Interaction and Effect Measure Modification - II

Mabel Carabali

EBOH, McGill University

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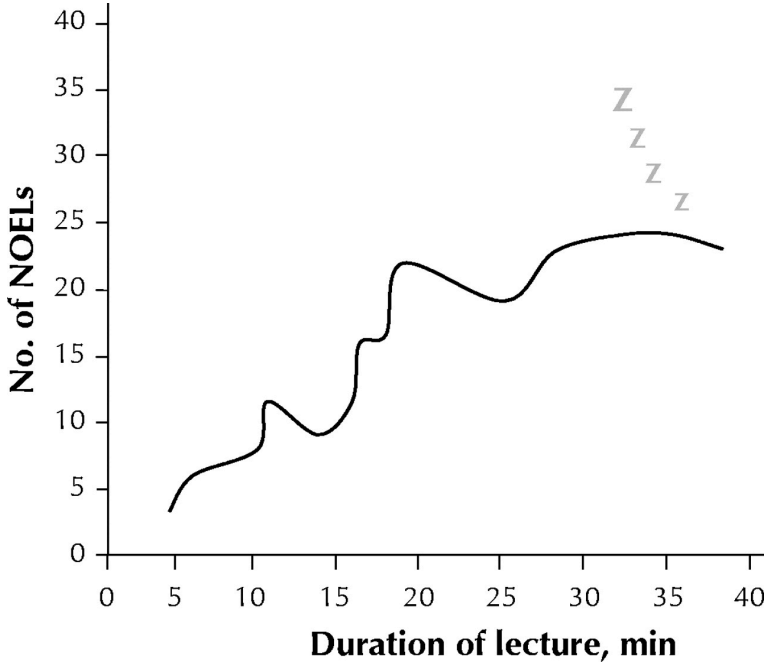
Incidence of and risk factors for nodding off at scientific sessions



Kenneth Rockwood, David B. Hogan, Christopher J. Patterson. CMAJ Dec 2004, 171 (12) 1443-1445; DOI: 10.1503/cmaj.1041570

Apply for 704 lectures 😴 😬

Table 1: Risk factors for nodding off at lectures

Factor	Odds ratio (and 95% CI)
Environmental	
Dim lighting	1.6 (0.8–2.5)
Warm room temperature	1.4 (0.9–1.6)
Comfortable seating	1.0 (0.7–1.3)
Audiovisual	
Poor slides	1.8 (1.3–2.0)
Failure to speak into microphone	1.7 (1.3–2.1)
Circadian	
Early morning	1.3 (0.9–1.8)
Post prandial	1.7 (0.9–2.3)
Speaker-related	
Monotonous tone	6.8 (5.4–8.0)
Tweed jacket	2.1 (1.7–3.0)
Losing place in lecture	2.0 (1.5–2.6)

Note: CI = confidence interval.

Incidence of and risk factors for nodding off at scientific sessions

Key Messages

1. Interaction term (the tool `X*M` or `X*E`)
2. EMM or Interaction?
    - Depends, One exposure or Two exposures of interest
3. How to obtain them:
    - EMM: Stratification and **correct interpretation** of joint vs individual effects by the *"interaction term"*
    - Statistical Interaction measures: RERI (ICR), AP, SI
    - !Be aware of "preventive" exposures
4. Additive vs Multiplicative
    - Could obtain both, but additive measures provide meaningful PH information
    - Sub additive (sub/less than multiplicative) or super additive (super/more than multiplicative)
5. Interpretation?
    - Descriptive, statistical, causal (granted the assumptions are met)!

Notes on Interaction (statisitcal, causal)

From: **Hernan & Robins book, What if?**

and some **worked** examples.

Causal interaction

- Present when the combined effect of two factors on an outcome differs from their separate effects when no bias is present.
- Unlike EMM, **both factors have to be causally related** to an outcome in order for causal interaction to be present.
    - This distinction is important, especially if an intervention on the secondary factor is of interest.
- **Positive causal interaction:** the effect of two factors together is larger than the two factors considered separately.
- **Negative causal interaction:** the joint effect is smaller than these effects considered separately.

ASSESSMENT OF STATISTICAL INTERACTION

If we think of a `second` variable of interest, that we aim at intervening, we think about *interaction* not EMM.

- When that second variable or treatment of interest `E` is randomly assigned, then the concepts of interaction and effect modification coincide.

- The methods described to identify modification of the effect of `X by M` can now be applied to identify interaction of **X AND E** by simply replacing the effect modifier `M` by the (second) treatment **E**.

H&R What if? 5.2 Identifying interaction within the counterfactual framework

Because interaction is concerned with the joint effect of two (or more) treatments X and **E**, identifying interaction requires exchangeability, positivity, consistency **for both treatments**.

- If these assumptions hold, then we can rewrite the definition of interaction on the additive scale in terms of potential outcomes as:

$$Pr[Y^{x=1} = 1|E = 1] - Pr[Y^{x=0} = 1|E = 1] \neq Pr[Y^{x=1} = 1|E = 0] - Pr[Y^{x=0} = 1|E = 0]$$

which is exactly the definition of modification of the effect of **X by E** on the additive scale.

Again, when treatment **E** is randomly assigned, then the concepts of interaction and EMM coincide.

H&R What if? 5.2 Identifying interaction within the counterfactual framework

Now suppose treatment **E** was not assigned by investigators.

- To assess the presence of interaction between **X** and **E**, one still needs to compute the four marginal risks $Pr[Y^{x,e} = 1]$.

In the absence of marginal randomization, these risks can be computed for both treatments **X** and **E**, under the usual identifying assumptions, by standardization or IP weighting conditional on the measured covariates. An equivalent way of conceptualizing this problem:

- Rather than viewing **X** and **E** as two distinct treatments with two possible levels (1 or 0) each
  - We can view **XE** as a combined treatment with four possible levels (11, 01, 10, 00).

H&R What if? 5.2 Identifying interaction within the counterfactual framework

Under **XE** as a combined treatment with four possible levels (11, 01, 10, 00), the identification of interaction between two treatments is not different from the identification of the causal effect of one treatment that we have discussed previously.

- The same methods, under the same identifiability conditions, can be used.

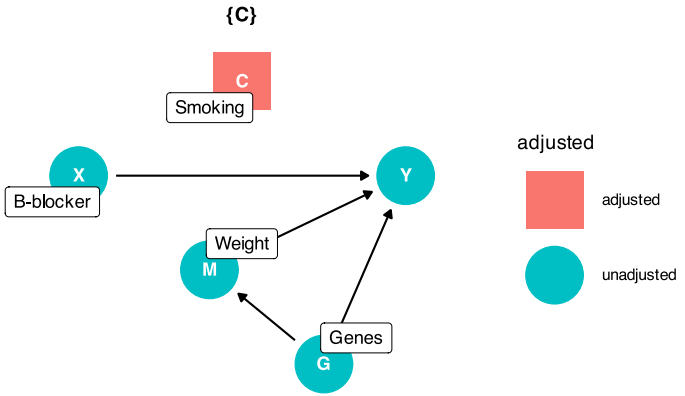
- The only difference is that now there is a longer list of values that the treatment of interest can take, and therefore a greater number of counterfactual outcomes.

