- You've seen an example of what additive scale effect modification and relative scale effect modification look like using causal pies.
- Two factors do not biologically interact if they do not appear together in a causal pie. (Jewell)

Berkeley School of Public Health

The potential outcomes model & causal interaction

PHW250B

Effect measure modification topics

- **Types of interaction**
  - Statistical interaction
  - Effect measure modification
  - Biologic / causal interaction
    - Sufficient component cause model
    - Potential outcomes / counterfactual model **Focus of this video**
- **Detecting interaction**
  - Assess homogeneity of effects across levels of a potential modifier
  - Test for statistical interaction using a chi square test of homogeneity
  - Detect additive scale interaction using either additive or relative scale measures

Pearl, Glymour & Jewell 2016

Punchline of this video

- In this video, we'll show you why many epidemiologists today argue that the presence of additive interaction implies causal or biologic interaction.
- To do this, we'll expand on the counterfactual "types" (doomed, immune, etc) and will develop a list of 16 counterfactual "types" that could occur under 2 exposures.
  - 10 of these types reflect a true causal interaction, and the other 6 do not.
- We'll discuss why the presence of additive scale interaction suggests that at least some causal types occur in our population.
- Note: throughout this video, when we talk about the RR or RD, we are estimating the causal RR or RD because we do so using counterfactual types.

Pearl, Glymour & Jewell 2016

Quick recap of the potential outcomes framework

- Y_a: individual outcome when exposure = *a*
- $E[Y_a]$: expectation of the outcome in a population in which all people experienced exposure *a*
- $E[Y_1-Y_0]$: population causal effect
  - Expected difference in the outcome in the population if all experienced exposure 1 vs. all experienced exposure 0 with everything else the same

Pearl, Glymour & Jewell 2016

Quick recap of counterfactual "types"

Type	Response[a] under Exposure	Response[a] under Nonexposure	Description
1	1	1	Doomed
2	1	0	Exposure is causal
3	0	1	Exposure is preventive
4	0	0	Immune

$RR = (p_1 + p_2)/(p_1 + p_3)$

$RD = p_2 - p_3$

- The RR depends not only on the people amenable to intervention (types 2 and 3) but also on the people who are doomed.
- The RD only depends on people amenable to intervention.

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Counterfactual types with two exposures

- Counterfactual “types” can be expanded to involve two exposures (X and Z)
- Each row represents the counterfactual outcomes that would be observed for a “type” of person given each potential combination of exposure to two factors, X and Z
- We imagine that our study population can be categorized into these types but we cannot know the proportion of each type because counterfactuals are unobserved
- Counterfactual outcomes – 1=disease, 0=no disease

	Outcome (Risk) Y when Exposure Combination Is			
Type	$X = 1$ $Z = 1$	$X = 0$ $Z = 1$	$X = 1$ $Z = 0$	$X = 0$ $Z = 0$
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Counterfactual types with two exposures

- Types with **no causal interaction**
- At least one factor never has an effect, so there can be no interaction
- Examples:
  - Type 1: get the disease regardless of values of X and Z (doomed)
  - Type 6: disease is caused by exposure to X=1, Z has no effect
  - Type 4: only get the disease when Z=1

Type	Outcome (Risk) Y when Exposure Combination Is			
	$X = 1$ $Z = 1$	$X = 0$ $Z = 1$	$X = 1$ $Z = 0$	$X = 0$ $Z = 0$
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Counterfactual types with two exposures

- Types **with causal interaction**
- Don't know what the effect of X will be without knowing the value of Z (and vice versa)
- Examples:
  - Type 8: get the disease only when X and Z are present
  - Type 5: X=0 with Z=1 blocks disease

	Outcome (Risk) Y when Exposure Combination Is			
Type	$X = 1$ $Z = 1$	$X = 0$ $Z = 1$	$X = 1$ $Z = 0$	$X = 0$ $Z = 0$
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

