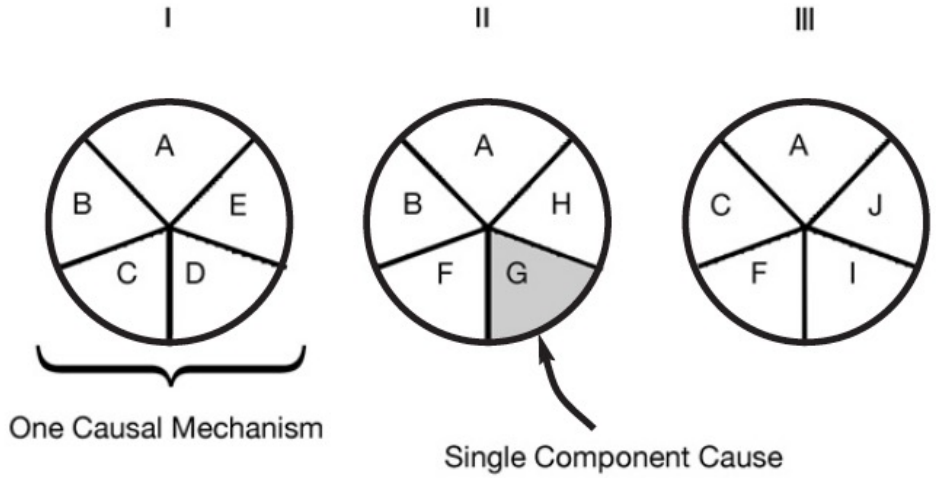
Lecture 14: Effect Modification and Interaction

Lecture prepared by Dr. Hailey Banack, PhD

Interaction and effect modification are of interest when you want to understand a situation where causes work together

Recall….. Rothman's causal pies



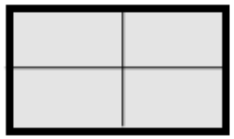
Each individual instance of disease – each case – occurs through a single causal mechanism, also referred to as a sufficient cause. A sufficient cause is the minimum set of component causes necessary to cause disease.

Interaction and sufficient causes

- Component causes of disease rarely act in isolation
- Exposures are one of a set of component causes that have to work together in order for a change to occur in the health outcome
- Interaction: when multiple component causes work together to produce a particular health outcome
- Causes interact when they work together as part of the same sufficient cause
- Causes that interact are causes in which both factors are necessary to cause disease in at least one sufficient cause

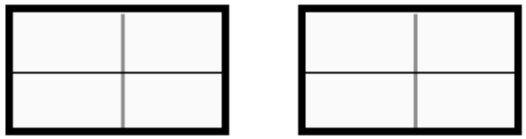
Clarification: Confounding vs. Interaction

- **Confounding** is a problem we want to eliminate (control or adjust for) in a study, it is a type of BIAS
  - Evaluated by comparing crude vs. adjusted effect estimates
- **Interaction/EMM** is a natural occurrence that we want to describe and study further
  - Interaction: evaluated by comparing observed and expected joint effects
  - EMM: evaluated by comparing stratum specific estimates: are they different from one another?



Calculate crude measure of association

Stratify by confounder



Calculate stratum-specific associations

Are stratum-specific associations similar?

If yes, calculate pooled estimate

If not, do not pool estimates*

**Evidence of effect measure modification*

If crude association > or < adjusted association then confounding is likely

If crude association similar to adjusted association then confounding is **not** likely

A note about terminology

- Interaction
- Statistical interaction
- Biological interaction
- Effect modification
- Effect measure modification
- Heterogeneity of effects
- Synergy / Antagonism

EMM vs. Interaction

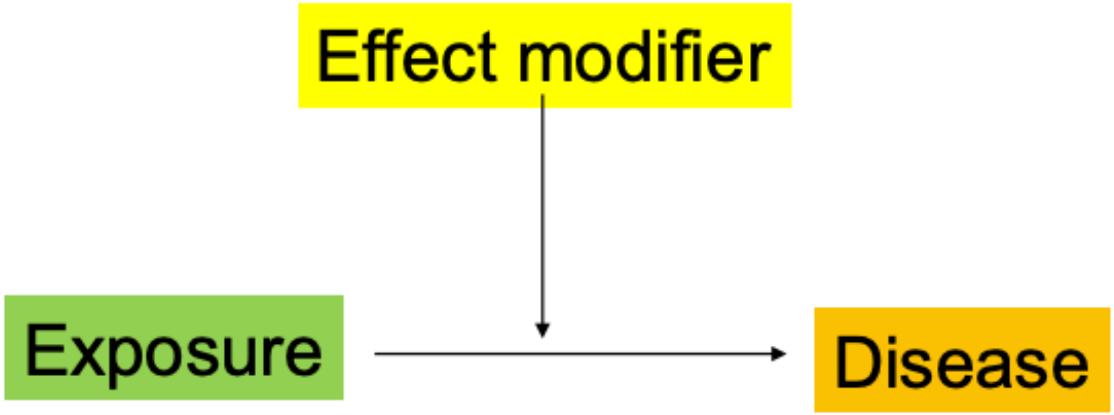
- We will focus on the terms effect measure modification (EMM) and interaction
- When are we concerned with EMM? If we have an exposure and outcome of interest and want to examine whether the relationship differs in strata of a 3rd variable
- When are we concerned with interaction? If we have TWO exposures we are interested in and want to see if the joint effect of these two exposures on the outcome differs from the effect of either exposure independently

What is Effect Modification?

- Effect modification occurs when the effect of a risk factor (X) on an outcome (Y) differs in strata formed by a third variable (Z)
- Effect of exposure on disease is modified depending on the value of a third variable called an “effect modifier”
- Effect measure (i.e. risk difference, risk ratio) differs across different levels/strata of the third variable

When is Effect Modification of Interest?

- If you have an exposure-outcome association you are interested in, and want to know whether that relationship varies in strata of a third variable



Heterogeneity

- When effect estimates are different in strata of the effect modifier→ heterogeneity is present

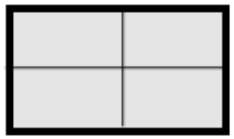
  Strata 1: OR=1.8

  Strata 2: OR=5.7

- When effect estimates are similar in strata of the effect modifier → homogenous effect estimates

  Strata 1: OR=2.3

  Strata 2: OR=2.5



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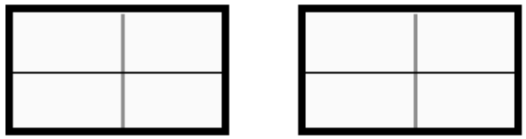


Calculate stratum-specific associations

Are stratum-specific associations similar?

If yes, calculate pooled estimate

If not, do not pool estimates*

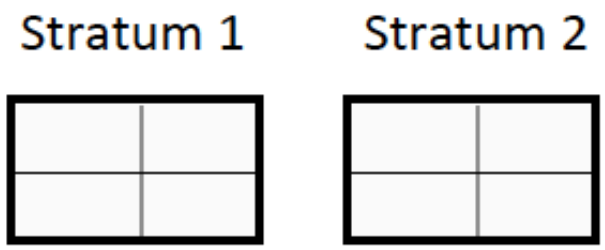
**Evidence of effect measure modification*

If crude association > or < adjusted association then confounding is likely

If crude association similar to adjusted association then confounding is **not** likely

Stratification

- The concept of stratification is essential to understanding interaction and EMM
- Creating 2x2 tables (“cross-tabulating”) for the exposure-disease relationship by categories of another variable
- E.g. young/old, smokers/non-smokers



Example: EMM

Research question: what is the association between smoking and MI?

Step 1: Calculate crude measure of association

	MI	no MI	Total
Smokers	42	158	200
Nonsmokers	21	175	196
Total	63	333	396

$$OR = \frac{ad}{bc}$$

OR = 2.22 (95% CI 1.26, 3.91)

Is there effect modification by dietary fat consumption?