H&R What if? 5.2 Identifying interaction within the counterfactual framework

Sometimes we may be willing to assume (conditional) exchangeability for treatment **X** but not for **E**, e.g., when estimating the causal effect of **X** in subgroups defined by **E** in a RCT.

- In that case, we cannot generally assess the presence of interaction between **X** and **E**, but can still assess the presence of EMM by **E**. [1]
  - Because one does not need any identifying assumptions involving **E** to compute the effect of **X** in each of the strata defined by **E**.

Recall:



[1] See extra note in appendices for this lecture.

H&R What if? 5.5 Sufficient cause interaction

- Rothman (1976) described the concepts of synergism and antagonism within the sufficient-component cause framework.
- The definition of interaction within the counterfactual framework **does not require any knowledge about those mechanisms**.
    - Sufficient cause interaction is defined as the joint presence of treatments **`X` and `E`** in the same causal mechanism, that is, in the same sufficient cause. [2]
- Synergism between treatment `X` and treatment `E` when `X=1` and `E=1` are present in the `same sufficient cause`,
- Antagonism between treatment `X` and treatment `E` when `X=1` and `E=0` (or `X=0 and E=1`) are present in the same sufficient cause.
    - Alternatively, antagonism between `X` and `E` can be viewed as synergism between treatment `X` and no treatment `E` (or between no treatment `X` and treatment `E`). [3]

[2,3] See extra notes on sufficient causes and synergism in appendices for this lecture.

Interaction: Scales

Interaction requires a **joint intervention**.

- When the causal effect is measured on the risk difference scale, we say that there is interaction between X and E on the additive scale in the population if:

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

$$Pr[Y^{x=1,e=0} = 1] - Pr[Y^{x=0,e=0} = 1] + Pr[Y^{x=0,e=1} = 1] - Pr[Y^{x=0,e=0} = 1]$$

This equality is another compact way to show that treatments X and E have equal status in the definition of interaction.

- If there is equality, there is no interaction between X and E on the additive scale,
- The interaction is super additive if the $\neq$ symbol can be replaced by a 'greater than' (>) symbol.
- The interaction is sub additive if the $\neq$ symbol can be replaced by a 'less than' (<) symbol.

Interaction: Scales

Analogously, one can define interaction on the multiplicative scale when the effect measure is the causal risk ratio, rather than the causal risk difference.

We say that there is interaction between X and E on the multiplicative scale if

$$= \left(\frac{Pr[Y^{x=1,e=1}=1]}{Pr[Y^{x=0,e=0}=1]}\right) \neq \left(\frac{Pr[Y^{x=1,e=0}=1]}{Pr[Y^{x=0,e=0}=1]}\right) \times \left(\frac{Pr[Y^{x=0,e=1}=1]}{Pr[Y^{x=0,e=0}=1]}\right)$$

- The interaction is super multiplicative if the $\neq$ symbol can be replaced by a 'greater than' (>) symbol.
- The interaction is sub multiplicative if the $\neq$ symbol can be replaced by a 'less than' (<) symbol.

Forms of statistical/causal interaction

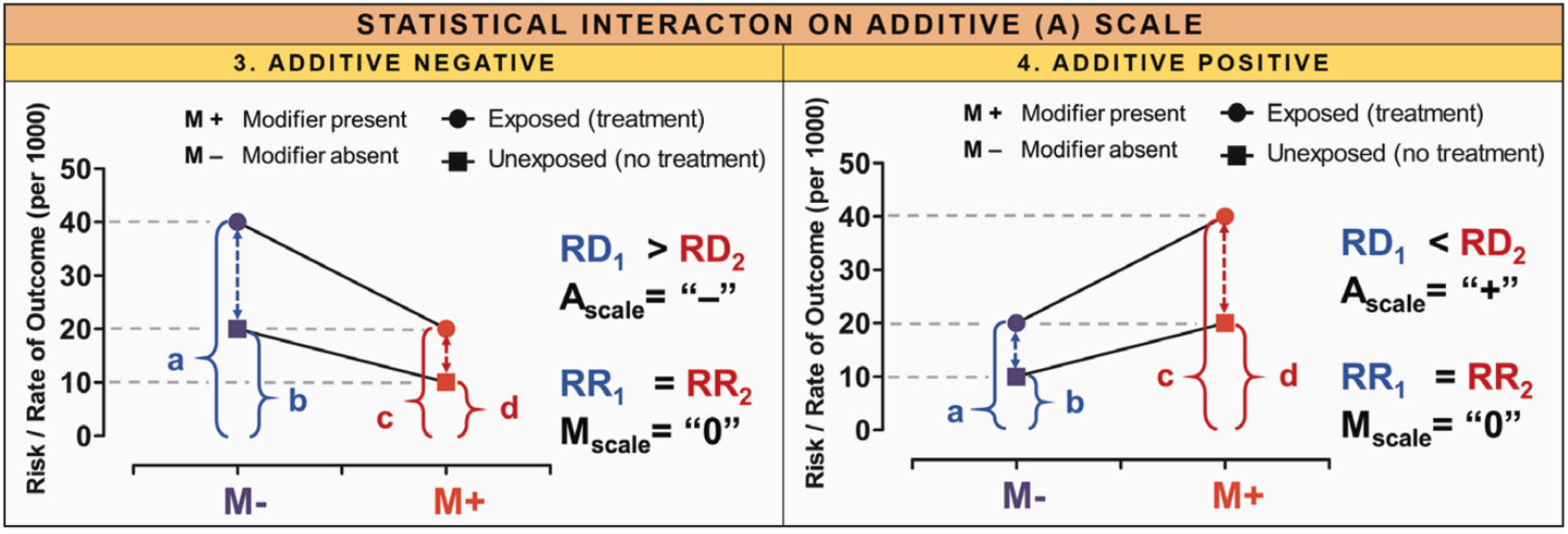
Statistical interaction can take either quantitative or qualitative form.

- The quantitative form (synonym: “non-crossover”) is the most common and is present when an effect of one factor has a different magnitude, but in the same direction, across strata of another factor.

- **Additive Interaction:** Positive (super additive), Negative (sub additive)

- **Multiplicative Interaction:** Super multiplicative (Positive), Negative (sub multiplicative)

Additive Interaction:

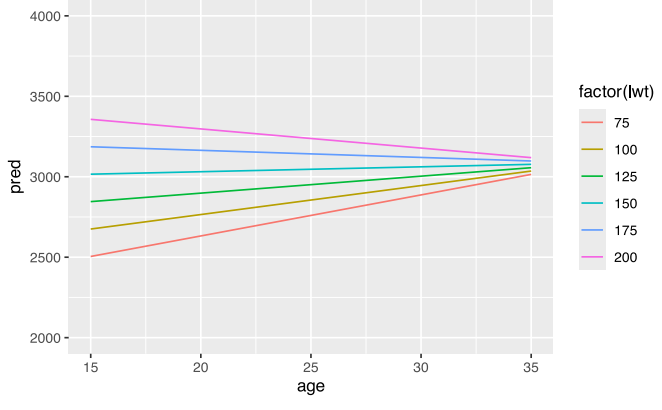


From: *HEART-KIDNEY INTERACTIONS · M. Brankovic*

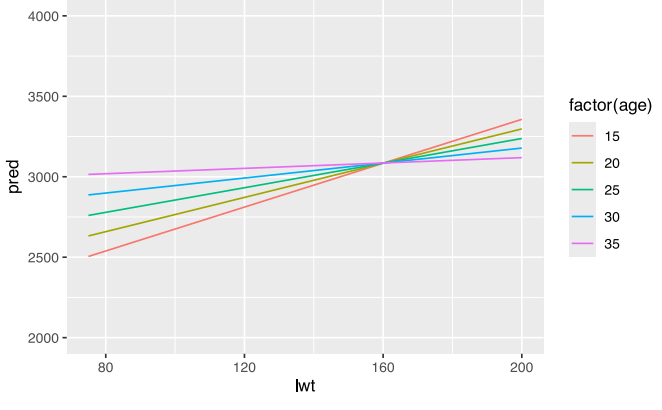
Additive Interaction:

Recall?

