



Interaction and effect measure modification

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Highlights from Week #9

- **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

- Measures of interaction
- Mechanistic Interaction
- Statistical Modeling
- Presentation of interaction analyses

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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.
 - Ex: gene-environment interactions, gene-gene interactions, environment-environment interactions, behavior-behavior interactions, and more



Interaction – another example

	No alcohol	Moderate alcohol	High alcohol
High folate	1.0	1.01 (0.84-1.21)	1.10 (0.90-1.33)
Low folate	1.08 (0.78-1.49)	1.37 (0.89-2.11)	1.45 (0.95-2.23)

- Alcohol increases risk for breast cancer. Folate plays role in DNA methylation and repair.
- Objective was to study interaction between alcohol and folate intake in risk of breast cancer
- Prospective cohort analysis of 34,387 postmenopausal women from Iowa Women's Health Study

Sellers et al. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 2001.

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	No alcohol	Moderate alcohol	High alcohol
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Low folate	1.08 (0.78-1.49)	1.37 (0.89-2.11)	1.45 (0.95-2.23)

- Alcohol has a moderate increase in the risk of breast cancer among women with high folate.
- Alcohol has a high increase in the risk of breast cancer among women with low folate.

Sellers et al. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 2001.

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Table 2 | **Selected examples of gene-environment interactions observed in at least two studies**

Gene symbol	Variant(s)	Environmental exposure	Outcome and nature of interaction	References
Genes for skin pigmentation (for example, <i>MC1R</i>)	Variants for fair skin colour	Sunlight or ultraviolet light B	Risk of skin cancer is higher in people with fair skin colour that are exposed to higher amounts of sunlight	62
<i>CCR5</i>	Δ -32 deletion	HIV	Carriers of the receptor deletion have lower rates of HIV infection and disease progression	41
<i>MTHFR</i>	Ala222Val polymorphism	Folic acid intake	Homozygotes for the low activity Ala222Val variant are at different risk of colorectal cancer and adenomas if nutritional folate status is low	63
<i>NAT2</i>	Rapid versus slow acetylator SNPs	Heterocyclic amines in cooked meat	Red meat intake is more strongly associated with colorectal cancer among rapid acetylators	33
<i>F5</i>	Leiden prothrombotic variant	Hormone replacement	Venous thromboembolism risk is increased in factor V Leiden carriers who take exogenous steroid hormones	64
<i>UGT1A6</i>	Slow-metabolism SNPs	Aspirin	Increased benefit of prophylactic aspirin use in carriers of the slow metabolism variants	58
<i>APOE</i>	<i>E4</i> allele	Cholesterol intake	Exaggerated changes in serum cholesterol in response to dietary cholesterol changes in <i>APOE4</i> carriers	65
<i>ADH1C</i>	γ -2 alleles	Alcohol intake	Inverse association between ethanol intake and myocardial infarction; risk is stronger in carriers of slow-oxidizing γ -2 alleles	66
<i>PPARG2</i>	Pro12Ala	Dietary fat intake	Stronger relation between dietary fat intake and obesity in carriers of the Pro12Ala allele	67
<i>HLA-DPB1</i>	Glu69	Occupational beryllium	Exposed workers who are carriers of the Glu69 allele are more likely to develop chronic beryllium lung disease	68
<i>TPMT</i>	Ala154Thr and Tyr240Cys	Thiopurine drugs	Homozygotes for the low-activity alleles of <i>TPMT</i> are likely to experience severe toxicity when exposed to thiopurine drugs	69
<i>ADRB2</i>	Arg16Gly	Asthma drugs	Arg16Gly homozygotes have a greater response in the airway to albuterol	70

Hunter DJ. Gene-environment interactions in human diseases. *Nature Review Genetics* 2005

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Gene-Environment Interactions