What we are about to do:

Take home point: When EM is present on the additive scale, causal effect modification is implied (if you can make a set of other assumptions)

To show this, we will:

1. Get the RD for Z (RD_{01}) assuming no causal types
2. Get the RD for X (RD_{10}) assuming no causal types
3. Get the RD for X and Z (RD_{11}) assuming no causal types
4. Show that $RD_{11} = RD_{01} + RD_{10}$ when there are no causal types in the population (i.e. the RD is homogeneous)
5. By this logic, we can infer that if we observe $RD_{11} \neq RD_{01} + RD_{10}$, there are at least some causal types in our population (i.e. the RD is not homogeneous)

Pearl, Glymour & Jewell 2016

Counterfactual types with two exposures

- So far we have discussed individual counterfactual risks
- Now, let's consider the average risk of Y in a study population
  - Causal risks of outcome for combinations of exposures X and Z
  - Notation: R_{XZ}
- Sum types that have value 1 down each column:
  - R_{11} = p1+p2+p3+p4+p5+p6+p7+p8
  - R_{01} = p1+p2+p3+p4+p9+p10+p11+p12
  - R_{10} = p1+p2+p5+p6+p9+p10+p13+p14
  - R_{00} = p1+p3+p5+p7+p9+p11+p13+p15

Type	Outcome (Risk) Y when Exposure Combination Is: $X=1, Z=1$	$X=0, Z=1$	$X=1, Z=0$	$X=0, Z=0$
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Counterfactual types with two exposures

- **Calculate the RD for Z if no X assuming there are no interacting causal types**
  - R_{11} = p1+p4+p6
  - R_{01} = p1+p4+p11
  - R_{10} = p1+p6+p13
  - R_{00} = p1+p11+p13
- $RD_{01} = R_{01} - R_{00}$
- RD_{01} = (p1+p4+p11) – (p1+p11+p13)
- RD_{01} = p4-p13
- In words: This is the net causal effect of Z if there are no preventive types

Type	Outcome (Risk) Y when Exposure Combination Is: X = 1, Z = 1	X = 0, Z = 1	X = 1, Z = 0	X = 0, Z = 0
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Counterfactual types with two exposures

- **Calculate the RD for X if no Z assuming there are no interacting causal types**
  - R_{11} = p1+p4+p6
  - R_{01} = p1+p4+p11
  - R_{10} = p1+p6+p13
  - R_{00} = p1+p11+p13
- $RD_{10} = R_{10} - R_{00}$
- RD_{10} = (p1+p6+p13) – (p1+p11+p13)
- RD_{10} = p6-p11
- In words: This is the net causal effect of X if there are no preventive types

Type	Outcome (Risk) Y when Exposure Combination Is: $X=1, Z=1$	$X=0, Z=1$	$X=1, Z=0$	$X=0, Z=0$
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Counterfactual types with two exposures

- **Calculate the observed RD for X and Z assuming there are no interacting causal types**
  - R_{11} = p1+p4+p6
  - R_{01} = p1+p4+p11
  - R_{10} = p1+p6+p13
  - R_{00} = p1+p11+p13
- $RD_{11} = R_{11} - R_{00}$
- RD_{11} = (p1+p4+p6) – (p1+p11+p13)
- RD_{11} = (p4+p6) – (p11+p13)

Type	Outcome (Risk) Y when Exposure Combination Is: X = 1, Z = 1	X = 0, Z = 1	X = 1, Z = 0	X = 0, Z = 0
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Implications for assessment of additive scale interaction

RD_{01} = p4-p13

RD_{10} = p6-p11

RD_{11} = (p4+p6) – (p11+p13)

- **What do we conclude if $RD_{01} + RD_{01} = RD_{11}$?**
  - Either there are no interacting types, or they are canceling each other out (example – a type 3 and a type 14 would cancel)
- **What do we conclude if $RD_{01} + RD_{01} \neq RD_{11}$?**
  - There are at least some interacting types (if we can assume that the RD estimates are not confounded).