- Investigators decided to look at dietary fat as a potential effect modifier

Step 2: Calculate stratum-specific measures of association

STRATUM 1: Dietary fat consumption <30% of calories

	MI	noMI	Totals
Smokers	12	133	145
Nonsmokers	11	123	134
Total	23	256	279

OR = 1.01
(0.429, 2.37)

STRATUM 2: Dietary fat consumption > 30% of calories

	MI	noMI	Totals
Smokers	30	25	55
Nonsmokers	10	52	62
Total	40	77	117

OR = 6.29
(2.64, 14.75)

Interpretation

- Crude OR = 2.22
- Stratum specific ORs
  - Dietary fat <30% = 1.01 (0.43, 2.37)
  - Dietary fat >30% = 6.29 (2.64, 14.75)
- Is there effect modification? Is there confounding?

Effect **measure** modification

- We refer to effect measure modification (EMM) because assessment of EMM depends on the scale that is being used in the analysis
  - Additive EMM: assessment of EMM using risk differences
    - Looking at absolute effect estimates (difference measures)
    - Is the risk difference heterogenous across strata?
  - Multiplicative EMM: assessment of EMM using a ratio measure such as RR, OR
    - Looking at relative effect estimates
    - Is the RR/OR heterogeneous across strata?

Interpretation

Assessing EMM on the **additive scale** using the risk difference:

RD strata 1= -0.005 **RD strata 2=** -0.005

No evidence of EMM on the additive scale (heterogeneity of the effect)

Assessing EMM on the **multiplicative scale** using the risk ratio:

RR strata 1= 0.9 **RR strata 2 =** 0.4

Some evidence of heterogeneity of the effect of green tea on ulcers by level of bacon consumption

Which is right?

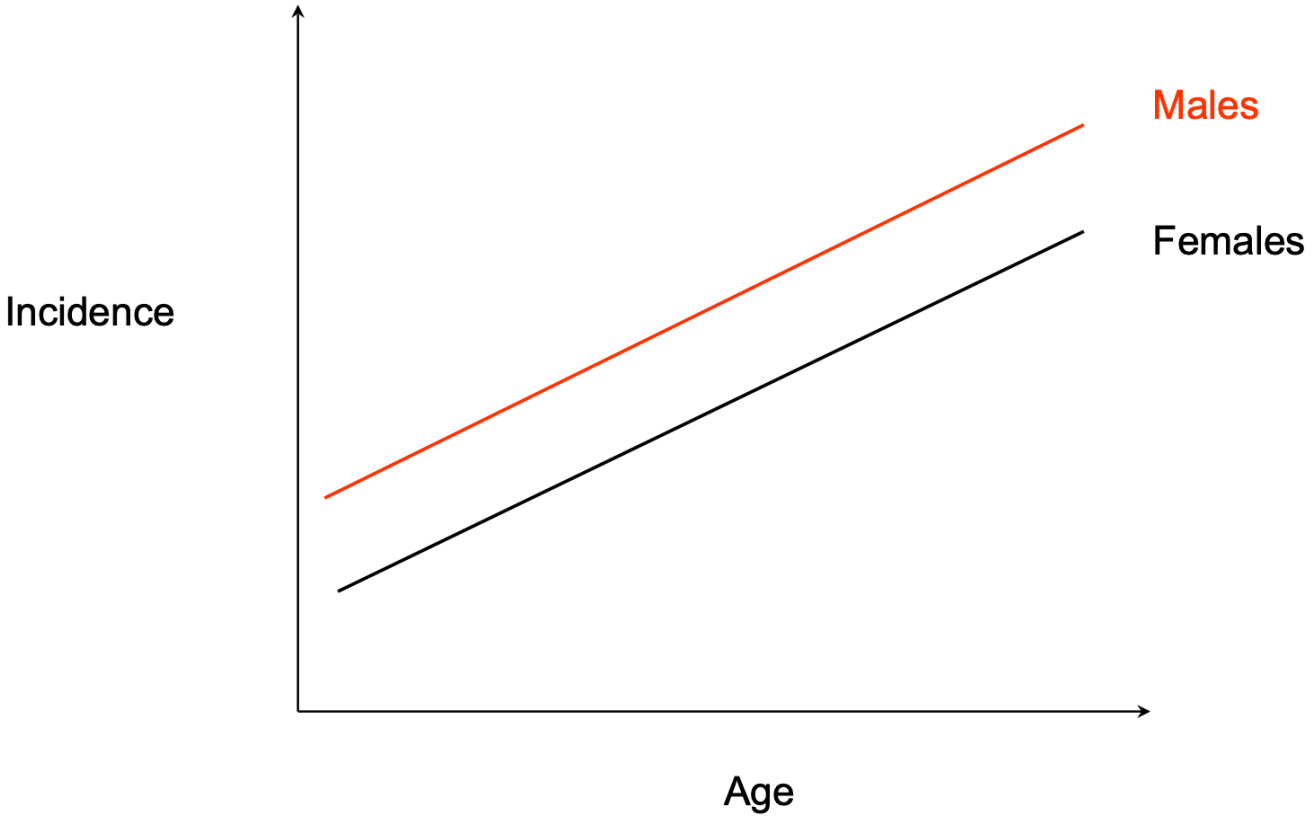
- Both are correct!
- If both the exposure variable and modifier have a *non-null* effect on the outcome, at least one type of EMM will always be present
- Make sure you are explicit about which measures you're reporting:
  - Comparing RD = "risk-difference heterogeneity," "additive EMM"
  - Comparing RR or OR = "risk-ratio heterogeneity," "multiplicative EMM"

EMM example

What is the relationship between age and disease incidence?

EMM example

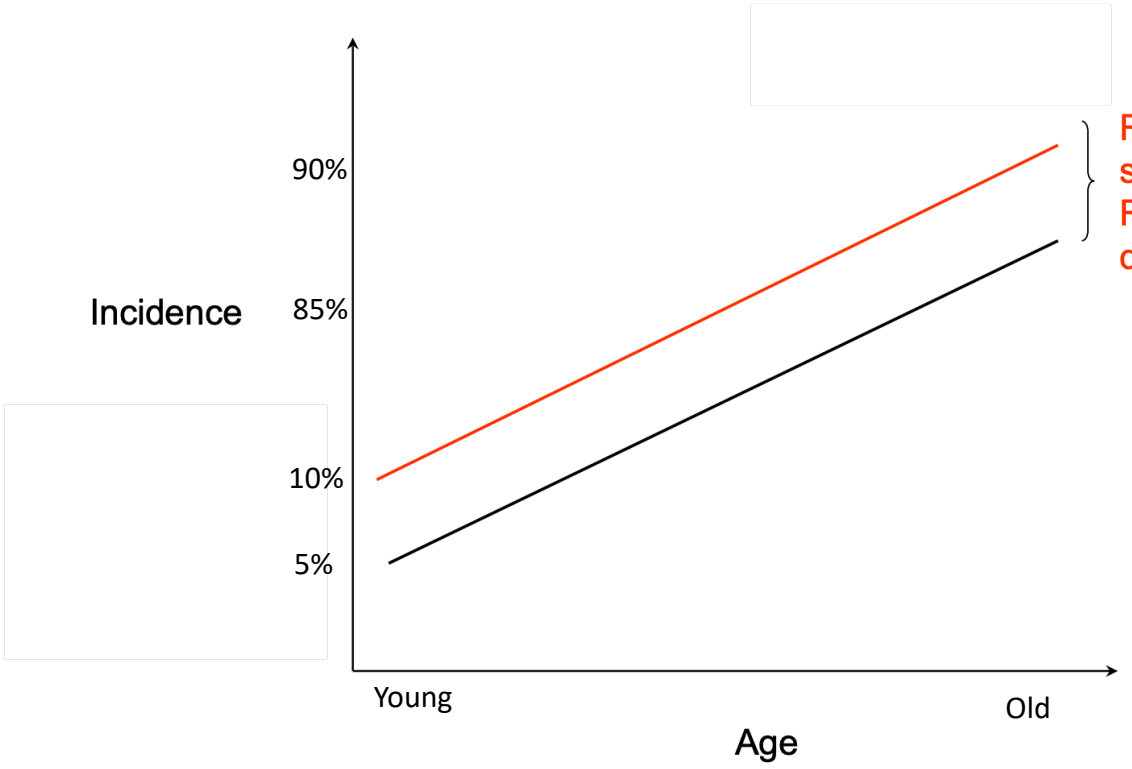
Is the relationship between age and disease incidence modified by sex?



