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Interaction and effect measure modification

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Highlights from Week #8

- **Expanded definition of confounding**
  - Natural vs. artefactual confounding
  - Caveats for three criteria for confounding (e.g. not mediator, collider, antecedent)
- **Types of relationships between variables**
- **Methods to control for confounding during study design**
- **Methods to control for confounding during study analysis**
  - Multivariate adjustment models
  - Under or over-adjustment and estimation of amount of confounding
  - Propensity scores
  - Structural measures and g-estimation
- **New methods to control for residual and unmeasured confounders**

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Learning Objectives

- Review effect modification
- Explain the concept of biologic interaction
  - Defined under the counterfactual approach
  - Defined under the sufficient cause approach
- Measures of interaction
- Describe methods to assess effect modification
  - Graphical assessment
  - Stratification
  - Comparing expected vs. observed joint effects
  - Estimating interaction magnitude

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Learning Objectives

Looking ahead:

- Learn how to estimate attributable fraction and other indices
- Discuss ways of presenting the results of analyses for interaction and for effect modification

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Effect modification – an example

- Causal effect of interest depends on the characteristics of study population
- Consider example from Hernan and Robins, Chapter 4:
  - What is the average causal effect?
    - $Pr[Y^{a=1} = 1] = 10 / 20 = 0.5$
    - $Pr[Y^{a=0} = 1] = 10 / 20 = 0.5$
    - Causal risk ratio = $Pr[Y^{a=1} = 1] / Pr[Y^{a=0} = 1] = 0.5 / 0.5 = 1$
    - Causal risk difference = $Pr[Y^{a=1} = 1] - Pr[Y^{a=0} = 1] = 0.5 - 0.5 = 0$

Table 4.1

	M	Y^0	Y^1
Rheia	1	0	1
Demeter	1	0	0
Hestia	1	0	0
Hera	1	0	0
Artemis	1	1	1
Leto	1	0	1
Athena	1	1	1
Aphrodite	1	0	1
Persephone	1	1	1
Hebe	1	1	0
Kronos	0	1	0
Hades	0	0	0
Poseidon	0	1	0
Zeus	0	0	1
Apollo	0	1	0
Ares	0	1	1
Hephaestus	0	0	1
Cyclope	0	0	1
Hermes	0	1	0
Dionysus	0	1	0

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Effect modification – an example

- What is the average causal effect in men?
  - Causal risk ratio: $Pr[Y^{a=1} = 1 \mid M=0] / Pr[Y^{a=0} = 1 \mid M=0] = 0.4 / 0.6 = 0.667$
  - Causal risk difference: $Pr[Y^{a=1} = 1 \mid M=0] - Pr[Y^{a=0} = 1 \mid M=0] = 0.4 - 0.6 = -0.2$
- What is the average causal effect in women?
  - Causal risk ratio: $Pr[Y^{a=1} = 1 \mid M=1] / Pr[Y^{a=0} = 1 \mid M=1] = 0.6 / 0.4 = 1.5$
  - Causal risk difference: $Pr[Y^{a=1} = 1 \mid M=1] - Pr[Y^{a=0} = 1 \mid M=1] = 0.6 - 0.4 = 0.2$

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Ares	0	1	1
Hephaestus	0	0	1
Cyclope	0	0	1
Hermes	0	1	0
Dionysus	0	1	0

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Effect modification – an example

Take-away points:

1. The average causal effects are different from the stratum-specific causal effects.
2. The causal effect of A on Y is different for men and women.

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Effect modification - definitions

- **Effect modifier**: M is a modifier of the effect of A on Y when the average causal effect of A on Y differs across levels of M.
- **Effect measure modification**: dependent on the measure being used
  - Sex (M) is an effect modifier of the effect of A on Y on the multiplicative scale because the causal risk ratio (0.667 vs. 1.5) differs across levels of M.
  - Sex (M) is an effect modifier on the effect of A on Y on the additive scale because the causal risk difference (0.2 vs. -0.2) differs across levels of M.
  - Effect modification on one scale does not guarantee effect modification on another scale.
- **Qualitative effect modification**: The average causal effects within levels of M are in opposite directions.
  - In presence of qualitative effect modification, additive effect modification implies multiplicative effect modification, and vice versa.