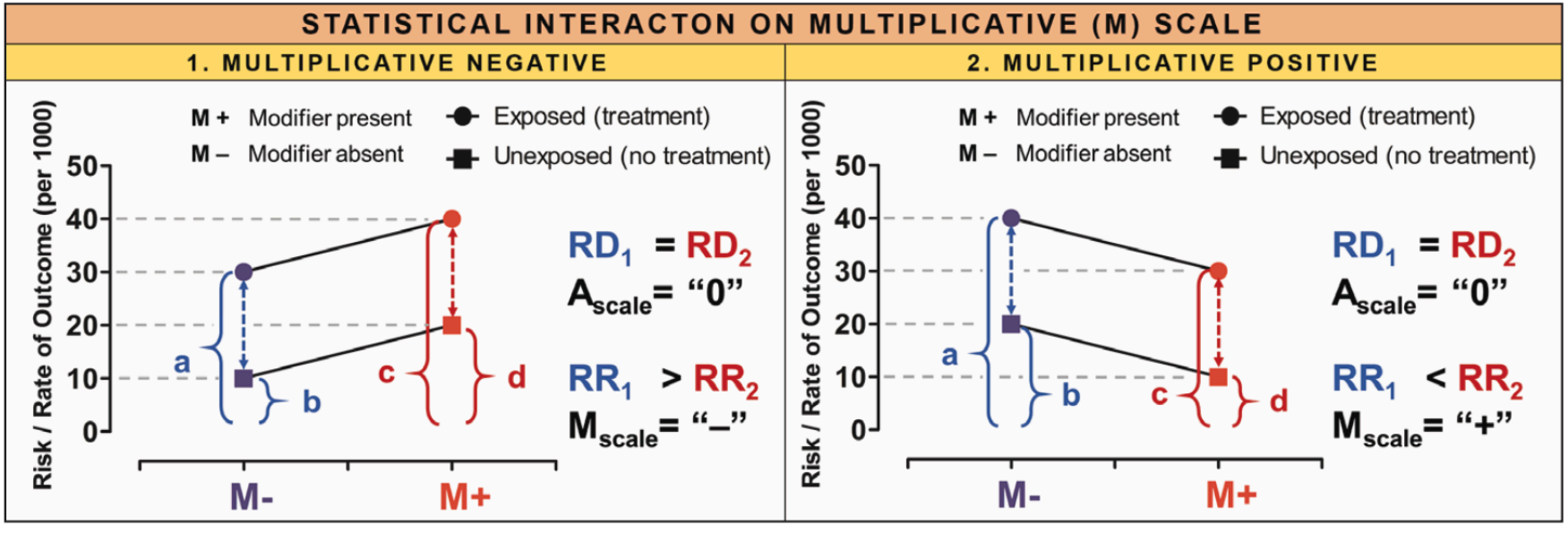
```
qplot(age, pred, data = nd,
      color = factor(lwt), geom = "line") +
```




```
qplot(lwt, pred, data = nd,
      color = factor(age), geom = "line") +
```

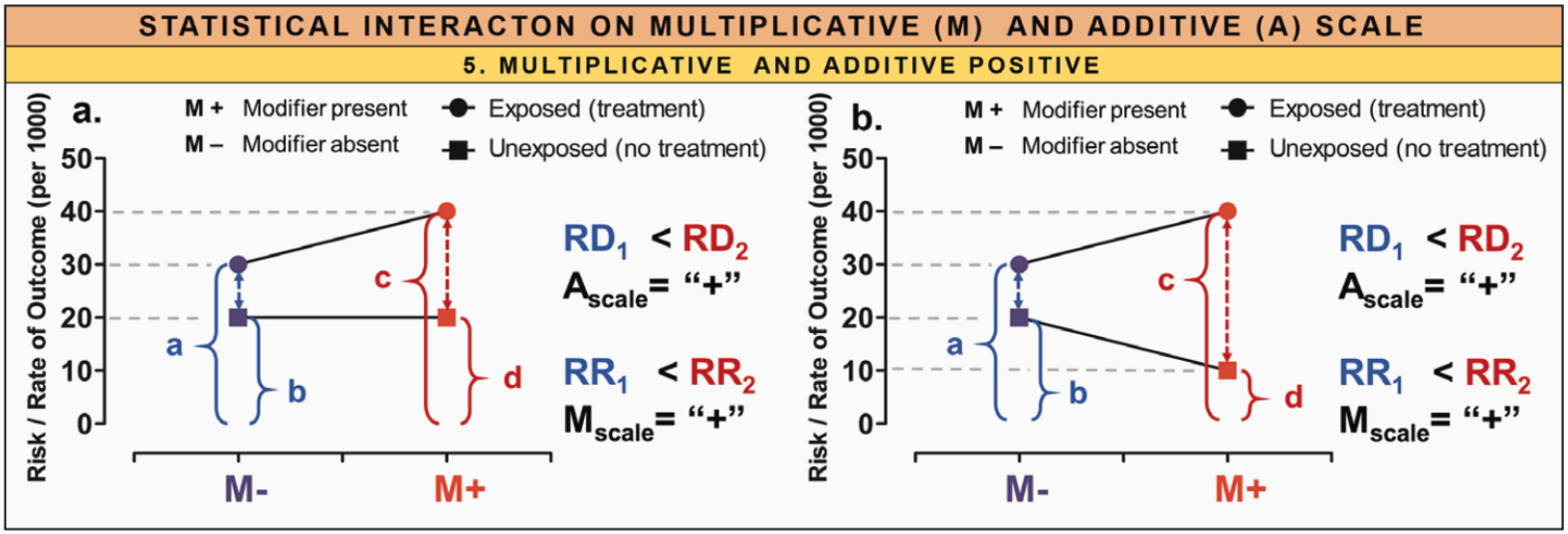


Multiplicative Interaction:



From: *HEART-KIDNEY INTERACTIONS · M. Brankovic*

Multiplicative & Additive Interaction:

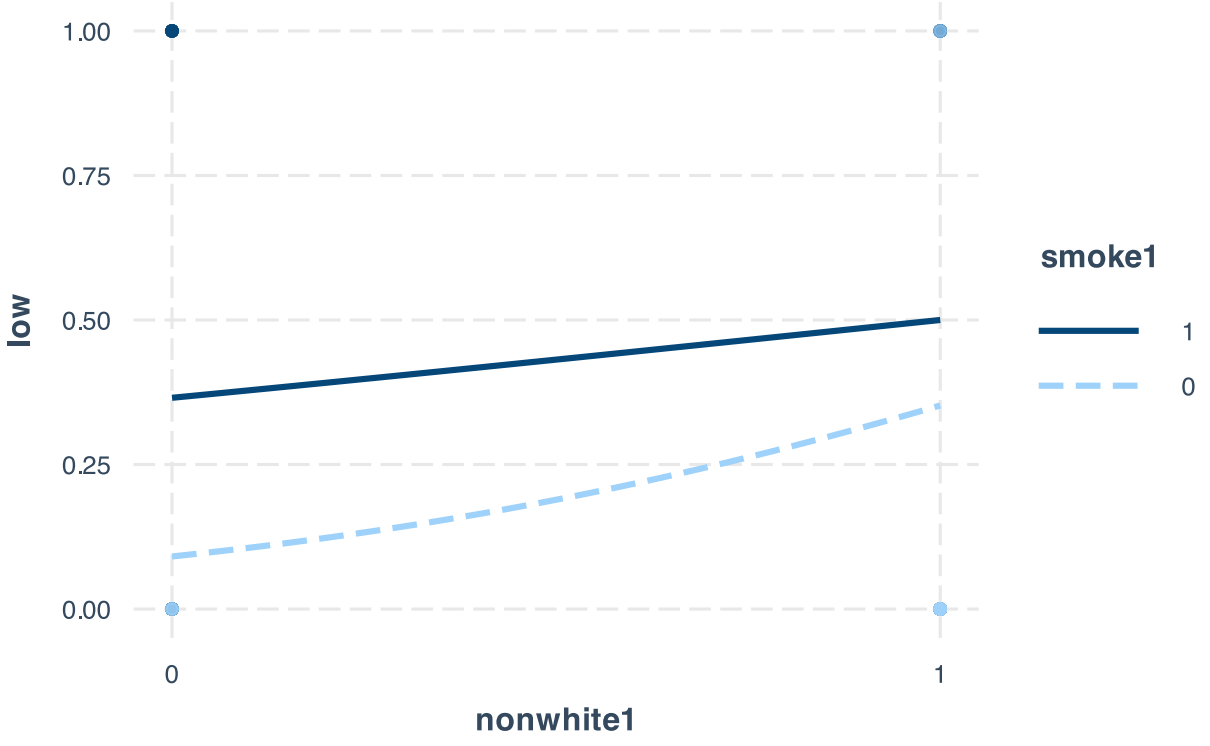


From: *HEART-KIDNEY INTERACTIONS · M. Brankovic*

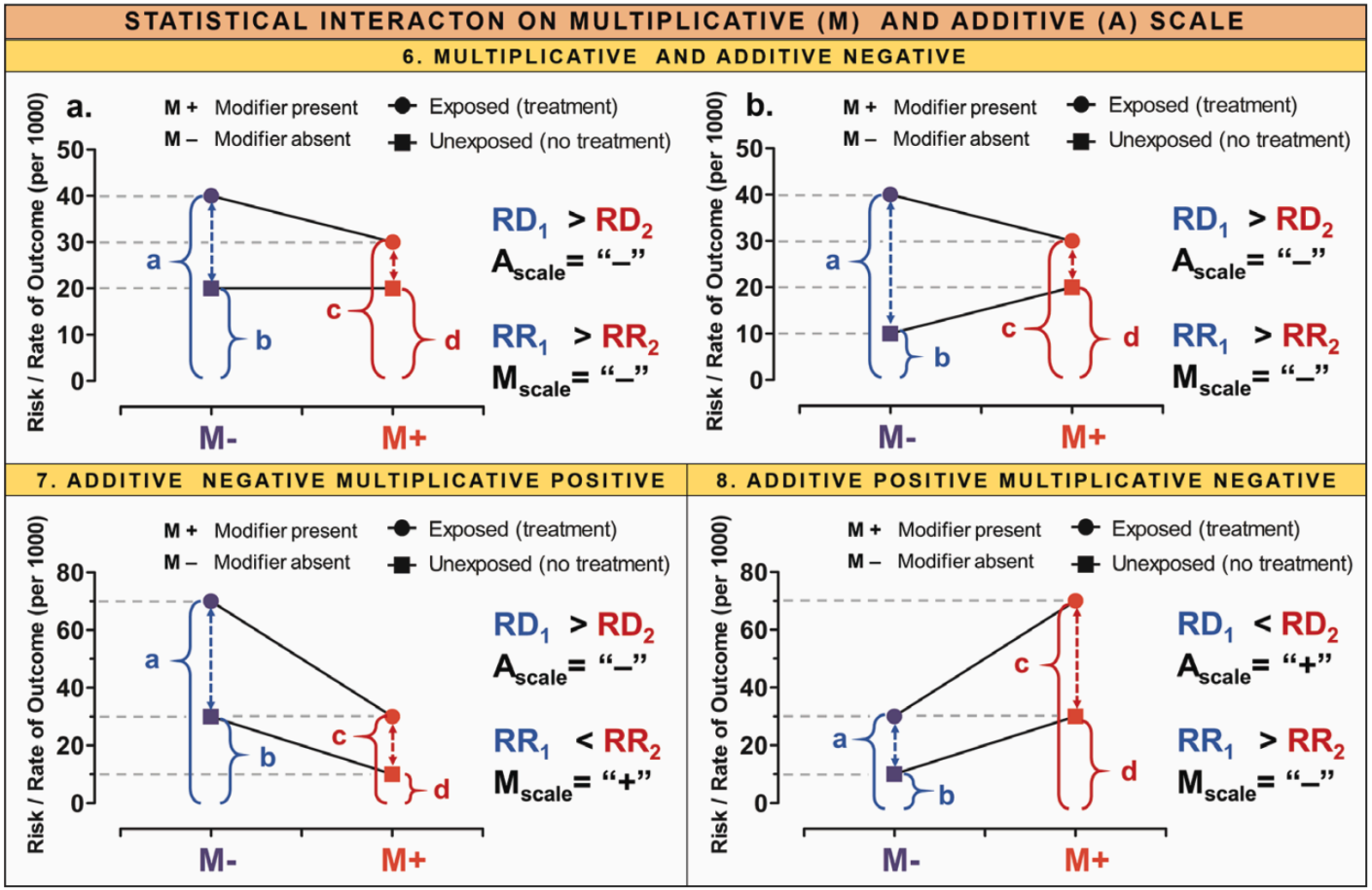
Multiplicative & Additive Interaction:

Recall?

```
l13.mod4a <- glm(low ~ smoke1 + nonwhite1 +smoke1:nonwhite1,
                 data = birthwt, family = binomial)
interact_plot(l13.mod4a, pred = nonwhite1, modx = smoke1,  plot.points = TRUE)
```



Multiplicative & Additive Interaction:



From: *HEART-KIDNEY INTERACTIONS · M. Brankovic*

Assessment of Interaction

1. Stratification (i.e., stratified or subgroup analysis) in which the effect of one factor is assessed within strata of another factor separately,
2. Interaction modeling in which both factors are included into a statistical model together with their cross-product term $(V_1 + V_2 + V_1 * V_2)$ or *four possible levels (11, 01, 10, 00)*.