Credit: Dr. Sam Harper

EMM example

Answer: it depends on the scale used!



Young age:

RD =10% - 5% = 5%

RR = 10% / 5% = 2

Old age:

RD = 90% - 85%= 5%

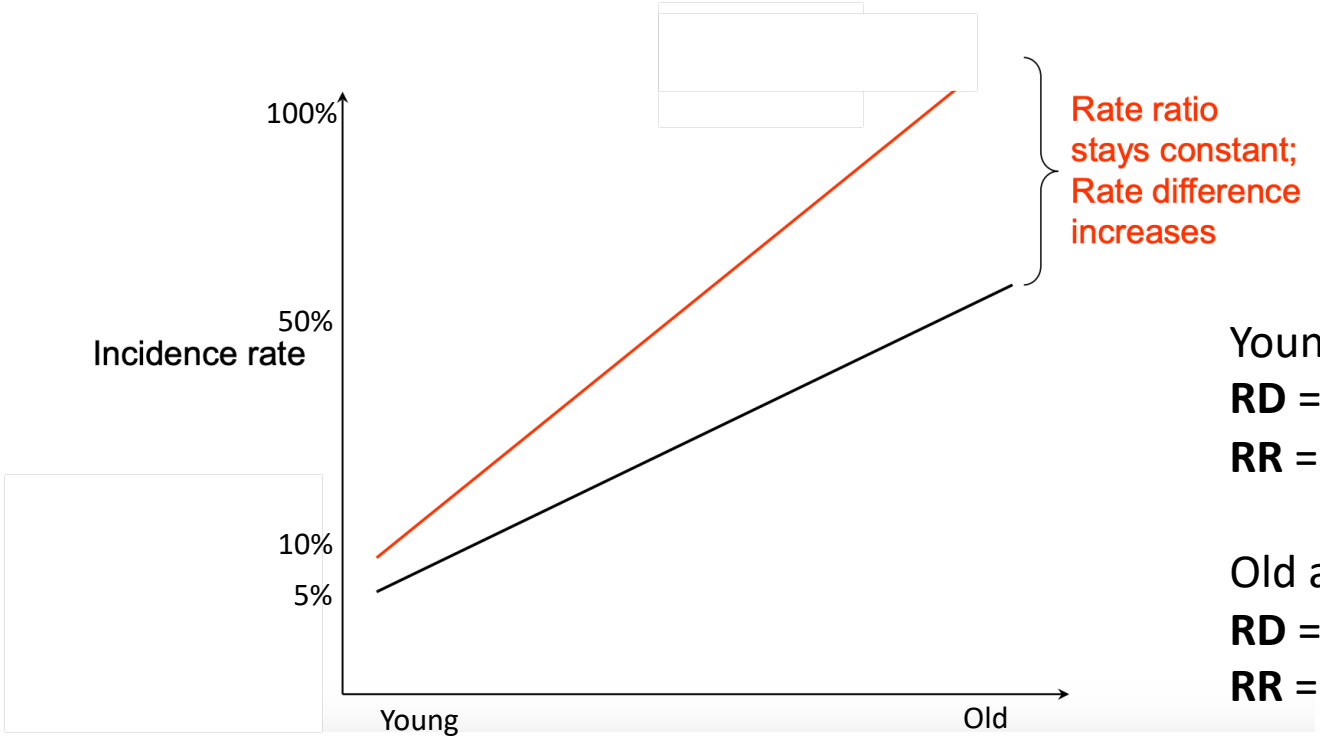
RR = 90% / 85%= 1.05

Credit: Dr. Sam Harper

EMM example

____ Males ____Females

What if the results looked like this?



Young age:

RD =10% - 5% = 5%

RR = 10% / 5% = 2

Old age:

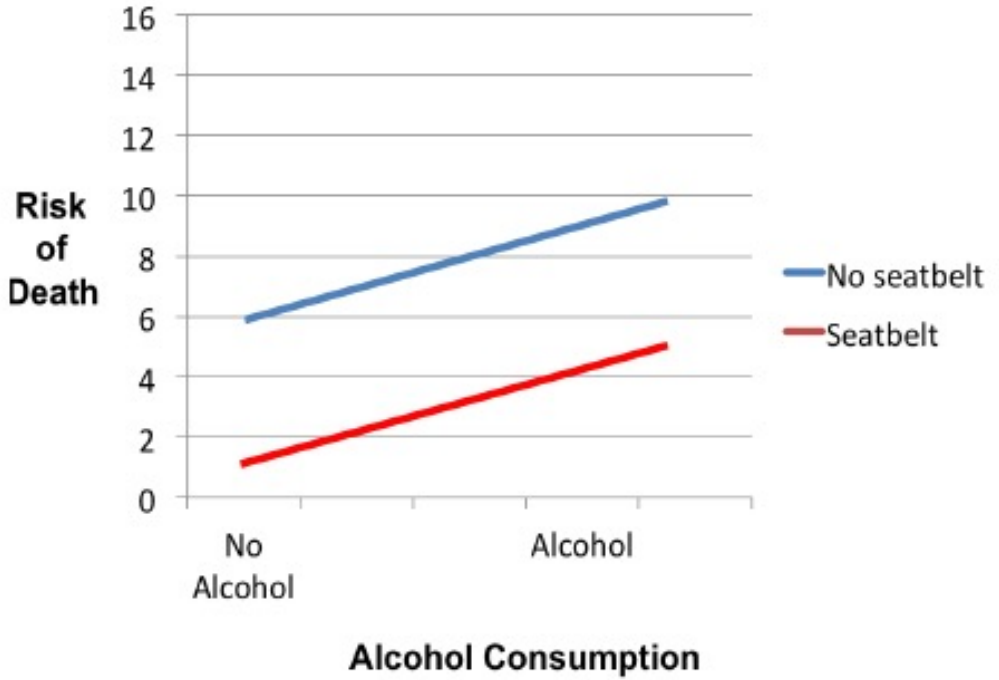
RD = 100% - 50%= 50%

RR = 100% / 50%= 2

Example: Alcohol and Driving

- **Question: Is consuming alcohol before driving associated with risk of dying in a motor vehicle crash?**
- Other factors that can contribute to risk of dying in a motor vehicle crash include **time of day** and **wearing a seatbelt**
- Key questions of interest here are
  - Does alcohol consumption cause a greater risk of dying in a motor vehicle crash?
  - Does alcohol consumption interact with either time of day and seatbelt use in its causing motor vehicle crashes?

Alcohol consumption and death stratified by seatbelt use



Seatbelt use (Strata 1)

Risk of death in exposed: 5%

Risk of death in unexposed: 1%

No seatbelt use (Strata 2)

Risk of death in exposed: 10%

Risk of death in unexposed: 6%

Credit: Dr. Sam Harper

Alcohol consumption and death seatbelt use

Alcohol use is always associated with greater risk of death

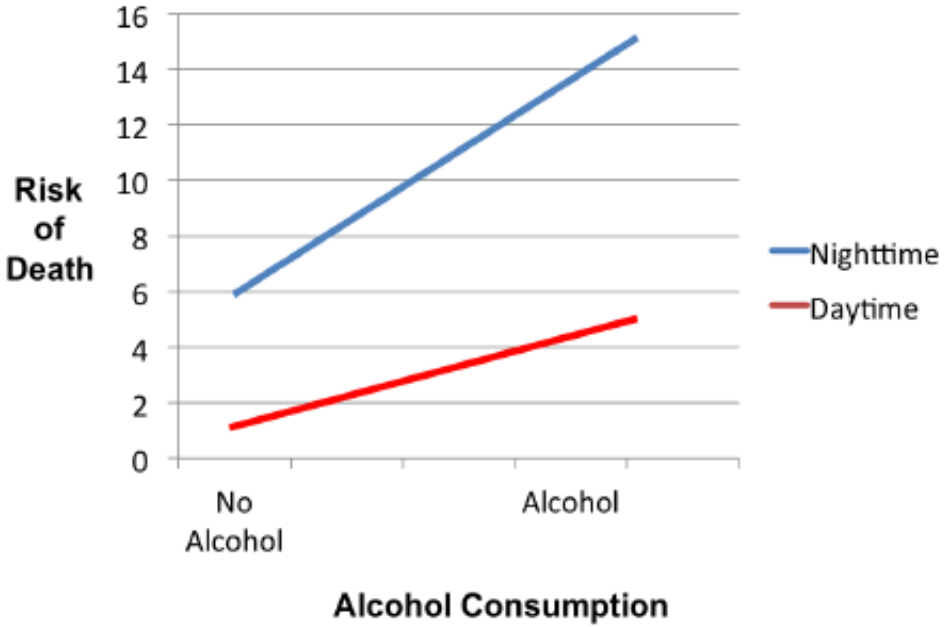
- Among those who did not wear a seatbelt (Strata 1)
  - Risk difference (RD) = 0.10 - 0.06 = 0.04
- Among those who did wear a seatbelt (Strata 2)
  - Risk difference (RD) = 0.05 – 0.01 = 0.04

No heterogeneity in the risk difference between those who do and do not use a seatbelt.