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Effect modification

- **What if there is no effect modification on either of the two scales?**
  - Then, one of the two exposures has no effect on the outcome at all.

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Effect modification - definitions

- **Surrogate effect modifier**: an effect modifier that is likely not involved in the mechanisms of effect modification, but used as a marker for a causal effect modifier
  - E.g. Nationality in the effect of heart transplant on the risk of death
- **Causal effect modifier**: an effect modifier that is involved in the mechanisms of effect modification
  - E.g. Quality of care in the effect of heart transplant on the risk of death
- **Heterogeneity of effects**: a neutral term to characterize when effect estimates differ across strata of M, without attributing a causal role of the effect modifier

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Effect modification – why care?

- If the causal effect varies within levels of an effect modifier, M, then the average causal effect will differ in populations with different distributions of M.
  - Improves transportability of causal inferences in the population
- Understanding effect modification is helpful to identify which populations may benefit most from public health interventions
- Helps to understand mechanisms linking exposure and outcome

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Interaction vs. Effect modification

- **Effect modification**: The average causal effect of exposure on outcome differs across levels of a third variable, M.
  - Focus is on the causal effect of A on Y
  - The independent causal effect of M on Y is not a primary focus
- **Interaction**: Joint causal effects of two (or more) treatments on the outcome
  - Focus is equally on the effects of A and E on the outcome.

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Interaction – an example

- Consider example from Hernan and Robins, Chapter 5:
  - Outcome (Y): Death
  - Treatment 1 (A): Heart transplant
  - Treatment 2 (E): Taking multivitamin complex
- Four treatment groups:
  - A = 1, E = 1: Heart transplant and vitamins
  - A = 1, E = 0: Heart transplant and no vitamins
  - A = 0, E = 1: No heart transplant and vitamins
  - A = 0, E = 0: No heart transplant and not vitamins
- Each treatment group corresponds to one potential counterfactual outcome
- Each individual has four counterfactual outcomes

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Interaction– an example

$$\Pr[Y^{a=1,e=1} = 1] - \Pr[Y^{a=0,e=1} = 1] \neq \Pr[Y^{a=1,e=0} = 1] - \Pr[Y^{a=0,e=0} = 1]$$

Causal risk difference of heart transplant on risk of death if everyone takes vitamins

Causal risk difference of heart transplant on risk of death if no one takes vitamins

$$\Pr[Y^{a=1,e=1} = 1] - \Pr[Y^{a=1,e=0} = 1] \neq \Pr[Y^{a=0,e=1} = 1] - \Pr[Y^{a=0,e=0} = 1]$$

Causal risk difference of vitamins on risk of death if everyone had a heart transplant

Causal risk difference of vitamins on risk of death if no one had a heart transplant

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Interaction – counterfactual response types

In the case of one intervention or treatment:

	$Y^{a=0}$	$Y^{a=1}$	Examples
Doomed	1	1	Artemis, Athena, Persephone, Ares
Preventative	1	0	Hebe, Kronos, Poseidon, Apollo, Hermes, Dionysus
Causative	0	1	Rheia, Leto, Aphrodite, Zeus, Hephaestus, Cyclope
Immune	0	0	Demeter, Hestia, Hera, Hades

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Cyclope	0	0	1
Hermes	0	1	0
Dionysus	0	1	0

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Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$
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

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Counterfactual types

Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$
1	1	1	1	1
16	0	0	0	0

- For Type 1 individuals, they would die if treated or untreated with heart transplant or vitamins
- For Type 16 individuals, they would survive if treated or untreated with heart transplant or vitamins
- Neither A nor E had a causal effect on Y

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Counterfactual types

Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$
4	1	1	0	0
6	1	0	1	0
11	0	1	0	1
13	0	0	1	1

- Type 4 individuals would die only if treated with vitamins. Heart transplant has no effect on Y.
- Type 13 individuals would die only if untreated with vitamins. Heart transplant has no effect on Y.
- Type 6 individuals would die only if treated with heart transplant. Vitamins have no effect on Y.
- Type 11 individuals would die only if untreated with heart transplant. Vitamins have no effect on Y.