- Statistical interaction is scale-dependent, observed only if there is a departure from an underlying measurement scale on which a statistical model estimates effects.
- Different statistical models estimate effects on different measurement scales.
- Additive and multiplicative scales do not always provide the same conclusion, whether a statistical interaction is present or in which direction it operates.

Assessment of Interaction

- p_{00} "jointly unexposed", i.e., exposed to neither X nor E.
- p_{01} are those exposed to E but not X.
- p_{10} are those exposed to X but not E.
- p_{11} "jointly exposed", i.e., exposed to both X and E.

	E=0	E=1
X = 0	Jointly unexposed	Exposed to E only
X = 1	Exposed to A only	Jointly exposed

Recall?

ln(odds)	M=0	M=1
X=0	β_0	$\beta_0 + \beta_2$
X=1	$\beta_0 + \beta_1$	$\beta_0 + \beta_1 + \beta_2 + \beta_3$
ln(OR)	M=0	M=1
X=0		
X=1	$(\beta_0 + \beta_1)$ - β_0 = β_1	$(\beta_0 + \beta_1 + \beta_2 + \beta_3)$ - $(\beta_0 + \beta_2)$ = $(\beta_1 + \beta_3)$
OR	M=0	M=1
X=0		
X=1	e^{β_1}	$e^{(\beta_1+\beta_3)}$

Additive interaction measures

A departure on an additive scale would mean that the combined effect of two factors is larger or smaller than the sum of their individual effects.

- **Example** from A Tutorial on Interaction by Tyler J. VanderWeele and Mirjam J. Knol

Risk of lung cancer by smoking and asbestos status

	No asbestos	Asbestos
Non-smoker	0.0011	0.0067
Smoker	0.0095	0.0450

D = binary outcome; **X** = binary exposure 1; **E** = binary exposure 2;
$P^{xe} = Pr(Y = 1|X = x, E = e)$

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

(joint effect) – [(effect of X) + (effect of E)], equivalently= $(p_{11} - p_{10} - p_{01} + p_{00})$

Additive interaction measures

- If this quantity is > 0, then interaction is above exact additivity (super-additive).
- If this quantity is = 0, there is no interaction on the additive scale (exact additivity of effects)
- If this quantity is < 0, then interaction is below exact additivity (sub-additive). For the data in the table:

$$(p11 - p10 - p01 + p00) = (0.0450 - 0.0095 - 0.00670 + 0.0011) = 0.0299$$

- The effect of smoking and asbestos is more than would be expected if the risks of these two exposures simply added together "super-additive".
- There are an additional 3 cases per hundred that occur because of this interaction.

Multiplicative interaction measures

A departure on a multiplicative scale would mean that the combined effect of two factors is larger or smaller than the product of their individual effects.

- Thus, the multiplicative scale corresponds to the ratios of effects rather than their difference as the additive scale does.

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

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

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

Interaction on the multiplicative scale for ratios

$$\left(\frac{RR_{11}}{RR_{10}RR_{01}}\right) = \left(\frac{p_{11}p_{00}}{p_{10}p_{01}}\right)$$

Multiplicative interaction measures

This measures the extent to which, on the risk ratio scale, the effect of both exposures together exceeds the product of the effects of the two exposures considered separately.

- If this quantity is > 1, then interaction is above exact multiplicativity (super- multiplicative).
- If this quantity is = 1, there is no interaction on the multiplicative scale (exact multiplicativity of effects)
- If this quantity is < 1, then interaction is below exact multiplicativity (sub-multiplicative)

$$\left(\frac{0.0450/0.0011}{0.0095/0.0011 \times 0.00670/0.0011} \right) = 0.78$$

- The joint effects are sub-multiplicative interaction (i.e. less than would be expected by exact multiplicativity).

Illustration that a measurement scale influences the presents and the direction of a statistical interaction.

Additive versus Multiplicative scale

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

In this case there is no additive interaction since:

$$(p11 - p10 - p01 + p00) = (0.10 - 0.07 - 0.05 + 0.02) = 0$$

- But sub (negative) multiplicative interaction: $\left(\frac{0.10/0.02}{0.07/0.02 \times 0.05/0.02} \right)$ = 0.57

Joint effects can fall anywhere on the continuum from:

$$-\infty - - - - - - - - - - additivity - - - - - - - multiplicativity - - - - - - - +\infty$$

The Interaction Continuum for Two Causative Exposures

TABLE 1. The Interaction Continuum for Two Causative Exposures

Type Interaction	Rank	Condition on Probabilities[a]	Condition on Risk Ratios[a]
Positive multiplicative positive additive	1	$p_{11} > p_{10}p_{01}/p_{00}$	$RR_{11} > RR_{10}RR_{01}$
No multiplicative positive additive	2	$p_{11} = p_{10}p_{01}/p_{00}$	$RR_{11} = RR_{10}RR_{01}$
Negative multiplicative positive additive	3	$p_{10} + p_{01} - p_{00} < p_{11} < p_{10}p_{01}/p_{00}$	$RR_{10} + RR_{01} - 1 < RR_{11} < RR_{10}RR_{01}$
Negative multiplicative zero additive	4	$p_{11} = p_{10} + p_{01} - p_{00}$	$RR_{11} = RR_{10} + RR_{01} - 1$
Negative multiplicative negative additive	5	$p_{10} < p_{11} < p_{10} + p_{01} - p_{00}$	$RR_{10} < RR_{11} < RR_{10} + RR_{01} - 1$
Single pure interaction for X_2	6	$p_{11} = p_{10}$	$RR_{11} = RR_{10}$
Single qualitative interaction for X_2	7	$p_{01} < p_{11} < p_{10}$	$RR_{01} < RR_{11} < RR_{10}$
Pure interaction for X_1, qualitative interaction for X_2	8	$p_{11} = p_{01}$	$RR_{11} = RR_{01}$
Double qualitative interaction	9	$p_{00} < p_{11} < p_{01}$	$1 < RR_{11} < RR_{01}$
Perfect antagonism	10	$p_{11} = p_{00}$	$RR_{11} = 1$
Inverted interaction	11	$p_{11} < p_{00}$	$RR_{11} < 1$

[a]Conditions presuppose that the exposures, X_1 and X_2, have been labeled so that X_1 has a larger main effect than X_2.

VanderWeele, Tyler J. The Interaction Continuum. Epidemiology: September 2019 - Volume 30 - Issue 5 - p 648-658

The Interaction Continuum for Two Causative Exposures

If both of the two exposures have an effect on the outcome, then the absence of interaction on the additive scale implies the presence of multiplicative interaction.

$$-\infty - - - - - - - - -additivity - - - - - - - - multiplicativity - - - - - - - - +\infty$$

Likewise, the absence of multiplicative interaction implies the presence of additive interaction.