Pearl, Glymour & Jewell 2016

What we just showed

Take home point: When EM is present on the additive scale, causal effect modification is implied (if you can make a set of other assumptions)

To show this, we will:

1. Get the RD for Z (RD_{01}) assuming no causal types
2. Get the RD for X (RD_{10}) assuming no causal types
3. Get the RD for X and Z (RD_{11}) assuming no causal types
4. Show that $RD_{11} = RD_{01} + RD_{10}$ when there are no causal types in the population (i.e. the RD is homogeneous)
5. By this logic, we can infer that if we observe $RD_{11} \neq RD_{01} + RD_{10}$, there are at least some causal types in our population (i.e. the RD is not homogeneous)

Pearl, Glymour & Jewell 2016

Counterfactual types with two exposures

- **Calculate the observed RR for X and Z assuming there are no interacting causal types**
  - R_{11} = p1+p4+p6
  - R_{01} = p1+p4+p11
  - R_{10} = p1+p6+p13
  - R_{00} = p1+p11+p13
- RR_{01} = (p1+p4+p11) / (p1+p11+p13)
- RR_{10} = (p1+p6+p13) / (p1+p11+p13)
- RR_{11} = (p1+p4+p6) / (p1+p11+p13)
- $RR_{01} \times RR_{10} \neq RR_{11}$

Type	Outcome (Risk) Y when Exposure Combination Is: $X=1, Z=1$	$X=0, Z=1$	$X=1, Z=0$	$X=0, Z=0$
1	1	1	1	1
2*	1	1	1	0
3*	1	1	0	1
4	1	1	0	0
5*	1	0	1	1
6	1	0	1	0
7*	1	0	0	1
8*	1	0	0	0
9*	0	1	1	1
10*	0	1	1	0
11	0	1	0	1
12*	0	1	0	0
13	0	0	1	1
14*	0	0	1	0
15*	0	0	0	1
16	0	0	0	0

*Defined as interaction response type in present discussion (types

Rothman et al., *Modern Epidemiology*, 3rd Ed.

Implications for assessment of relative scale interaction

RR_{01} = p4/p13

RR_{10} = p6/p11

RR_{11} = (p4/p6) x (p11/p13)

- $RR_{01} \times RR_{10} \neq RR_{11}$ when there are no interacting types.
- Cannot make statements about interaction as a causal concept based on multiplicative interaction
- Can make statements about effect modification only (measure of association modification)

Pearl, Glymour & Jewell 2016

Summary of key points

- If you see interaction on the additive scale:
  - There are at least some people in your population of an interactive “type” with respect to your X, Z and Y.
  - The population experienced exposures such that you could detect this interaction.
- Under the potential outcomes / counterfactual model, a departure from additivity implies the presence of causal interactive types in the population, which suggests that there is a biologic/causal interaction between two exposures.
- The absence of additive interaction does not imply a lack of causal interaction (since they could be present but canceling each other).

Berkeley School of Public Health

Detecting additive scale interaction

PHW250B

Effect measure modification topics

- **Types of interaction**
  - Statistical interaction
  - Effect measure modification
  - Biologic / causal interaction
    - Sufficient component cause model
    - Potential outcomes / counterfactual model
- **Detecting interaction**
  - Assess homogeneity of effects across levels of a potential modifier
  - Test for statistical interaction using a chi square test of homogeneity
  - Detect additive scale interaction using either additive or relative scale measures

Focus of this video

Pearl, Glymour & Jewell 2016

Why detect additive scale interaction?

- As shown in the video on the potential outcomes / counterfactual model and causal interaction, under this model, departures from additivity imply the presence of causal interactive types in the population, which suggests that there is a biologic/causal interaction between two exposures.
- In this video, you will learn how to measure departures from additivity.
- Assessing homogeneity of the risk difference is another simpler approach. The advantage of the methods in this video is that they allow you to potential use statistical tests to assess whether additive scale interaction is statistically significant. (Formulas for the chi square test for homogeneity are on the relative scale.)