- Obtain a better estimate of PAR for genetic and environmental risk factors by accounting for joint interactions
- Strengthen association between environmental factors and disease by examining these factors in genetically susceptible individuals
- Help to dissect disease mechanisms in humans by using information on susceptibility genes to focus on the biologic pathways most relevant to disease, and environment factors most relevant to pathways
- Determine which specific compounds in complex mixtures of compounds that humans are exposed to cause disease
- Use information on biological pathways to design new preventive and therapeutic strategies
- Offer tailored preventive advice based on knowledge if an individual carries susceptibility or resistance alleles

Hunter DJ. Gene-environment interactions in human diseases. *Nature Review Genetics* 2005

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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

$$\frac{(0.0450/0.011)}{(0.0095/0.011) \times (0.0067 / 0.0011)} = 0.78$$

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 – scale dependent

	E=0	E=1
G=0	0.02	0.05
G=1	0.07	0.10

- Interaction on one scale doesn't always imply interaction on another scale

- Measure of additive interaction:

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

$$= 0.10 - 0.05 - 0.07 + 0.02 = 0$$

No evidence of additive interaction

- Measure of multiplicative interaction:

$$= p_{11}p_{00} / p_{10}p_{01}$$

$$= (0.10 \cdot 0.02) / (0.05 \cdot 0.07) = 0.57$$

Evidence of negative multiplicative interaction

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Measures of interaction – scale dependent

	E=0	E=1
G=0	0.02	0.05
G=1	0.04	0.10

- Interaction on one scale doesn't necessarily imply interaction on another scale

- Measure of additive interaction:

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

$$= 0.10 - 0.05 - 0.04 + 0.02 = 0.03$$

Evidence of positive additive interaction

- Measure of multiplicative interaction:

$$= p_{11}p_{00} / p_{10}p_{01}$$

$$= (0.10 \cdot 0.02) / (0.05 \cdot 0.04) = 1$$

No evidence of multiplicative interaction

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Measures of interaction – scale dependent

	E=0	E=1
G=0	0.02	0.05
G=1	0.07	0.10

	E=0	E=1
G=0	0.02	0.05
G=1	0.04	0.10

- If both exposures have an effect on the outcome, then there must be interaction on some scale (Greenland, VanderWheele)
 - No interaction on the additive scale implies interaction on the multiplicative scale.
 - No interaction on the multiplicative scale implies interaction on the additive scale.
- **Exception: In the presence of qualitative interaction, there is interaction on both scales.**

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Importance of Additive Interaction

- Relevant for public health practice!

- Among G=0, RD_E is 0.03
- Among G=1, RD_E is 0.06

RD shows treating G=1 group has a bigger absolute impact

- Among G=0, RR_E is 2.5
- Among G=1, RR_E is 2.5

RR shows no difference between groups

- Using RR over RD would lead to different conclusions

	E=0	E=1
G=0	0.02	0.05
G=1	0.04	0.10

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Additive or Multiplicative Interaction?

- Additive interaction more relevant for public health practice!
 - Informs which group would benefit most from treatment
- Most published epidemiologic studies report only interaction on the multiplicative scale
 - 1 in 50 studies reported interaction on the additive scale (Knol 2009)
 - Easier to estimate from statistical models
- **If interaction is primary objective, report interaction on both scales!**

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Measures of interaction - $RERI_{RR}$

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

- $RERI$ = 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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Measures of interaction – Attributable Proportion

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

- Proportion of risk in the doubly exposed group that is attributable to the interaction itself

If $AP > 0$ then $RERI_{RR} > 0$. If $AP < 0$ then $RERI_{RR} < 0$.

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Measures of interaction – Synergy Index

$$\frac{RR_{11} - 1}{(RR_{10} - 1) + (RR_{01} - 1)}$$

Numerator represents extent to which RR for both exposures exceeds 1

Denominator represents sum of the extent to which each of the risk ratios considered separately each exceeds 1

If $S > 1$ then $RERI_{RR} > 0$. If $S < 1$ then $RERI_{RR} < 0$.