So if both of the exposures have an effect on the outcome, then there must be interaction on some scale.

Relative Excess Risk due to Interaction (RERI)

The RERI (synonym: interaction contrast ratio [ICR]) is the difference between joint relative effect of two factors and their relative effects considered separately. Could use RR, OR and HR

- "relative excess risk due to interaction" $(RERI) = RR_{11} - RR_{10} - RR_{01} + 1$
- RERI is an **additive interaction measure**, but it operates with ratios instead of absolute risks. Cannot in general use RERI to make statements about the relative magnitude of the underlying additive interaction for risks unless you also know p_{00}.
- The RERI indicates a super-additive interaction if RERI > 0 and sub-additive if RERI < 0.
- Interpretation of RERI may be less straightforward if additional covariates are included in the model because it varies across the levels defined by additional covariates.

Relative Excess Risk due to Interaction (RERI)

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

RERI = (0.0450/0.0011) - (0.0095/0.0011) - (0.00670/0.0011) + 1 = RERI = 27.18

Only the direction, rather than the magnitude, of $RERI_{RR}$ is needed to draw conclusions about the public health relevance of interaction.

- RERI > 0 if and only if (p11–p10 –p01+p00) > 0
- RERI=0 if and only if (p11 – p10 –p01 + p00) = 0
- RERI< 0 if and only if (p11 – p10 –p01 + p00) < 0

Attributable proportion due to interaction (AP)

The attributable proportion for the outcome (AP), indicates the proportion of the outcome in double exposed group that is due to the interaction itself.

- It is derived from RERI, and varies if additional covariates are included into the model.
- AP = RERI / RR11, if AP>0 =More than additivity; if <0 less than additivity
- AP = ((0.0450/0.0011) - (0.0095/0.0011) - (0.00670/0.0011) +1)/(0.0450/0.0011);
- AP = 0.66

AP > 0 if and only if RERI > 0, and AP < 0 if and only if RERI < 0.

- **Variation** The proportion of the joint effects of both exposures attributable to interaction:
- AP^* = RERI / (RR11 –1);
- AP^* = ((0.0450/0.0011) - (0.0095/0.0011) - (0.00670/0.0011) +1)/((0.0450/0.0011) -1)
- AP^* = 0.68

Synergy index (S-index)

Reflects the extent to which the joint relative effect of two factors together exceed 1 (one).

$S = \left(\frac{RR_{11}-1}{(RR_{10}-1)+(RR_{01}-1)} \right)$; >1 more than additivity, <1 less than additivity

- S = ((0.0450/0.0011) -1)/(((0.0095/0.0011)-1)+((0.00670/0.0011)-1))
- S = 3.14

- Whether the joint effect is greater than the sum of relative effects of two factors separately, exceed 1 (one). $S = 1$ means no interaction or exactly additivity.

- The S-index is independent of covariates adjustment.

- Interpretation may be difficult if one of the factors are preventive rather than causative, i.e., when denominator of S-index is negative.
- (This can't happen with RERI because the denominator of RERI is never negative.)

Assuming the denominator of S is positive, then if $S > 1, RERI > 0$ If $S < 1, RERI < 0$

Multiple testing

Multiple testing is common problem when testing statistical interactions because different data, hypotheses, and analyses are assessed simultaneously.

- Adjustment for multiple testing are required to reduce the probability of the false positive results, i.e., type 1 error.
- A multiple testing represents another reason why forming conclusions solely based on the p-value of an interaction test is unjustified.

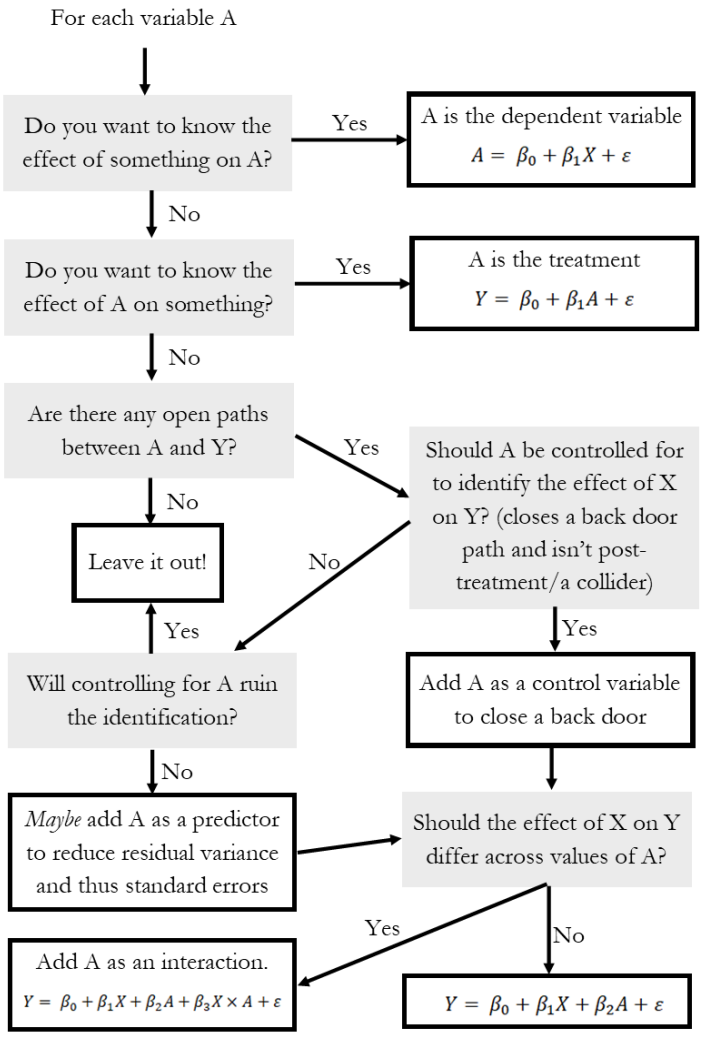
Sample size calculation

Always consider the sample size when planning to analyze statistical interaction, and especially if an important subgroup analysis is expected to be performed.

Recall

- You need 4 times the sample size to estimate an interaction that is the same size as the main effect
- You need 16 times the sample size to estimate an interaction that is half the size as the main effect

Constructing a Regression Equation Including interactions From The Effect



How to investigate heterogeneity, EMM or Interaction*: (1)

1. Research question: What's the relationship (effect) of interest (often $Y \rightarrow X$) ?
    - Overall effect of X, changing by other covariates (M = modifier)?
    - Overall effect of two potentially intervenable exposures X and *2nd exposure* E?
2. Do you think the relationship varies by levels of a 3rd variable ("M"), or *2nd exposure ("E")*?
    - NO: Stop, and continue with your "pooled" model.
    - YES: Consider how far do you need/want to go: a) description, b) estimation of interaction effect

- **Description only:** Stratification alone may suffice
- **Description with estimation of joint effect:** Stratification and regression with a product term (X*M) $\rightarrow$ EMM.
    - Requires correct interpretation of the product term (a.k.a. interaction term, interaction coefficient).

*For causal interaction, recall the need for the assumptions.