- Causal effect of A on Y is independent of E. Causal effect of E on Y is independent of A.

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Counterfactual types

Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$
8	1	0	0	0
12	0	1	0	0
14	0	0	1	0
15	0	0	0	1

- Type 8 individuals would die only if treated with both heart transplant and vitamins
- Type 12 individuals would die only if treated with vitamins and no heart transplant
- Type 14 individuals would die only if treated with heart transplant and no vitamins
- Type 15 individuals would die only if treated with no heart transplant and no vitamins

- Individuals would only develop outcome under **one** of four treatment combinations.

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Counterfactual types

Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$
7	1	0	0	1
10	0	1	1	0

- Type 7 individuals would die only if treated with both heart transplant and vitamins, or treated with no vitamins and no heart transplant
- Type 10 individuals would die only if treated with vitamins and no heart transplant, or treated with heart transplant and no vitamins

- Individuals would only develop outcome under **two** of four treatment combinations.

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Counterfactual types

Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$
2	1	1	1	0
3	1	1	0	1
5	1	0	1	1
9	0	1	1	1

- Type 2 individuals would survive only if treated with no heart transplant and no vitamins
- Type 3 individuals would survive only if treated with heart transplant and no vitamins
- Type 5 individuals would survive only if treated with no heart transplant and vitamins
- Type 9 individuals would survive only if treated with heart transplant and vitamins

- Individuals would only develop outcome under **three** of four treatment combinations.

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Interaction under counterfactual model

- The presence of additive interaction between A and E means individuals in at least one of the three classes:
  - Individuals develop disease only under one of four treatment conditions (Types 8, 12, 14, 15)
  - Individuals develop disease only under two of four treatment conditions (Types 7, 10)
  - Individuals develop disease only under three of four treatment conditions (Types 2, 3, 5, 9)
- If no additive interaction, then no individual in the study population belongs to these classes (or in rare cases, perfect cancellation)

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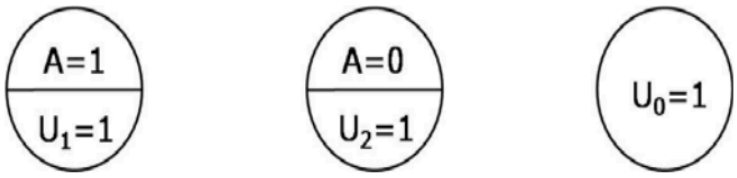
Interaction under the sufficient cause approach



- Interaction between component causes is implicit in the sufficient cause model
- Each component cause requires the presence of the others to act, their action is interdependent

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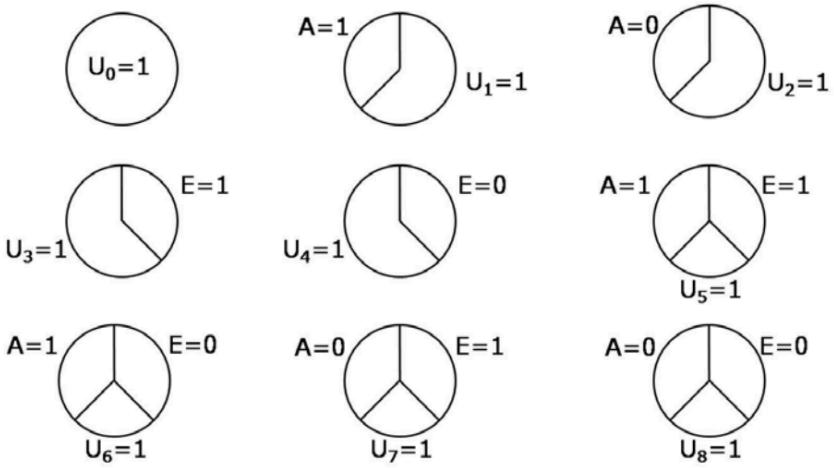
Interaction under the sufficient cause approach