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Application in studies

- In cohort studies, RERI, AP and S can all be estimated
- In case-control studies, can estimate quantities when the ORs approximate RRs
 - If outcome is rare, ORs approximate RRs
 - $RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1 \approx RR_{11} - RR_{10} - RR_{01} + 1 = RERI_{RR}$
 - Can then calculate AP and S

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Published measures of interaction

Table 3. Relative Excess Risk of Breast Cancer Due to Interaction^a Between the *RAD51L1* Single-Nucleotide Polymorphism rs10483813 and Body Mass Index After Designation of the Lowest Risk Category (Body Mass Index ≥ 30 and AA Genotype) as the Reference Category in the Breast and Prostate Cancer Cohort Consortium

rs10483813 ^b Genotype	Body Mass Index ^c					
	≥ 30		$\geq 25 < 30$		< 25	
	OR	95% CI	OR	95% CI	OR	95% CI
AA	1.00	Referent	1.81	1.15, 2.85	1.98	1.29, 3.04
TA	2.13	1.42, 3.20	2.21 ^d	1.48, 3.29	2.08 ^e	1.41, 3.09
TT	2.33	1.57, 3.47	2.27 ^f	1.54, 3.37	2.29 ^g	1.55, 3.38

Abbreviations: CI, confidence interval; OR, odds ratio; *RAD51L1*, DNA repair protein RAD51 homolog 2 gene; RERI, relative excess risk due to interaction.

^a The RERI is a measure of departure from additivity on the absolute risk scale. RERIs and 95% CIs were calculated using unconditional logistic regression models adjusting for age at baseline (5-year intervals) and cohort.

^b Some cohort studies genotyped the proxy single-nucleotide polymorphism rs999737 for rs10483813 ($r^2 = 1$ in the HapMap CEU population (65)). The T allele is the risk allele for rs10483813, and the A allele is the protective allele (4). The *P* value for multiplicative interaction between rs10483813 and body mass index was 0.002.

^c Weight (kg)/height (m)²; categorized into 3 levels based on the World Health Organization classification (66).

^d RERI = -0.73 (95% CI: -1.6, 0.14); *P*-RERI = 0.097; synergy index = 0.62 (95% CI: 0.45, 0.86).

^e RERI = -1.02 (95% CI: -1.95, -0.101); *P*-RERI = 0.030; synergy index = 0.51 (95% CI: 0.40, 0.67).

^f RERI = -0.87 (95% CI: -1.76, 0.015); *P*-RERI = 0.054; synergy index = 0.59 (95% CI: 0.45, 0.78).

^g RERI = -1.03 (95% CI: -1.91, -0.14); *P*-RERI = 0.023; synergy index = 0.56 (95% CI: 0.43, 0.73).

Joshi et al. Additive interactions between susceptibility SNPs identified in GWAS and breast cancer risk factors in Breast and Prostate Cancer Cohort Consortium. *AJE* 2014.

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Published measures of interaction

Table 2. Adjusted Hazard Ratios^a for Lung Cancer Mortality in Relation to Categorical Indicators of Cigarette Smoking and PM_{2.5} Concentration and Measures of Additive^b and Multiplicative^c Interaction, Cancer Prevention Study II, 1982–1988

Level of PM _{2.5} Exposure		Smoking Status									
Category	Mean (SD), μg/m ³	Never Smoker				Current Smoker				Smoking in Strata of PM _{2.5}	
		No. of Deaths	No. of Subjects	HR	95% CI	No. of Deaths	No. of Subjects	HR	95% CI	HR	95% CI
Low (≤25th percentile)	9.15 (1.17)	63	76,025	1.00	Referent	346	31,486	13.53	10.21, 17.93	13.77	10.21, 18.57
High (>75th percentile)	16.21 (1.94)	81	73,592	1.28	0.92, 1.78	447	33,789	15.99	12.11, 21.13	12.20	9.39, 15.87
PM _{2.5} in strata of smoking				1.26	0.90, 1.77			1.19	1.03, 1.38		

Abbreviations: AP, attributable proportion due to interaction; CI, confidence interval; HR, hazard ratio; PM_{2.5}, particulate matter less than or equal to 2.5 μm in diameter; RERI, relative excess risk due to interaction; S, synergy index; SD, standard deviation.