Description only: Low birthweight as a function of smoking and modification by race/ethnicity example

Pooled, "adjusted" regression

```
l13.lbwsmkpooled<- glm(low ~ smoke +nonwhite , family = binomial(link = "logit"), data = bir
round(cbind("OR" = exp(coef(l13.lbwsmkpooled)), exp(confint(l13.lbwsmkpooled))),2)
```

```
##                     OR 2.5 % 97.5 %
## (Intercept)       0.16  0.08   0.30
## smokesmoker       3.04  1.51   6.35
## nonwhitenonwhite 3.01  1.50   6.30
```

White strata

```
l13.lbwwhite<- glm(low ~ smoke, family = bi
                   data = subset(birthwt, n
round(cbind("OR" = exp(coef(l13.lbwwhite)),
```

```
##                OR 2.5 % 97.5 %
## (Intercept) 0.10  0.03   0.25
## smokesmoker 5.76  1.94  21.37
```

Non-white strata

```
l13.lbwnonwhite<- glm(low ~ smoke, family =
                      data = subset(birthwt
round(cbind("OR" = exp(coef(l13.lbwnonwhite
```

```
##                OR 2.5 % 97.5 %
## (Intercept) 0.54  0.33   0.88
## smokesmoker 1.84  0.70   4.90
```

Description with estimation of joint effect: Low birthweight as a function of smoking and modification by race/ethnicity example

```
l13.mod4 <- glm(low ~ smoke * nonwhite, data = birthwt, family = binomial)
round(cbind("OR" = exp(coef(l13.mod4)), exp(confint(l13.mod4))),2)
```

```
##                                 OR 2.5 % 97.5 %
## (Intercept)                   0.10  0.03   0.25
## smokesmoker                   5.76  1.94  21.37
## nonwhitenonwhite              5.43  1.91  19.63
## smokesmoker:nonwhitenonwhite 0.32  0.06   1.39
```

Joint effect for the exposure to Smoking and Non-white

```
round(exp(coef(l13.mod4)["smokesmoker"] + coef(l13.mod4)["nonwhitenonwhite"] +
            coef(l13.mod4)["smokesmoker:nonwhitenonwhite"]), 2)
```

```
## smokesmoker
##          10
```

```
round(5.76*5.43*0.32, 2)
```

```
## [1] 10.01
```

Description with estimation of joint effect: Low birthweight as a function of smoking and modification by race/ethnicity example

```
##                                    OR 2.5 % 97.5 %
## (Intercept)                      0.10  0.03   0.25
## smokesmoker                      5.76  1.94  21.37
## nonwhitenonwhite                 5.43  1.91  19.63
## smokesmoker:nonwhitenonwhite     0.32  0.06   1.39
```

Joint effect for the exposure to Smoking and Non-white + Stratification Results

```
table_objectlbw = interactionR(l13.mod4, exposure_names = c("smokesmoker", "nonwhitenonwhite
                               ci.type = "mover", ci.level = 0.95, em = F, recode = F)
kable(table_objectlbw$dframe[4:9,], digits = 2) #select stratified analysis
```

	Measures	Estimates	CI.ll	CI.ul	p
4	OR11	10.00	2.66	37.60	0.00
5	OR(nonwhitenonwhite on outcome [smokesmoker==0]	5.43	1.74	16.95	0.00
6	OR(nonwhitenonwhite on outcome [smokesmoker==1]	1.74	0.63	4.76	0.29
7	OR(smokesmoker on outcome [nonwhitenonwhite==0]	5.76	1.78	18.60	0.00
8	OR(smokesmoker on outcome [nonwhitenonwhite==1]	1.84	0.70	4.84	0.22
9	Multiplicative scale	0.32	0.07	1.46	0.14

How to investigate heterogeneity, EMM or Interaction*: (2)

Estimation of EMM/interaction effect (scales, direction):

- Regression with product term (X*M), identify the deviation from multiplicativity
- Regression with product term (X*E), identify the deviation from multiplicativity but requires a causal model for both X and E, Not Unmeasured Confounders
- Use of probabilities or log-odds (Additive scale)
- Use of RRs or ORs:
  - **RERI:** Relative Excess due to Interaction
  - **AP:** Attributable effect of the interaction*
  - **SI:** Synergy Effect*

*For causal interaction, recall the need to meet all the assumptions.

Estimation of EMM/interaction effect (scales, direction):

```
##                                    OR 2.5 % 97.5 %
## (Intercept)                      0.10  0.03   0.25
## smokesmoker                      5.76  1.94  21.37
## nonwhitenonwhite                 5.43  1.91  19.63
## smokesmoker:nonwhitenonwhite 0.32  0.06   1.39
```

Joint effect for the exposure to Smoking and Non-white + Comparison of effects

```
kable(table_objectlbw$dframe[1:4,], digits = 2) #select stratified analysis
```

Measures	Estimates	CI.ll	CI.ul	p
OR00	1.00			
OR01	5.43	1.74	16.95	0
OR10	5.76	1.78	18.60	0
OR11	10.00	2.66	37.60	0

Estimation of EMM/interaction effect (scales, direction): Low birthweight as a function of smoking and modification by race/ethnicity example

Recall?

ln(odds)	M=0	M=1
X=0	β_0	$\beta_0 + \beta_2$
X=1	$\beta_0 + \beta_1$	$\beta_0 + \beta_1 + \beta_2 + \beta_3$

Coefficients (log-Odds)

```
##                                    Coeff
## (Intercept)                     -2.302585
## smokesmoker                      1.750516
## nonwhitenonwhite                 1.692819
## smokesmoker:nonwhitenonwhite    -1.140751
```

Probabilities

	White	Non White
Non-Smoker	0.09	0.35
Smoker	0.38	0.51

Expected: 0.35 + 0.38 = 0.73

Observed: = 0.51

Less than expected from the sum of each probabilities $p_{01} + p_{10}$, then **the joint effect is sub-additive**

Estimation of EMM/interaction effect (scales, direction): Low birthweight as a function of smoking and modification by race/ethnicity example

Probabilities

	White	Non White
Non-Smoker	0.09	0.35
Smoker	0.38	0.51

$(p11 - p10 - p01 + p00) = (0.51 - 0.35 - 0.38 + 0.09) =$ -0.13,

then **<0 means that the effect of the double exposure is sub-additive**

Multiplicative scale:

$\left(\frac{RR_{11}}{RR_{10}RR_{01}}\right) = \left(\frac{p_{11}p_{00}}{p_{10}p_{01}}\right) = \left(\frac{0.52/0.09}{0.35/0.09 \times 0.38/0.09}\right) = 0.35,$

then **<1 means that the effect of the double exposure is sub-multiplicative**

RERI, AP, and SI using RRs

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

RERI = (0.51/0.09) - (0.35/0.09) - (0.38/0.09) + 1 = RERI = -1.44

$$AP = RERI / RR_{11}$$

AP = -1.44 / 5.67 = -0.25

$$SI = \left(\frac{RR_{11} - 1}{(RR_{10} - 1) + (RR_{01} - 1)} \right)$$

S = 5.67 -1 / (3.89 -1) + (4.22 -1)

S= 0.76

RERI, AP, and SI using RRs

```
l13.mod5 <- glm(low ~ smoke * nonwhite, data = birthwt,
                family = binomial(link = "log"))
round(cbind("RR" = exp(coef(l13.mod5)), exp(confint(l13.mod5))),2)
```

```
##                                   RR 2.5 % 97.5 %
## (Intercept)                     0.09  0.03   0.20
## smokesmoker                     4.02  1.66  13.10
## nonwhitenonwhite                3.87  1.64  12.50
## smokesmoker:nonwhitenonwhite 0.35  0.10   0.99
```

Using the `interactinR` function*

	Measures	Estimates	CI.ll	CI.ul	p
9	Multiplicative scale	0.35	0.11	1.09	0.07
10	RERI	-1.39	-11.44	4.59	
11	AP	-0.25	-1.13	0.26	
12	SI	0.76	0.41	1.41	

*Some difference to the second decimal due to rounding.