Seat belt use and alcohol use do not operate jointly to cause crash death.

This indicates no EMM on the additive scale.

Alcohol consumption and death stratified by time of day



Daytime (Strata 1)

Risk of death in exposed: 5%

Risk of death in unexposed: 1%

Nighttime (Strata 2)

Risk of death in exposed: 15%

Risk of death in unexposed: 6%

Alcohol consumption and death time of day

- Alcohol use is always associated with greater risk of death
- Among those who drove during the day (Strata 1)
  - Risk difference (RD) = 0.05 – 0.01 = **0.04**
- Among those who drove at night (Strata 2)
  - Risk difference (RD) = 0.15 – 0.06 = **0.09**

Heterogeneity presented in the risk differences

Time of day and alcohol use DO operate jointly to cause crash death.

This indicates EMM on the additive scale.

Qualitative vs. Quantitative EMM

Quantitative effect measure modification:

When the association between factor A and outcome Y exists and is of the same direction in each stratum formed by Z, but the strength of the association varies across strata

e.g. $RR_{strata1}$= 3.4 $RR_{strata2}$= 8.2

e.g. $RD_{strata1}$= -1.2 $RD_{strata2}$= -4.7

Qualitative effect measure modification:

When the effects of A on Y changes in direction (crosses over the null value) within levels of third variable Z

e.g. $RR_{strata1}$= 3.4 $RR_{strata2}$=0.6

e.g. $RD_{strata1}$= -1.2 $RD_{strata2}$=2.2

Heterogeneity of Effects

Can occur at the level of:

1. Individual study: within subgroups of a single study or trial
2. Across studies: if several studies are done on the same topic, the effect measures may vary across studies (seen in meta analyses)

Heterogeneity of effects: meta-analyses

Association between smoking and TB mortality

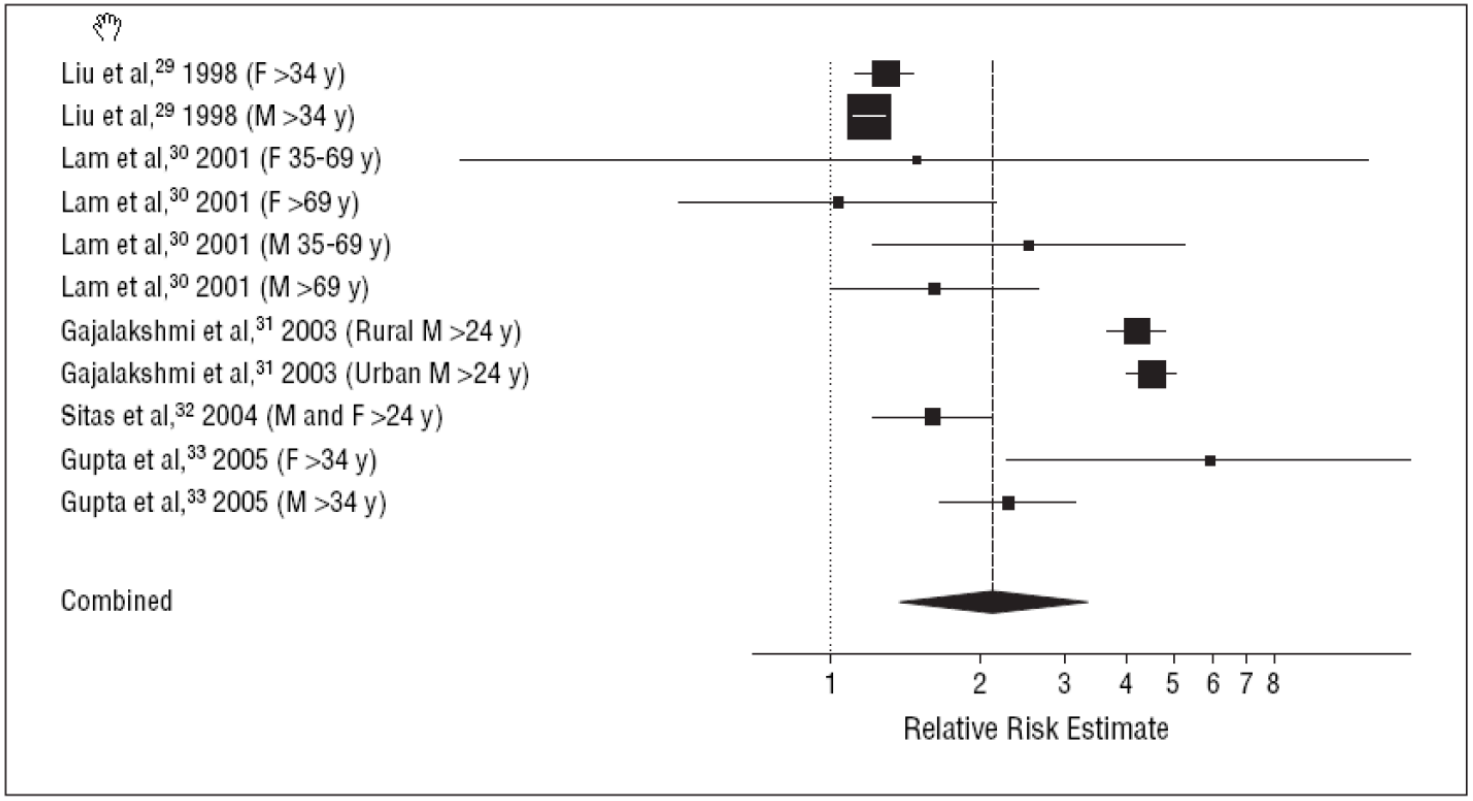
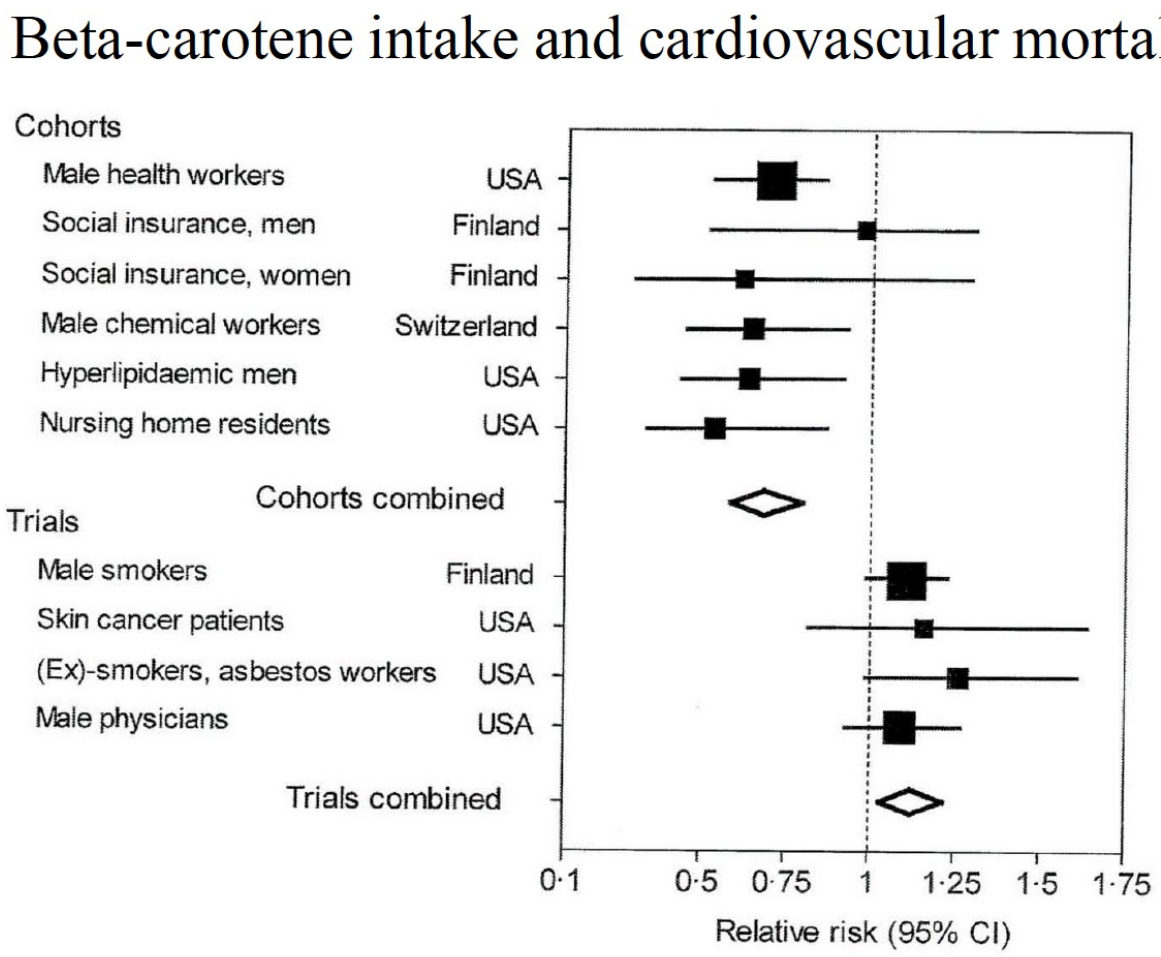