^a Adjusted for education; marital status; body mass index (weight (kg)/height (m)²); body mass index squared; secondhand smoke exposure (hours/day); quintiles of vegetable, fruit, fiber, and fat intake; alcohol consumption (beer, wine, and liquor); occupational exposures (asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, and diesel engine exhaust); and "occupational dirtiness index" (13).

^b RERI = 2.19 (95% CI: -0.10, 4.83); AP = 0.14 (95% CI: 0.00, 0.25); S = 1.17 (95% CI: 1.00, 1.37).

^c HR = 0.93 (95% CI: 0.65, 1.33).

Turner et al. Interactions between cigarette smoking and fine particulate matter in the risk of lung cancer mortality in Cancer Prevention Study II. *AJE* 2014.

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Learning Objectives

- Measures of interaction
- **Mechanistic Interaction**
- Statistical Modeling
- Presentation of interaction analyses

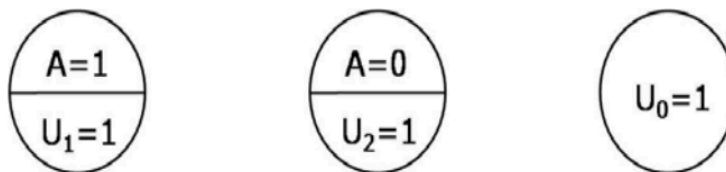
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Sufficient cause vs. counterfactual models

- 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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Interaction under the sufficient cause approach

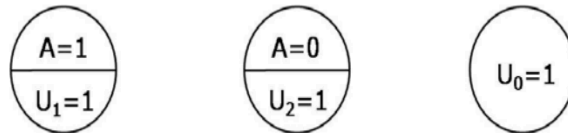


- Interaction between component causes is implicit in the sufficient cause model
- Each component cause requires the presence of the others to act, their action is interdependent
- Component cause = INUS – “an **insufficient** but **necessary** part of a condition which is itself **unnecessary** but **sufficient** for the result”

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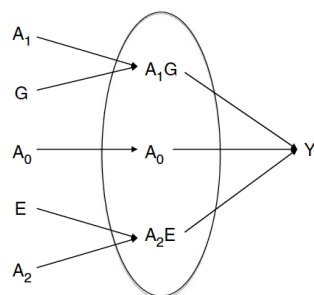
Interaction – more definitions

- **Synergism:** Individual would get disease only if exposed to both treatments. Individual would not get disease if only exposed to A or E.
 - When both exposures are present in the same component cause
- **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.
 - When one exposure is present and one is absent in the same component cause



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Another representation of mechanistic interaction



- Only three mechanisms for developing Y
 - A_1 and G
 - A_0
 - A_2 and E
- G and E do not exist in the same causal pie
- A_1 and A_2 do not exist in the same causal pie
- No synergism (interaction) between G/E or A_1/A_2 in a mechanistic sense

Figure 10.3 Example illustrating negative multiplicative interaction but no mechanistic interaction.

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Statistical interaction with no mechanistic interaction

G	E	Total	Cases	RR
G=0	E=0	3980	20	1
G=1	E=0	980	20	4.0
G=0	E=1	3920	80	4.0
G=1	E=1	965	35	7.0

- Multiplicative interaction: $RR_{11} / (RR_{10} * RR_{01})$
 $= 7.0 / (4.0 * 4.0) = 0.44$ = **Negative Multiplicative Interaction!**
- $RERI = 7.0 - 4.0 - 4.0 + 1 = 0$
- Can occur with both **positive** or **negative** interaction

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Counterfactuals and causal interactions

- Counterfactuals: $Y^{g,e}$ represents one's counterfactual outcome for an individual if $G=g$ and $E=e$
- Causal interaction: Exists if $Y^{g=1,e=1} = 1$ and $Y^{g=1,e=0} = Y^{g=0,e=1} = 0$
- In the presence of causal interaction, there must be synergism in Rothman's sufficient cause framework