Rothman et al. *Modern Epidemiology.* 3rd Ed.

What we will cover in this video

- You have learned how to assess for the presence of interaction by comparing the observed RD or RR for two exposures to the expected RD or RR.
- We will define formulas that allow us to formalize this approach in order to measure the presence of interaction on the additive and relative scales.
- We'll derive the relative excess risk due to interaction (RERI) — a measure of additive scale interaction that can be obtained using RRs or ORs.

Notation used in this video

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

Z denotes asbestos
X denotes smoking
Y denotes lung cancer

$p_{xz} = P(Y=1 \mid X=x, Z=z)$

$p_{00} = 0.0011$

$p_{10} = 0.0095$

$p_{01} = 0.0067$

$p_{11} = 0.0450$

Vanderweele & Knol 2014

Comparing observed vs. expected RD

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

Observed RD for both smoking and asbestos

$= (p_{11} - p_{00})$

Expected RD for both smoking and asbestos

$= (p_{10} - p_{00}) + (p_{01} - p_{00})$

Vanderweele & Knol 2014

Comparing observed vs. expected RD

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

Observed RD for both smoking and asbestos

$= (p_{11} - p_{00})$

$= 0.0450 - 0.0011 = 0.0439$

Expected RD for both smoking and asbestos

$= (p_{10} - p_{00}) + (p_{01} - p_{00})$

$= (0.0095 - 0.0011) + (0.0067 - 0.0011) = 0.014$

Vanderweele & Knol 2014

Defining a measure of interaction on the additive scale

Observed RD = $(p_{11} - p_{00})$

Expected RD = $(p_{10} - p_{00}) + (p_{01} - p_{00})$

To assess interaction on the additive scale, we could use the formula:

$(p_{11} - p_{00}) - [(p_{10} - p_{00}) + (p_{01} - p_{00})]$

Which can be re-written as:

$= p_{11} - p_{00} - p_{10} + p_{00} - p_{01} + p_{00}$

$= p_{11} - p_{10} - p_{01} + p_{00}$

Defining a measure of interaction on the additive scale

If the **exposures are harmful** (increase risk of disease):

- If $p_{11} - p_{10} - p_{01} + p_{00} > 0$ interaction is positive or synergistic
- If $p_{11} - p_{10} - p_{01} + p_{00} = 0$ no interaction is present
- If $p_{11} - p_{10} - p_{01} + p_{00} < 0$ interaction is negative or antagonistic

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

$p_{11} - p_{10} - p_{01} + p_{00} = 0.045 - 0.0095 - 0.0067 + 0.0011 = 0.0299$

We conclude that there is positive interaction. The observed risk difference associated with both asbestos and smoking is greater than the expected risk difference for both.

Vanderweele & Knol 2014

Defining a measure of interaction on the additive scale

If the **exposures are harmful** (increase risk of disease):

- If $p_{11} - p_{10} - p_{01} + p_{00} > 0$ interaction is positive or "super-additive"
  - The public health consequence of an intervention on Z (e.g., asbestos) would be larger in the X=1 (e.g., smoker) group.
- If $p_{11} - p_{10} - p_{01} + p_{00} = 0$ no interaction is present
  - The public health consequence of an intervention on Z (e.g., asbestos) would be the same in both groups X=1 and X=0 (e.g., smokers and non-smokers).
- If $p_{11} - p_{10} - p_{01} + p_{00} < 0$ interaction is negative or "sub-additive"
  - The public health consequence of an intervention on Z (e.g., asbestos) would be larger in the X=0 (e.g., non-smoker) group.