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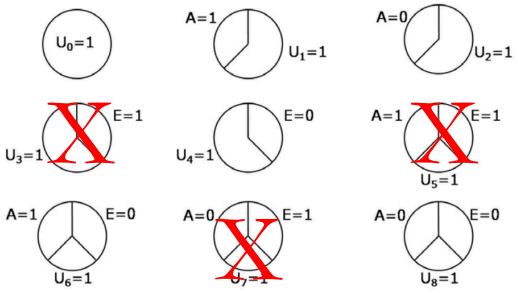
Interaction under the sufficient cause approach

- At the individual level, individual is susceptible to sufficient cause, k, if they have U_k factors present
  - An individual can be at risk of 0, 1 or many sufficient causes
- On population level, not all 9 sufficient component causes may exist in your study population.
  - If no one with E=1 develops outcome, independent of A, then sufficient causes with E=1 do not exist



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Interaction – more definitions

- **Synergism**: Individual would get disease only if exposed to both treatments. Individual would not get disease if only exposed to A or E.
  - Sometimes called biologic interaction
  - Causal synergism: Both treatments work to cause the outcome
  - Preventive synergism: Both treatments work to prevent the outcome
- **Antagonism**: Individual would only get the disease if exposed to one treatment but not the other, and vice versa. One treatment blocks the effect of another treatment.
  - Causal antagonism: Treatment 1 blocks harmful effect of Treatment 2
  - Preventive antagonism: Treatment 1 blocks preventative effect of Treatment 2

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Type	$Y^{a=1,e=1}$	$Y^{a=0,e=1}$	$Y^{a=1,e=0}$	$Y^{a=0,e=0}$	Description of Causal Type
1	1	1	1	1	Doomed (no effect)
2	1	1	1	0	Single plus joint causation
3	1	1	0	1	Preventive antagonism
4	1	1	0	0	A has causal effect. E has no effect
5	1	0	1	1	Preventive antagonism
6	1	0	1	0	E has causal effect. A has no effect
7	1	0	0	1	Preventive antagonism (mutual blockage)
8	1	0	0	0	Causal synergism
9	0	1	1	1	Preventive synergism
10	0	1	1	0	Causal antagonism (mutual blockage)
11	0	1	0	1	E has causal effect. A has no effect
12	0	1	0	0	Causal antagonism
13	0	0	1	1	A has causal effect. E has no effect.
14	0	0	1	0	Causal antagonism
15	0	0	0	1	Single plus joint prevention
16	0	0	0	0	Immune (no effect)

Sufficient cause vs. counterfactual models

- Sufficient cause model considers actions, events, or states of nature which act together to bring about the outcome of interest
  - Requires detailed knowledge about mechanisms underlying effects
  - "Given a particular effect, what are the various events that could have caused it?"
- Counterfactual model considers one cause/intervention and the various effects it could have
  - Does not require detailed knowledge of mechanisms
  - "What would have occurred if a particular factor was intervened upon?"

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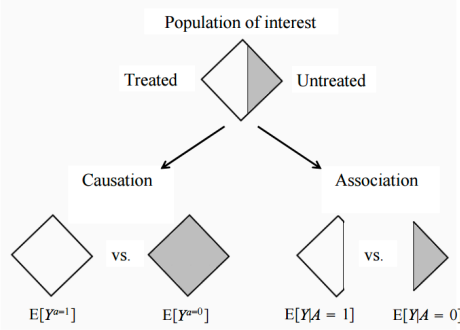
Review measures of association

- **Effect measures vs. measures of association**
  - Can never achieve counterfactual ideal
  - Logically impossible to observe population under both conditions and to estimate true effect measures
- **Measures of association**
  - Compares what happens in two distinct populations
  - Constructed to equal the effect measure of interest