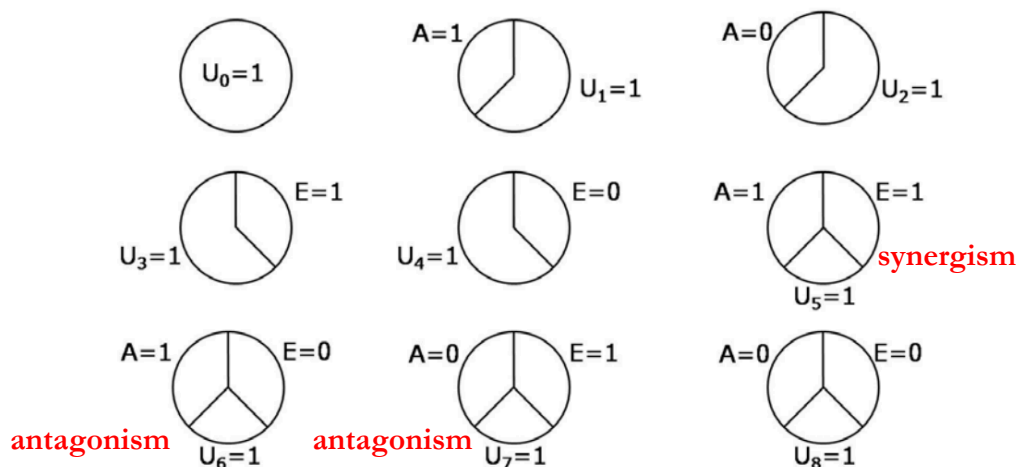
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Mechanistic Interaction

- Assumptions for mechanistic/ sufficient cause interaction:
 - **Monotonicity:** the effect of each exposure on the outcome always operates in the same direction for all individuals (e.g. the effect of smoking on lung cancer is always harmful)
 - G has a positive “monotonic effect” on the outcome if $Y^{g,e}$ is non-decreasing in g and e
 - Both exposures need to be monotonic
 - Cannot be verified empirically
 - **Unconfoundedness:** confounding for both exposures is controlled for
 - The effects of G and E on Y are unconfounded if $P(Y^{g,e}=1) = P(Y=1 | G=g, E=e)$

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Mechanistic Interaction



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Mechanistic Interaction

Rothman and Greenland 1998:

- Assuming both monotonicity and unconfoundedness, mechanistic interaction can be evaluated by:

$$p_{11} - p_{10} - p_{01} + p_{00} > 0$$

$$RERI > 0$$

- If this quantity is greater than 0, then there is positive additive interaction

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Mechanistic Interaction

VanderWeele and Robins 2007:

- Assuming ~~both monotonicity and~~ unconfoundedness, mechanistic interaction can be evaluated by:

$$p_{11} - p_{10} - p_{01} > 0$$

$$RERI > 1$$

- If this quantity is greater than 0, then there is positive additive interaction
- Stricter criteria than Rothman and Greenland but does not require monotonicity assumption

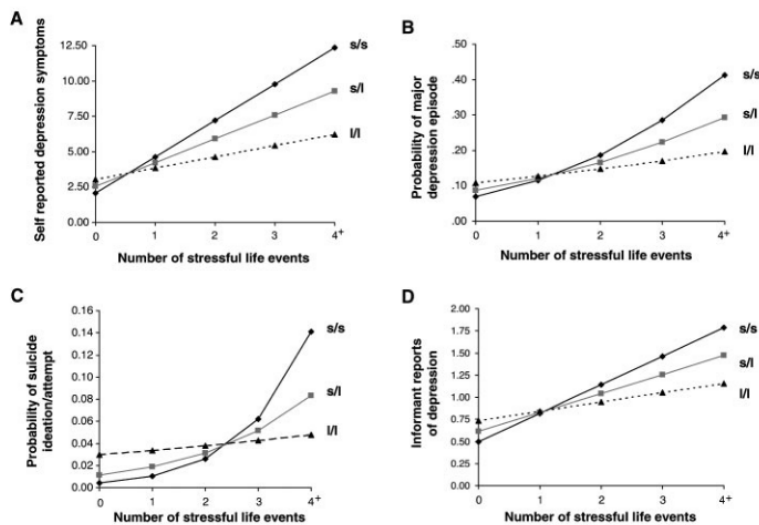
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Learning Objectives