Figure 5. Forest plot of studies[29-33] that examined smoking and tuberculosis mortality. The sex and age of the study population are shown on the y-axis.

Bates et al. Arch Intern Med 2007

Beta- Carotene and CVD Mortality



Interaction

How is it different from EMM?

Interaction

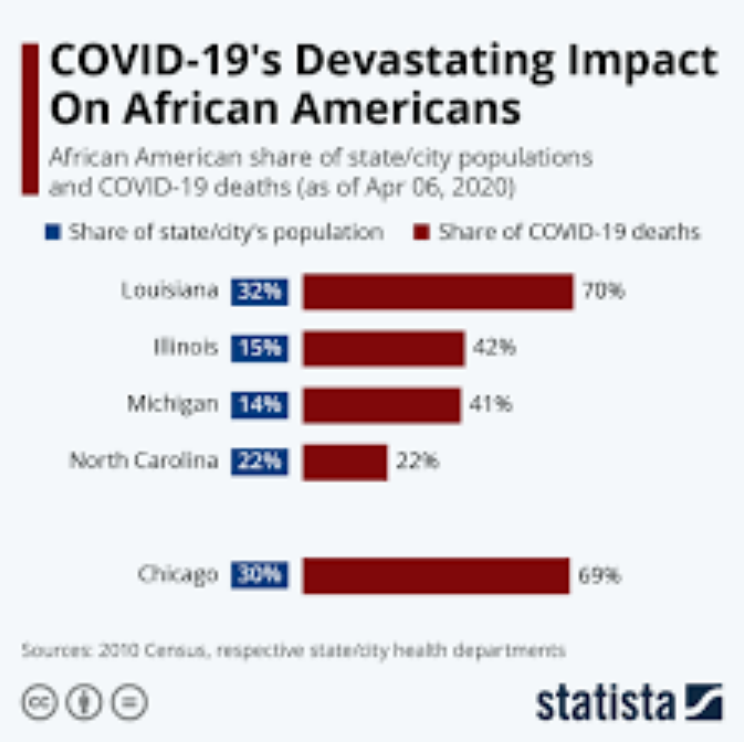
"When the incidence rate of disease in the presence of two or more risk factors differs from the incidence rate expected to result from their individual effects."

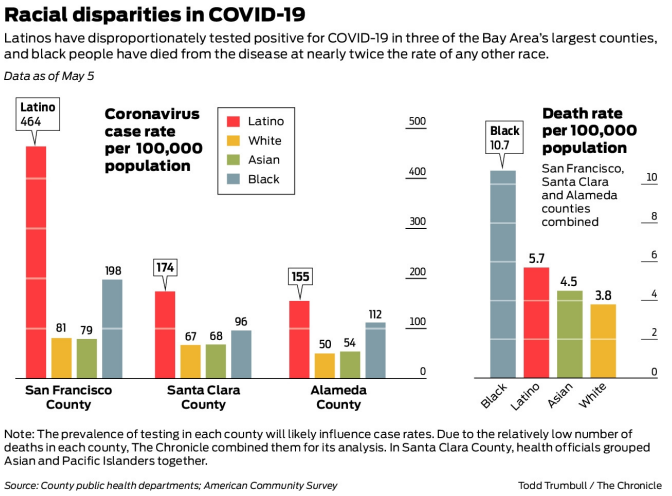
- Positive interaction: The effect of two risk factors combined is greater than what we would expect (also called synergism)
- Negative interaction: The effect of two risk factors combined is less than what we would expect from either risk factor independently (also called antagonism).

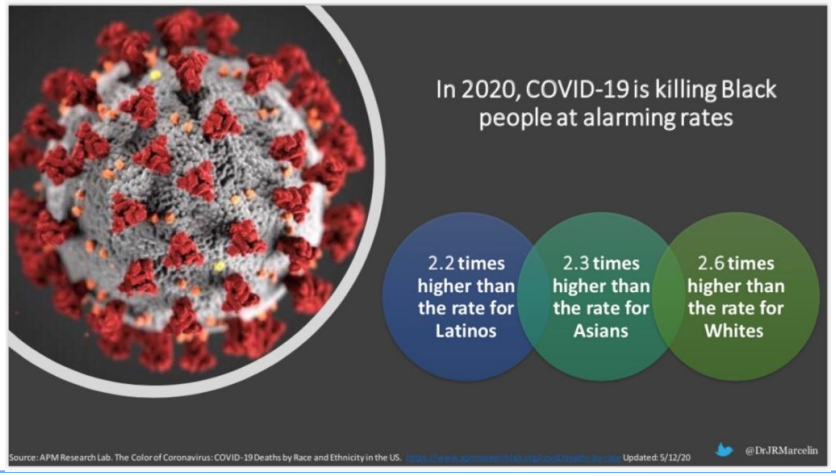
Why do we care about interaction?

- When you are interested in the joint effects of two (or more) exposures
- Drinking and driving are independent causes for injury, but together they increase risk much more than either exposure independently greater risk
- Interaction is often a critical question for public health
  - Identifying high risk groups is of public health importance
  - E.g., vaccine distribution for COVID-19
  - Phase 1: healthcare workers and residents of long term care facilities → recognizes interaction in COVID 19 outcomes