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Review measures of association

- **Measures of association**
  - Absolute: differences in occurrence measures (rate or risk difference)
    - Risk difference: -1 to 1
    - Rate difference: -∝ to + ∝ (units of 1/time)
  - Relative: ratios of occurrence measures (rate or risk ratio, odds ratio)
    - Risk ratio: 0 to ∝
    - Rate ratio: 0 to ∝

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Measures of interaction – on the additive scale

Assume a binary outcome Y and two binary exposures of interest:

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

Effect of both exposures | Effect of exposure #1 | Effect of exposure #2

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

If greater than 0, interaction is positive or super-additive.

If less than 0, interaction is negative or sub-additive.

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Measures of interaction – on the additive scale

	No Asbestos	Asbestos
Non-Smoker	0.0011	0.0067
Smoker	0.0095	0.0450

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

$$0.0450 - 0.0095 - 0.0670 + 0.011$$

$$= 0.0299$$

Evidence of positive or super-additive interaction

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Measures of interaction – on the multiplicative scale

Assume a binary outcome Y and two binary exposures of interest:

$RR_{10} = p_{10} / p_{00}$

$RR_{01} = p_{01} / p_{00}$

$RR_{11} = p_{11} / p_{00}$

$$\frac{RR_{11}}{RR_{10}RR_{01}} = \frac{p_{11}p_{00}}{p_{10}p_{01}}$$

If greater than 1, interaction is positive or super-multiplicative.
If less than 1, interaction is negative or sub-multiplicative.

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Measures of interaction – on the multiplicative scale

	No Asbestos	Asbestos
Non-Smoker	0.0011	0.0067
Smoker	0.0095	0.0450

$$\frac{(0.0450/0.011)}{(0.0095/0.011) \text{ X } (0.0067 / 0.0011)}$$

= 0.78

Evidence of negative multiplicative interaction

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Measures of interaction – on the multiplicative scale

Assume a binary outcome Y and two binary exposures of interest:

$OR_{10} = [p_{10} / (1- p_{10})] /[p_{00}/ (1- p_{00})]$

$OR_{01} = [p_{01} / (1- p_{01})] /[p_{00}/ (1- p_{00})]$

$OR_{11} = [p_{11} / (1- p_{11})] /[p_{00}/ (1- p_{00})]$

$$\frac{OR_{11}}{OR_{10}OR_{01}}$$

If greater than 1, interaction is positive.
If less than 1, interaction is negative.

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Measures of interaction – scale dependent

	No Asbestos	Asbestos
Non-Smoker	0.0011	0.0067
Smoker	0.0095	0.0450

- Positive/ super-additive interaction on additive scale
  - Effect of both exposures together exceeds sum of effects individually on the risk difference scale
- Negative interaction on multiplicative scale
  - Effect of both exposures together is less than the product of the effects of the two exposures on the multiplicative scale
- If both exposures have independent effect on the outcome, there must be interaction on some scale.

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Measures of interaction - RERI

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

- RERI = Relative excess risk due to interaction (Rothman 1986)
- ICR = Interaction contrast ratio (Greenland 2008)
  - If $RERI_{RR} > 0$ only if $p_{11} - p_{10} - p_{01} + p_{00} < 0$
  - If $RERI_{RR} < 0$ only if $p_{11} - p_{10} - p_{01} + p_{00} < 0$
  - If $RERI_{RR} = 0$ if $p_{11} - p_{10} - p_{01} + p_{00} = 0$