- Measures of interaction
- Mechanistic Interaction
- **Statistical Modeling**
- Presentation of interaction analyses

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Assessing interaction by graphic representation

Caspi et al. *Science* 2003

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Assessing interaction by stratification

- Interaction 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 comparing expected vs. observed joint effects

- What is the individual effect of cause A in the absence of exposure to cause B? $1.RD_{E,-} = 0.17 - 0.10 = 0.07$ $1.RR_{E,-} = 0.17 / 0.10 = 1.7$
- What is the individual effect of cause B in the absence of exposure to cause A? $2.RD_{-,G} = 0.10 - 0.10 = 0$ $2.RR_{-,G} = 0.10 / 0.10 = 1.0$
- What is the observed joint effect of A and B? $3.RD_{OBSERVED\ E,G} = 0.33 - 0.10 = 0.23$ $3.RR_{OBSERVED\ E,G} = 0.33 / 0.10 = 3.3$
- What is the expected joint effect of A and B in the absence of interaction? $4.RD_{EXPECTED\ E,G} = 0.07 + 0 = 0.07$ $4.RR_{EXPECTED\ E,G} = 1.7 * 1.0 = 1.7$
- Is the observed similar to the expected in the absence of interaction? $5.RD_{OBSERVED\ E,G} > RD_{EXPECTED\ E,G}$ $5.RR_{OBSERVED\ E,G} > RR_{EXPECTED\ E,G}$
- What is the interaction magnitude? $6.RD_{E/G\ IS\ PRESENT} - RD_{E/G\ IS\ ABSENT} = 0.23 - 0.07 = 0.16$ $6.RR_{E/G\ IS\ PRESENT} / RR_{E/G\ IS\ ABSENT} = 3.3 / 1.7 = 1.9$
Interaction Contrast Interaction Contrast Ratio

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Assessing interaction by statistical modeling

- Linear model: $E(Y|A,B) = \beta_0 + \beta_1 * A + \beta_2 * B + \beta_3 * A * B$
 - β_0 = mean of Y when A=0 and B=0
 - β_1 = change in mean of Y for a one-unit increase in A
 - β_2 = change in mean of Y for a one-unit increase in B
 - β_3 = additive interaction based on risk

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Assessing interaction by statistical modeling

- Linear model: $E(Y|A,B) = \beta_0 + \beta_1 * A + \beta_2 * B + \beta_3 * A * B$
 - β_0 = mean of Y when A=0 and B=0 = p_{00}
 - β_1 = change in mean of Y comparing A=1 to A=0 = $p_{10} - p_{00}$
 - β_2 = change in mean of Y comparing B=1 to B=0 = $p_{01} - p_{00}$
 - β_3 = additive interaction based on risk = $p_{11} - p_{10} - p_{01} + p_{00}$

	A=0	A=1
B=0	p_{00}	p_{10}
B=1	p_{01}	p_{11}

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Assessing interaction by statistical modeling

- Logistic model: $\text{logit Pr}(Y=1|A,B) = \alpha_0 + \alpha_1 * A + \alpha_2 * B + \alpha_3 * A * B$
 - α_0 = log odds of Y when A=0 and B=0
 - α_1 = log odds ratio of Y for A=1 vs. A=0
 - e^{α_1} = odds ratio of Y for A=1 vs. A=0 (main effect of A)
 - α_2 = log odds ratio of Y for B=1 vs. B=0
 - e^{α_2} = odds ratio of Y for B=1 vs. B=0 (main effect of B)
 - α_3 = multiplicative interaction based on risk ratios

Assessing interaction by statistical modeling

- Linear model: $E(Y|A,B) = \beta_0 + \beta_1 * A + \beta_2 * B + \beta_3 * A * B + \beta_4 * \text{covariates}$
- Logistic model: $\text{logit Pr}(Y=1|A,B) = \alpha_0 + \alpha_1 * A + \alpha_2 * B + \alpha_3 * A * B + \alpha_4 * \text{covariates}$
- Logistic models are preferred for assessing interaction.
 - Linear and log-linear models may not converge in ML estimation models because of continuous covariates. Logistic models do not have this issue.
 - Can incorporate from cohort or case-control data.