Interaction and public health: COVID-19

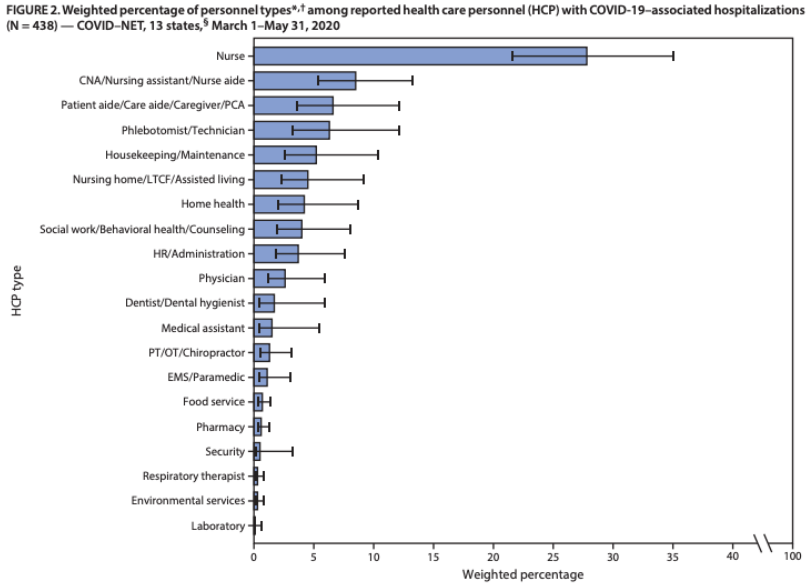




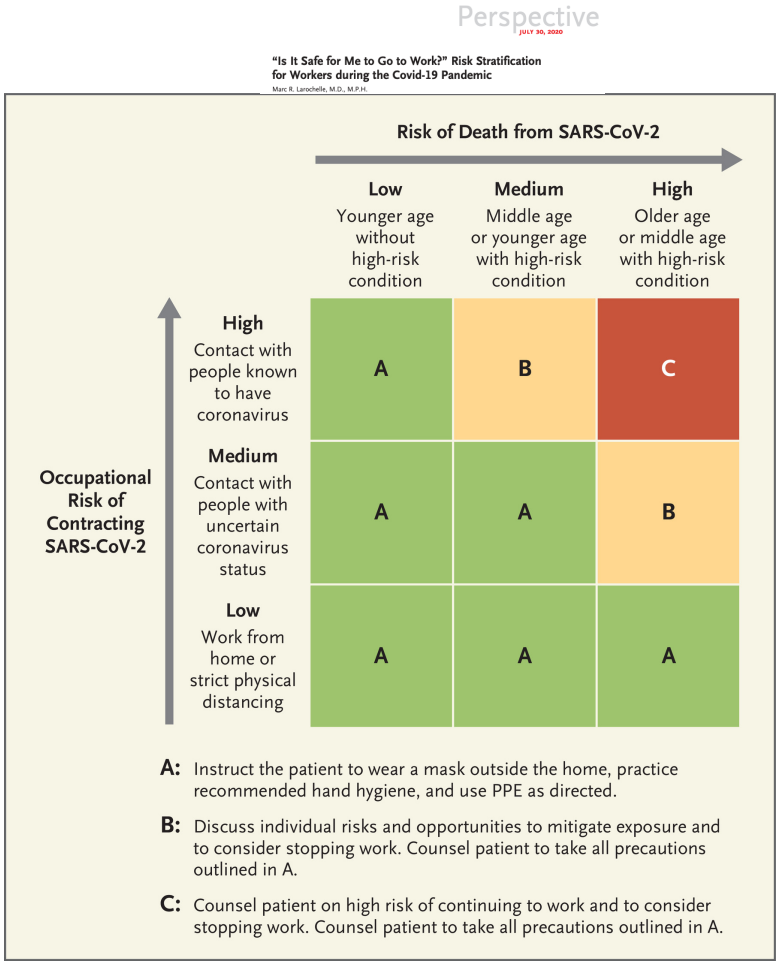


Occupation & COVID-19

Of 6,760 adults hospitalized March-May 2020, for whom HCP status was determined
5.9% were HCP



https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6943e3-H.pdf



Occupation *x* gender *x* race/ethnicity

- Health care system relies on thousands of low-wage workers, including health care aides and environmental services workers to keep facilities clean and operational
- Women and minorities are disproportionately represented in these jobs
  - 1/2 of black female and Latina healthcare workers earn less than $15/hours
- Many people are unable to stop working without additional financial support/protection despite being at increased risk for poor outcomes related to COVID-19

Gene-environment interactions

- Many researchers are interested in the question of genetic susceptibility to environmental factors
- Example: smoking and the factor v Leiden mutation
  - Smoking increases MI risk
  - Factor v Leiden (genetic) mutation increases blood clot risk
  - Risk of MI is higher in smokers but much higher in smokers with mutation

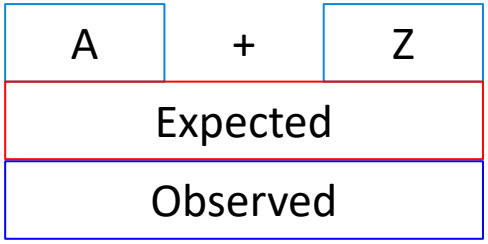
Odds Ratio (95% CI)	**factor v genotype**	
Current Smoker	**Wildtype**	**Leiden**
No	1.0 (ref)	1.1 (0.1, 8.5)
Yes	9.0 (5.1, 15.7)	32.0 (7.7, 133)

Interaction is scale dependent

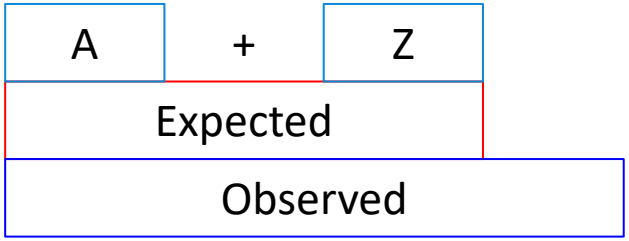
- Additive: if two exposures do not interact, the risk of disease among exposed to both exposures = sum of risk of disease given exposure to one factor + risk of disease given exposure to the other factor
- Multiplicative: If two exposures do not interact, the risk of disease among those exposed to both = product of risk of disease given exposure to one factor * risk of disease given exposure to the other factor

How do we detect interaction? We compare observed effects of exposures to what should be expected if **summed (additive)** or multiplied (multiplicative)

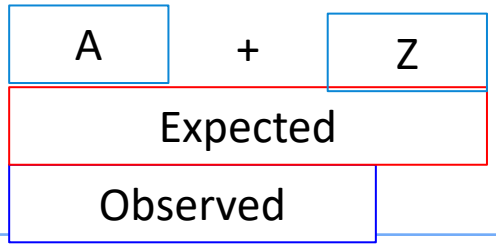
No Interaction



Positive Additive Interaction



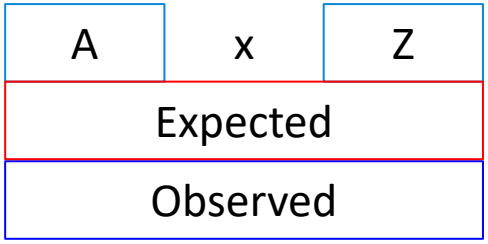
Negative Additive Interaction



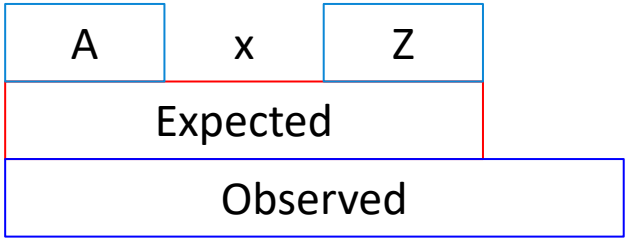
What is the combined effect of factors A and Z on outcome Y?

How do we detect interaction? We compare observed effects of exposures to what should be expected if summed (additive) or **multiplied (multiplicative)**

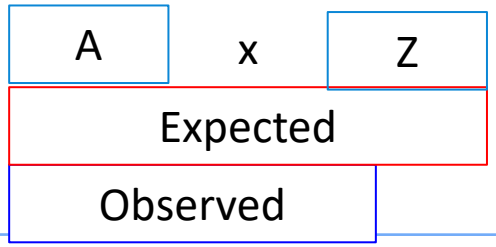
No Interaction



Positive Multiplicative Interaction



Negative Multiplicative Interaction



What is the combined effect of factors A and Z on outcome Y?