- $RERI_{RR}$ gives direction of additive interaction, but not magnitude

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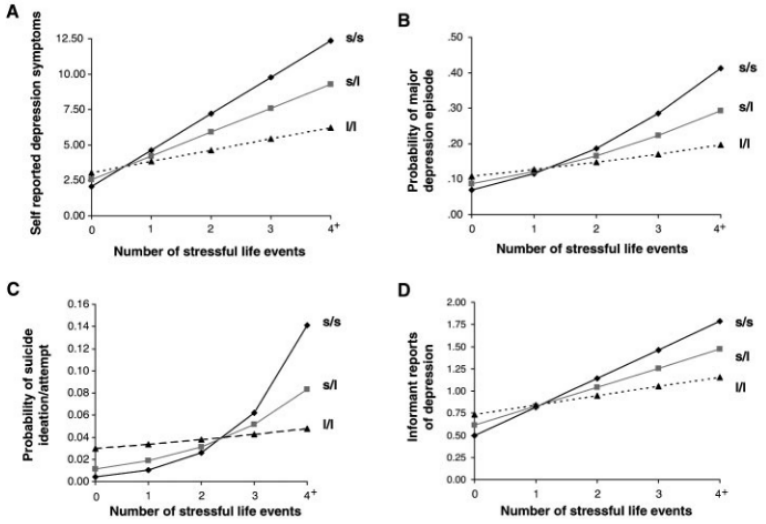
Assessing interaction by graphic representation



Caspi et al. *Science* 2003

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Assessing interaction by stratification

- Effect modification by presence of short allele G on the association between stressful life events E and risk of depression
  - When G is present:
    - RD = 0.33 – 0.10 = 0.23
    - RR = 0.33 / 0.10 = 3.3
  - When G is absent:
    - RD = 0.17 – 0.10 = 0.07
    - RR = 0.17 / 0.10 = 1.7

4+ Stressful life events	Genotype with short allele	
	Yes	No
Yes	33%	17%
No	10%	10%

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Assessing interaction by stratification

- Effect modification by presence of short allele G on the association between stressful life events E and risk of depression
  - When G is present:
    - RD = 0.33 – 0.10 = 0.23
    - RR = 0.33 / 0.10 = 3.3
  - When G is absent:
    - RD = 0.17 – 0.10 = 0.07
    - RR = 0.17 / 0.10 = 1.7
- Not to be confused with stratification to adjust for confounding
  - Cannot be used to estimate average causal effects
  - Restriction = another form of stratification

Both RDs and RRs are heterogeneous: for both measures of association, the effect of E when G is present is larger than the effect of E when G is absent

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Assessing interaction by stratification

Table 2

Relative Risk and 95% Confidence Interval for Acute Myocardial Infarction Within 2 Hours of Anger Outburst According to Patient Characteristics.

	Number Exposed in the Past Year	Number Exposed in the Past 2 Hours	Relative Risk (95% Confidence Interval)	P-Value for χ^2 Test for Homogeneity
All Patients	3886	110	2.43 (2.01–2.92)	
Sex				
Male	2627	73	2.26 (1.79–2.84)	0.26
Female	1259	37	2.83 (2.04–3.93)	
Age (Years)				
<50	766	36	1.93 (1.36–2.72)	0.19
50–69	1982	62	2.85 (2.23–3.64)	
≥70	1135	12	2.35 (1.40–3.96)	
Education				
<High School	924	32	3.54 (2.45–5.11)	0.03
Completed High School	2161	52	1.96 (1.51–2.55)	
Some College	801	26	2.67 (1.79–3.98)	
Frequency of Weekly Activity				
<3	3264	73	2.20 (1.75–2.76)	0.11
≥3	622	37	3.05 (2.20–4.25)	

Mostofsky et al. AJC 2013

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Assessing interaction by comparing expected vs. observed joint effects

1. What is the individual effect of cause A in the absence of exposure to cause B?
2. What is the individual effect of cause B in the absence of exposure to cause A?
3. What is the observed joint effect of A and B?
4. What is the expected joint effect of A and B in the absence of interaction?
5. Is the observed joint effect similar to the expected joint effect in the absence of interaction?