Assessing interaction by statistical modeling

- Linear model: $E(Y|A,B) = \beta_0 + \beta_1 * A + \beta_2 * B + \beta_3 * A * B + \beta_4 * covariates$
- Logistic model: $\text{logit Pr}(Y=1|A,B) = \alpha_0 + \alpha_1 * A + \alpha_2 * B + \alpha_3 * A * B + \alpha_4 * covariates$
 - β_3 or e^{α_3} represent important measures of multiplicative interaction
- On the additive scale: $RERI_{OR} = OR_{11} - OR_{10} - OR_{01} + 1 = e^{\alpha_1 + \alpha_2 + \alpha_3} - e^{\alpha_1} - e^{\alpha_2} + 1$
 - Under the rare disease assumption, the $RERI_{OR} \approx RERI_{RR}$
 - If outcome is not rare, then use log-linear model and estimate $RERI_{RR}$ directly.
 - To estimate standard errors for $RERI_{OR}$, can you Delta method (see Excel sheet on course website) or bootstrapping
 - STATA and SAS code available in VanderWheele Chapter 9

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Learning Objectives

- Measures of interaction
- Mechanistic Interaction
- Statistical Modeling
- **Presentation of interaction analyses**

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Presenting stratum-specific effects

- 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: $\Pr[Y^{a=1} = 1 \mid M=0] - \Pr[Y^{a=0} = 1 \mid M=0] = 0.4 - 0.6 = -0.2$
 - Reference group: unexposed men
- 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: $\Pr[Y^{a=1} = 1 \mid M=1] - \Pr[Y^{a=0} = 1 \mid M=1] = 0.6 - 0.4 = 0.2$
 - Reference group: unexposed women

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Presenting stratum-specific effects

Table 9-5. RISK RATIOS WITH SEPARATE REFERENCE GROUPS
(UNINFORMATIVE PRESENTATION)

	No Asbestos ($E = 0$)	Asbestos ($E = 1$)
Non-smoker ($G = 0$)	1 (reference)	RR = 6.09
Smoker ($G = 1$)	1 (reference)	RR = 4.74

- Examining effects of asbestos within levels of smoking? YES
- Examining effects of smoking within levels of asbestos? NO
- Which group has highest risk of outcome? NO

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Using a common reference group

Table 9-6. RISK RATIOS WITH A COMMON REFERENCE GROUP

(INFORMATIVE PRESENTATION)

	No Asbestos ($E = 0$)	Asbestos ($E = 1$)
Non-smoker ($G = 0$)	1 (reference)	6.09
Smoker ($G = 1$)	8.64	40.91

- Current guidelines recommend a common reference group for presentation of effect modification and interaction analyses
- Examining effects of asbestos within levels of smoking? **YES**
- Examining effects of smoking within levels of asbestos? **YES**
- Which group has highest risk of outcome? **YES**

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Using a common reference group

- In practice, code two exposures into one categorical exposure variable representing different exposure combinations
 - Rather than having two binary variables, E and G
 - Create a new 4-level categorical variable that represents each exposure combinations
 - EG_new = 1 if E==0 and G==0
 - EG_new = 2 if E==1 and G==0
 - EG_new = 3 if E==0 and G==1
 - EG_new = 4 if E==1 and G==1

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Using a common reference group

TABLE 6. Incidence Rates, Rate Differences, and Relative Risks (RRs) for the Joint Relation of Alcohol and Total Folate Intake on Risk of Postmenopausal Breast Cancer