Vanderweele & Knol 2014

Comparing observed vs. expected RR

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

Observed RR for both smoking and asbestos

$= (p_{11} / p_{00})$

Expected RR for both smoking and asbestos

$= (p_{10} / p_{00}) \times (p_{01} / p_{00})$

Vanderweele & Knol 2014

Comparing observed vs. expected RR

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

Observed RR for both smoking and asbestos

$= (p_{11} / p_{00})$

$= 0.0450 / 0.0011 = 41$

Expected RR for both smoking and asbestos

$= (p_{10} / p_{00}) \times (p_{01} / p_{00})$

$= (0.0095 / 0.0011) \times (0.0067 / 0.0011) = 53$

Vanderweele & Knol 2014

Defining a measure of interaction on the relative scale

Observed RR = $(p_{11} / p_{00}) = RR_{11}$

Expected RR = $(p_{10} / p_{00}) \times (p_{01} / p_{00}) = RR_{10} \times RR_{01}$

To assess interaction on the additive scale, we could use the formula:

$(p_{11} / p_{00}) / [(p_{10} / p_{00}) \times (p_{01} / p_{00})] = RR_{11} / (RR_{10} \times RR_{01})$

Vanderweele & Knol 2014

Defining a measure of interaction on the relative scale

If the **exposures are harmful** (increase risk of disease):

- If $RR_{11} / (RR_{10} \times RR_{01}) > 1$ interaction is positive or "super-additive"
- If $RR_{11} / (RR_{10} \times RR_{01}) = 1$ no interaction is present
- If $RR_{11} / (RR_{10} \times RR_{01}) < 1$ interaction is negative or "sub-additive"

Table 1 Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

$RR_{11} / (RR_{10} \times RR_{01}) = (0.0450/0.0011) / [(0.0095/0.0011) \times (0.0067/0.0011)] = 0.78$

We conclude that there is negative interaction. The observed risk ratio associated with both asbestos and smoking is less than the expected risk ratio for both.

Vanderweele & Knol 2014

Assessing additive interaction when only RRs are available

- In some cases, we may only be able to estimate an RR, or we may want to evaluate additive scale interaction in a study that only reported RRs.
- We can use the "relative excess risk due to interaction" (RERI) to do so.

We start with our formula for assessing additive scale interaction:
$p_{11} - p_{10} - p_{01} + p_{00}$

Then divide it through by p_{00}:

$(p_{11} / p_{00}) - (p_{10} / p_{00}) - (p_{01} / p_{00}) + (p_{00} / p_{00})$

$RERI = RR_{11} - RR_{10} - RR_{01} + 1$

Vanderweele & Knol 2014

Defining a measure of interaction on the additive scale

For **harmful exposures** that increase the risk of disease:

- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 > 0$ interaction is positive or "super-additive"
- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 = 0$ no interaction is present
- If RERI = $RR_{11} - RR_{10} - RR_{01} + 1 < 0$ interaction is negative or "sub-additive"

The Vanderweele & Knol 2014 paper includes a derivation for the odds ratio as well.

The paper also includes example code for estimating the RERI and obtaining standard errors for the RERI.

What if measures of association are protective?

So far we've shown how to calculate the RERI for **harmful exposures** that increase the risk of disease.

If an **exposure is protective** (ie, RR or OR < 1) we need to recode the variable for the exposure to reverse its direction before we calculate the RERI.

Example if the exposure is vaccination:

- Original coding: "vaccine ==1" for vaccinated and "vaccine==0" for unvaccinated
- Recoding: "vaccine==0" for vaccinated and "vaccine==1" for unvaccinated.

For categorical preventive exposures, refer to Knol et al., 2011 *Eur J Epidemiol* (2011) 26:433–438 DOI 10.1007/s10654-011-9554-9.

Summary of key points

- We have defined formulas that allow us to formalize this approach in order to measure the presence of interaction on the additive and relative scales.
- We derived the relative excess risk due to interaction (RERI) — a measure of additive scale interaction that can be obtained using RRs or ORs.