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Assessing interaction by comparing expected vs. observed joint effects

1. What is the individual effect of cause A in the absence of exposure to cause B?
   1. $RD_{E,-}=0.17-0.10=0.07$
2. What is the individual effect of cause B in the absence of exposure to cause A?
   2. $RD_{-,G}=0.10-0.10=0$
3. What is the observed joint effect of A and B?
   3. $RD_{OBSERVED\ E,G}=0.33-0.10=0.23$
4. What is the expected joint effect of A and B in the absence of interaction?
   4. $RD_{EXPECTED\ E,G}=0.07+0=0.07$
5. Is the observed joint effect similar to the expected joint effect in the absence of interaction?
   5. $RD_{OBSERVED\ E,G} > RD_{EXPECTED\ E,G,}$ additive interaction (superadditivity)

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Assessing interaction by comparing expected vs. observed joint effects

1. What is the individual effect of cause A in the absence of exposure to cause B?
2. What is the individual effect of cause B in the absence of exposure to cause A?
3. What is the observed joint effect of A and B?
4. What is the expected joint effect of A and B in the absence of interaction?
5. Is the observed joint effect similar to the expected joint effect in the absence of interaction?

1. $RR_{E,-}=0.17/0.10=1.7$
2. $RR_{-,G}=0.10/0.10=1.0$
3. $RR_{OBSERVED\ E,G}=0.33/0.10=3.3$
4. $RR_{EXPECTED\ E,G}=1.7*1.0=1.7$
5. $RR_{OBSERVED\ E,G} > RD_{EXPECTED\ E,G,}$ multiplicative interaction

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Assessing interaction by comparing expected vs. observed joint effects

1. What is the individual effect of cause A in the absence of exposure to cause B?
2. What is the individual effect of cause B in the absence of exposure to cause A?
3. What is the observed joint effect of A and B?
4. What is the expected joint effect of A and B in the absence of interaction?
5. Is the observed similar to the expected in the absence of interaction?
6. What is the interaction magnitude?

1. $RD_{E,-}=0.17-0.10=0.07$
2. $RD_{-,G}=0.10-0.10=0$
3. $RD_{OBSERVED\ E,G}=0.33-0.10=0.23$
4. $RD_{EXPECTED\ E,G}=0.07+0=0.07$
5. $RD_{OBSERVED\ E,G} > RD_{EXPECTED\ E,G,}$
6. $RD_{E/\ G\ IS\ PRESENT} - RD_{E/\ G\ IS\ ABSENT}$ = 0.23 - 0.07 =0.16 Interaction Contrast

1. $RR_{E,-}=0.17/0.10=1.7$
2. $RR_{-,G}=0.10/0.10=1.0$
3. $RR_{OBSERVED\ E,G}=0.33/0.10=3.3$
4. $RR_{EXPECTED\ E,G}=1.7*1.0=1.7$
5. $RR_{OBSERVED\ E,G} > RD_{EXPECTED\ E,G,}$
6. $RR_{E/\ G\ IS\ PRESENT} / RR_{E/\ G\ IS\ ABSENT}$ = 3.3 / 1.7 =1.9 Interaction Contrast Ratio

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Assessing interaction by estimating interaction magnitude

- How is this related to RERI?
  - Same for relative scale!
- On the risk difference scale:
  - Interaction contrast: $RD_{E/\ G\ IS\ PRESENT} - RD_{E/\ G\ IS\ ABSENT} = 0.23 - 0.07 = 0.16$
  - RERI: $p_{11} - p_{10} - p_{01} + p_{00n} = 0.33 - 0.17 - 0.10 + 0.10 = 0.16$
- On the relative risk scale:
  - Interaction contrast ratio: $RR_{E/\ G\ IS\ PRESENT} / RR_{E/\ G\ IS\ ABSENT} = 3.3 / 1.7 = 1.9$
  - RERI: $(RR_{11})/ (RR_{10}RR_{01)} = (3.3) / (1.0*1.7) = 1.9$

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Summary

- There is a distinct difference between biological interaction and effect (measure) modification
- In epidemiology, we are interested in biological interaction on an additive scale
- Various methods exist to evaluate biological interaction and to estimate the magnitude of interaction

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