Using formulas to represent interaction

- Risk among those exposed to both X and Z: R_{11}
- Risk among those exposed to X but not Z: R_{10}
- Risk among those exposed to Z but not X: R_{01}
- Risk among those exposed to neither Z nor Y: R_{00}

R_{00}	**R_{10}**
R_{01}	**R_{11}**

Additive scale: No interaction when:

$$R_{11} - R_{00} = (R_{10} - R_{00}) + (R_{01} - R_{00})$$

Multiplicative scale. No interaction when:

$$R_{11}/R_{00} = (R_{10}/R_{00}) * (R_{01}/R_{00})$$

Risk

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	

Under an additive model, we **expect** that the effect of exposure A plus the effect of exposure B will equal the joint effect of both exposures A and B

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	21.0

However, this is the data we observe (collected)

Risk

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	

Under a multiplicative model, we **expect** that the effect of exposure A multiplied by the effect of exposure B will equal the join effect of both exposures A and B

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	45.0

However, this is the data we observe (collected)

Risk

Risk

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	21.0

Risk Difference

Factor B	Factor A: −	Factor A: +
−	0	6
+	12	

6+12=18

Assessing additive interaction

1) Subtract out the risk in R00
2) Add R01 and R10 cells
3) Sum of R01+R10=expected RD

Risk

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	45.0

Risk Ratio

Factor B	Factor A: −	Factor A: +
−	1	3
+	5	

3 x 5=15

Assessing multiplicative interaction

1) Divide out the risk in R00
2) Multiply R01 and R10 cells
3) Product of R01+R10=expected RR

Risk of mortality due to lung Cancer among Individuals with and without exposure to cigarette smoking and asbestos

Cigarette Smoking	Asbestos Exposure *No*	*Yes*
No	11.3	58.4
Yes	122.6	601.6

Adapted from Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci 330:473–490, 1979.

OBSERVED RD

11.3-11.3= 0	58.4-11.3=47.1
122.6-11.3=111.3	601.6-11.3=590.3

0	47.1
111.3	590.3

OBSERVED RR

11.3/11.3= 1	58.4/11.3=5.2
122.6/11.3=10.8	601.6/11.3=53.2

1	5.2
10.8	53.2

OBSERVED RD

0	47.1
111.3	**590.3**

OBSERVED RR

1	5.2
10.8	**53.2**

How to calculate the expected Risk Difference and Expected Risk Ratios:

EXPECTED RD

0	47.1
111.3	47.1+111.3= 158.4

EXPECTED RR

1	5.2
10.8	5.2*10.8=56.2

Observed RD= 590.3

Expected RD= 158.4

Observed RR= 53.2

Expected RR= 56.2

If observed > expected?

Super multiplicative

If observed < expected?

Sub multiplicative

If observed= expected

Exactly multiplicative

If observed > expected?

Super additive (synergism)

If observed < expected?

Sub additive (antagonism)

If observed= expected

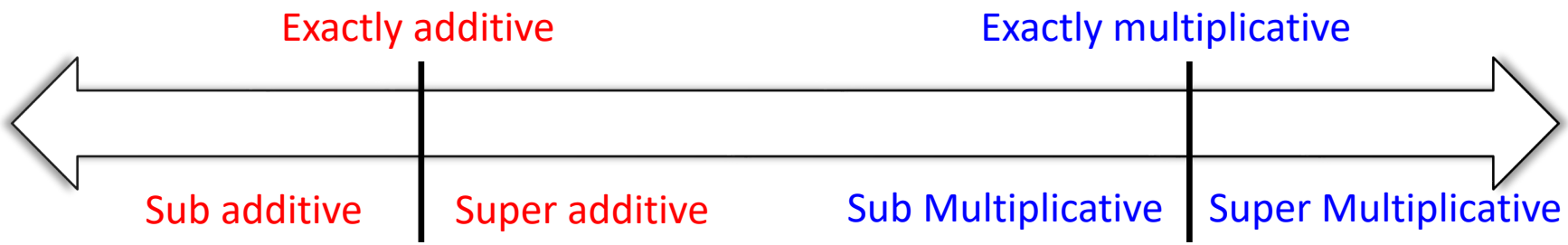
Exactly additive

Is there evidence of interaction for the effects of exposure to smoking and asbestos on mortality?

Yes!

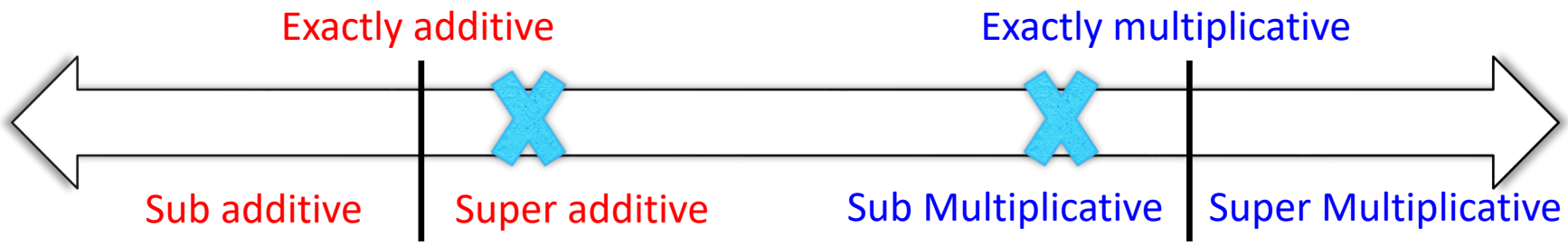
The effect is **super-additive (observed RD > expected RD)**
and
sub-multiplicative (observed RR < expected RR)

Continuum of Interaction



Interaction is said to exist on a continuum; if there is a non-null effect of exposure on outcome there will always be interaction on one scale or another

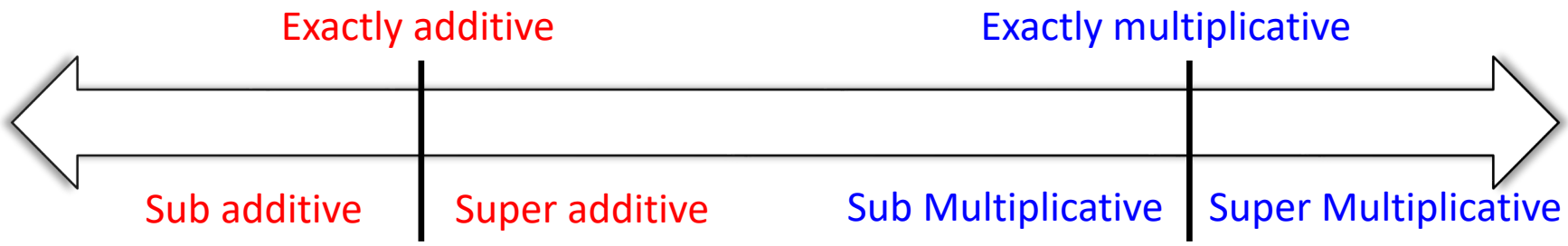
Continuum of Interaction



Smoking and asbestos example:

The effect is **super-additive (observed RD > expected RD)**
and
sub-multiplicative (observed RR < expected RR)

Continuum of Interaction

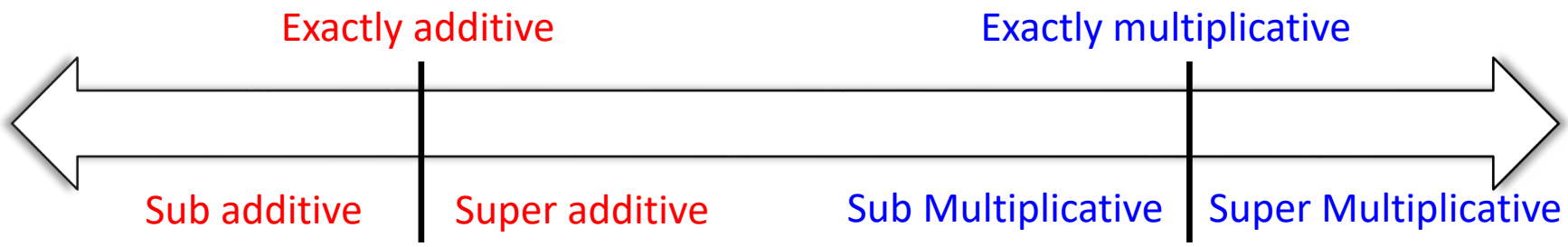


Example:

Observed RR= 1.2 Expected RR=1.2

Observed RD= 10.6 Expected RD= 114.9

Continuum of Interaction



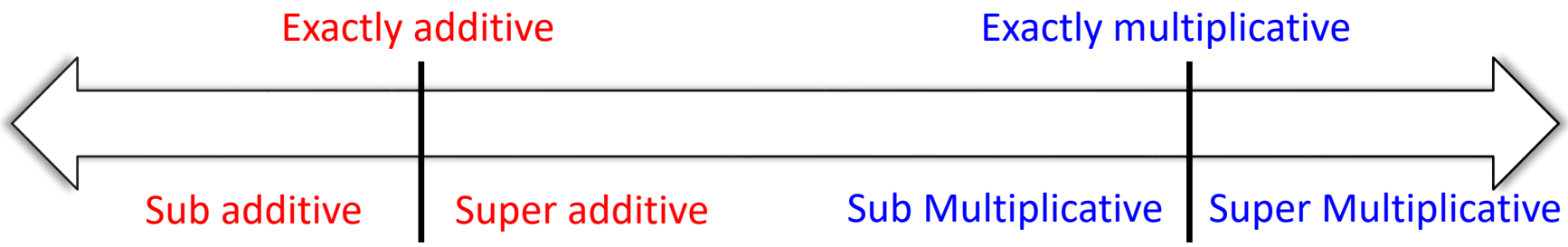
Example:

Observed RR= 1.2 Expected RR=1.2

Observed RD= 10.6 Expected RD= 114.9

Exactly multiplicative & sub-additive

Continuum of Interaction

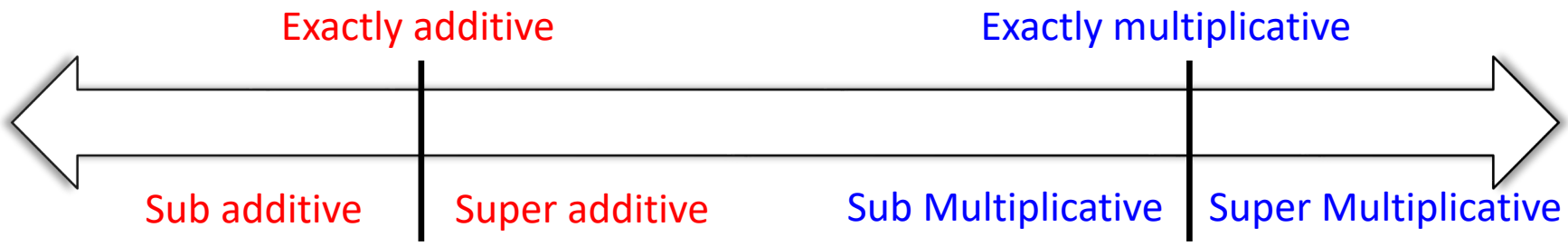


Example:

Observed RR= 1.88 Expected RR= 5.71

Observed RD= -0.4 and Expected RD= -0.4

Continuum of Interaction

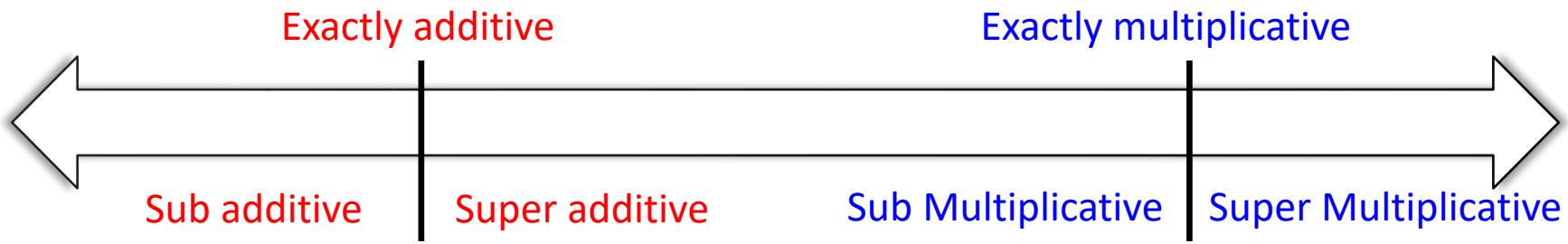


Example:

Observed RR= 1.88 Expected RR= 5.71

Observed RD= -0.4 and Expected RD= -0.4

Sub-multiplicative & exactly additive



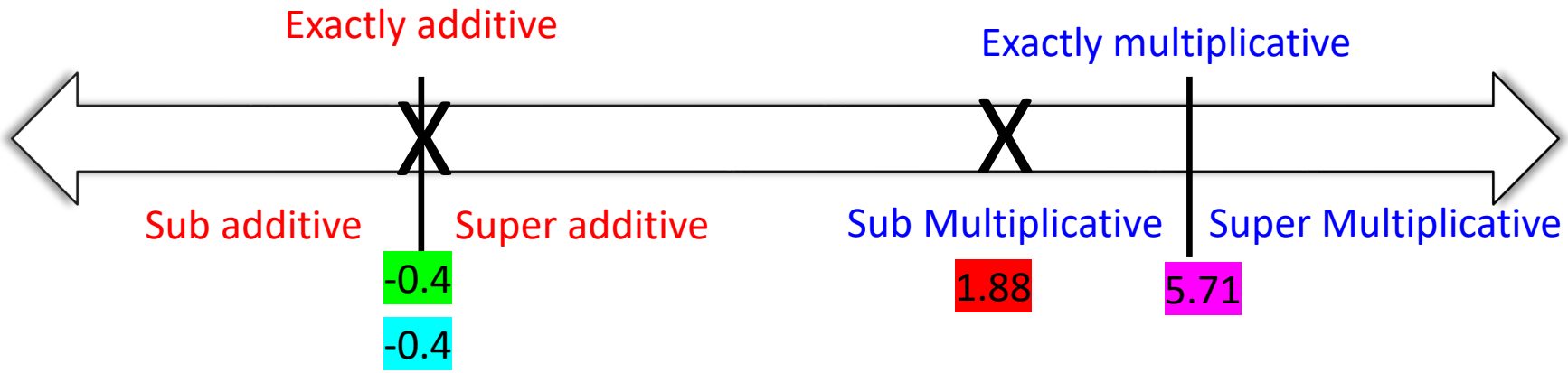
1) Draw out the continuum of interaction

2) Write out the expected RR and RD values at the benchmarks

3) Assess whether the observed RR and RD values are greater or less than expected

4) Draw an X on the continuum corresponding to the location of the observed value

Continuum of Interaction



Example:

Observed RR= 1.88 Expected RR= 5.71

Observed RD= -0.4 and Expected RD= -0.4

Sub-multiplicative & exactly additive

Additive Interaction and Public Health

Additive interaction is said to be more important for public health

E.g. **outcome:** Lung Cancer **exposures:** smoking, asbestos

Risk of lung cancer in non-smokers, no asbestos: 1/1000
Risk of lung cancer in smokers, no asbestos: 10/1000
} RR=10

Risk of lung cancer in non-smokers, asbestos: 3/1000
Risk of lung cancer in smokers, asbestos: 30/1000
} RR=10

	Smk -	Smk +
Asbestos -	1	10
Asbestos +	3	30

Risk Ratio Smoking = 10
Risk Ratio Asbestos = 10

-Prevention of asbestos exposure: reduce cancer cases by 20/1000 **among smokers (=30-10)**

-Prevention of asbestos exposure: reduce cancer cases by 2/1000 **among non-smokers (=3-1)**

-Number of lung cancer cases depends on how many of the smokers are exposed to asbestos, or vice versa

-Public health implications of smoking and asbestos depend on the segment of the population in which the exposures occur *together* (i.e., jointly)

Assessing additive interaction

- RD values are often not reported in the literature, more often RR or OR values are reported
- To calculate additive interaction when only data on RR or OR values are reported, can calculate the **relative excess risk of interaction (RERI)**
- RERI is sometimes referred to as the **interaction contrast ratio (ICR)**

Relative Excess Risk of Interaction (RERI)

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

RERI >0 super-additive interaction present

RERI <0 sub-additive interaction present

RERI= 0 no additive interaction present

RERI Example

Table 4 Odds ratios for breast cancer by strata of alcohol consumption and XRCC3-T241M

	No alcohol	Alcohol
T/T or T/M	1	1.12
M/M	1.21	2.09

Only have a table of odds ratio values (*approximating RR)

$$RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1$$
$$= 2.09 - 1.21 - 1.12 + 1 = 0.76$$

0.76 > 0

Super-additive interaction