Folate* (μg)	Alcohol†	No. Cases	Person-Years	Incidence Rate‡	Rate Difference‡	RR§	95% CI
>351	0	417	99,575	410	0	1.0	
	≤ 4	197	47,341	414	4	1.01	0.84–1.21
	>4	171	38,905	445	35	1.10	0.90–1.33
271–351	0	160	40,784	386	–24	0.90	0.73–1.12
	≤ 4	74	18,863	397	–13	0.92	0.69–1.22
	>4	65	15,258	439	29	1.03	0.77–1.39
187–270	0	191	41,956	457	47	1.13	0.89–1.42
	≤ 4	82	17,800	474	64	1.17	0.88–1.56
	>4	66	15,029	441	31	1.09	0.79–1.50
≤ 186	0	92	22,931	400	–10	1.08	0.78–1.49
	≤ 4	35	7,260	486	76	1.37	0.89–2.11
	>4	36	6,940	530	120	1.45	0.95–2.23

* Cutpoints represent approximate upper 50th, 31st–50th, 11th–30th, and lowest 10th percentiles of folate per day in micrograms.

† Cutpoint of 4 gm is the approximate median among drinkers.

‡ Per 100,000 per year, adjusted to the mean age of the cohort at baseline.

§ Adjusted for age, education, family history of breast cancer, age at menarche, age at menopause, oral contraceptive use, hormone replacement therapy, parity, age at first birth, body mass index, waist-to-hip ratio, height, body mass index at age 18, smoking physical activity, and other B vitamins.

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Sellers et al. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 2001.

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Using a common reference group

TABLE 3 Results of multivariate logistic regression models for the association between household food security and depression according to SNAP participation among 3518 low-income adults¹

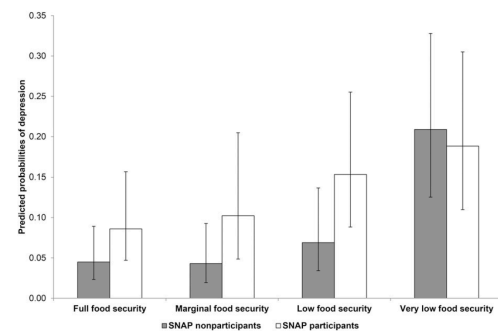
	SNAP nonparticipants		SNAP participants	
	% ²	OR (95% CI) ³	% ²	OR (95% CI) ³
Full food security	4.5	Referent	8.6	Referent
Marginal food security	4.3	0.98 (0.50, 1.92)	10.2	1.22 (0.64, 2.34)
Low food security	6.9	1.64 (0.93, 2.92)	15.3	2.12 (1.31, 3.42)
Very low food security	20.9	5.10 (3.09, 8.41)	18.8	2.21 (1.54, 3.17)

¹ SNAP, Supplemental Nutrition Assistance Program.

² Predicted probabilities of depression by household food security status from multivariate logistic regression model.

³ Multivariate logistic regression model adjusted for age, sex, race/ethnicity, education, marital status, household size, poverty level, smoking status, and BMI categories.

FIGURE 1 Predicted probabilities of depression from multivariate logistic regression models by household food security and SNAP participation among 3518 low-income adults. Values are predicted probabilities and the ranges are the 95% CIs. SNAP, Supplemental Nutrition Assistance Program.



Leung et al. Household food insecurity is associated with depression in low-income SNAP and non-SNAP participants. J Nutrition 2015.

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Presentation of results – key points

- Present RRs, ORs, or RDs, with confidence intervals for each stratum of the exposures with a single reference category (often the lowest risk group)
- Present measures of interaction on both the additive (e.g. RERI) and multiplicative scales with CIs and P-values
- List the confounders for which the relations between both exposures and outcomes were adjusted for.

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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 the additive scale
 - Additive interaction most relevant for public health
 - Though sometimes it may be helpful to present biologic interaction on additive and multiplicative scales
- Various methods exist to evaluate biological interaction and to estimate the magnitude of interaction
 - Statistical modeling is a popular approach
 - RERI, AP, and S are measures that can be applied to cohort and case-control data
- Mechanistic interaction is distinct from statistical interaction
- When presenting interaction analyses, it is recommended to use a common reference group to facilitate comparison of main effects and joint effects

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