Example - `low birthweight` using ORs

```
table_objectlbw = interactionR(l13.mod4, exposure_names = c("smokesmoker", "nonwhitenonwhite
                               ci.type = "mover", ci.level = 0.95, em = F, recode = F)
#interactionR_table(table_objectlbw)
```

Interaction of smokesmoker and nonwhitenonwhite

*	nonwhitenonwhite absent	nonwhitenonwhite present	Effect of nonwhitenonwhite within the strata of smokesmoker
	OR [95% CI]	OR [95% CI]	OR [95% CI]
smokesmoker absent	1 [Reference]	5.43 [1.74, 16.95]	5.43 [1.74, 16.95]
smokesmoker present	5.76 [1.78, 18.6]	10 [2.66, 37.6]	1.74 [0.63, 4.76]
Effect of smokesmoker within the strata of nonwhitenonwhite	5.76 [1.78, 18.6]	1.84 [0.7, 4.84]	
Multiplicative scale	0.32 [0.07, 1.46]		
RERI	-0.19 [-18.59, 22.67]		
AP	-0.02 [-1.73, 0.52]		
SI	0.98 [0.35, 2.77]		

Example - `low birthweight` using ORs Recall this?

Measures	Estimates	CI.ll	CI.ul	p
OR00	1.00			
OR01	5.43	1.74	16.95	0.00
OR10	5.76	1.78	18.60	0.00
OR11	10.00	2.66	37.60	0.00
OR(nonwhitenonwhite on outcome [smokesmoker==0]	5.43	1.74	16.95	0.00
OR(nonwhitenonwhite on outcome [smokesmoker==1]	1.74	0.63	4.76	0.29
OR(smokesmoker on outcome [nonwhitenonwhite==0]	5.76	1.78	18.60	0.00
OR(smokesmoker on outcome [nonwhitenonwhite==1]	1.84	0.70	4.84	0.22
Multiplicative scale	0.32	0.07	1.46	0.14
RERI	-0.19	-18.59	22.67	
AP	-0.02	-1.73	0.52	
SI	0.98	0.35	2.77	

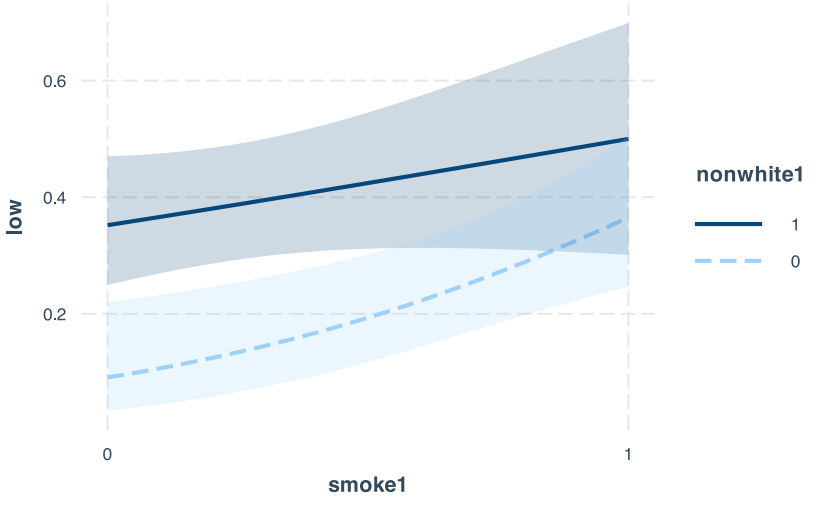
Example - `low birthweight` using ORs

Resources Using `epiR`, `interactions` and `interactionR` packages

RERI Estimation

```
library(epiR)
#RERI
epi.interaction(model = l13.mod4a, #to obta
    param = "product",
    coef = c(2,3,4),
   conf.level = 0.95)$reri
```

```
##          est     lower    upper
## 1 -0.1923582 -9.621692 9.236976
```



Multiplicative interaction

```
#Multiplicative Interaction term
epi.interaction(model = l13.mod4a, #to obta
                param = "product", coef = c
   conf.level = 0.95)$multiplicative
```

```
##        est      lower    upper
## 1 0.319579 0.06421315 1.394265
```

R Function for Additive Interaction Measures. Mathur, Maya B.; VanderWeele, Tyler J

Additional Notes

- The synergy index is preferred because when the regression models include potential confounders (as in the majority of cases) RERI and AP may be biased measures of additive interaction, while S was unbiased (Skrondal et al. 2003).
- The methods for additive interaction are all derived from the case where `X` and `E`'s effect on `Y` is risk-based. That is the ratio measure >1.0.
- In the case where `X` and `E`'s effect on `Y` is protective (ratio measure <1.0), the variables need to be reparameterized to risk factors (Knol et al. 2012)
  - For categorical measures, this means changing the reference group to the one with the lowest risk, thus all other groups convey excess risk.
  - This should be done for all variables as warranted in the same model (not one at a time).
- In all cases, the preferred method for reporting the precision of the additive measure is bootstrapping.
  - See variance recovery method by Zou (2008) and MOVER-R for Confidence Intervals of Ratios.

REPORTING OF STATISTICAL INTERACTION

For effect-measure modification between two categorical factors, the results should include:

1. Effects per each stratum of both factors using a single reference category that should be a subgroup with the lowest risk,
2. Effects of the primary factor in strata of the secondary factor,
3. Effect per each multivariable adjusted models;
4. Additive and multiplicative interaction measures with 95%CI;
5. The set of confounders for the primary factor–outcome relationship

For causal interaction, the results should also include

1. Effects of the secondary factor in strata of the primary factor;
2. The set of confounders for the secondary factor–outcome relationship .

Key Messages

1. Interaction term (the tool `X*M` or `X*E`)
2. EMM or Interaction?
    - Depends, One exposure or Two exposures of interest
3. How to obtain them:
    - EMM: Stratification and **correct interpretation** of joint vs individual effects by the *"interaction term"*
    - Statistical Interaction measures: RERI (ICR), AP, SI
    - !Be aware of "preventive" exposures
4. Additive vs Multiplicative
    - Could obtain both, but additive measures provide meaningful PH information
    - Sub additive (sub/less than multiplicative) or super additive (super/more than multiplicative)
5. Interpretation?
    - Descriptive, statistical, causal (granted the assumptions are met)

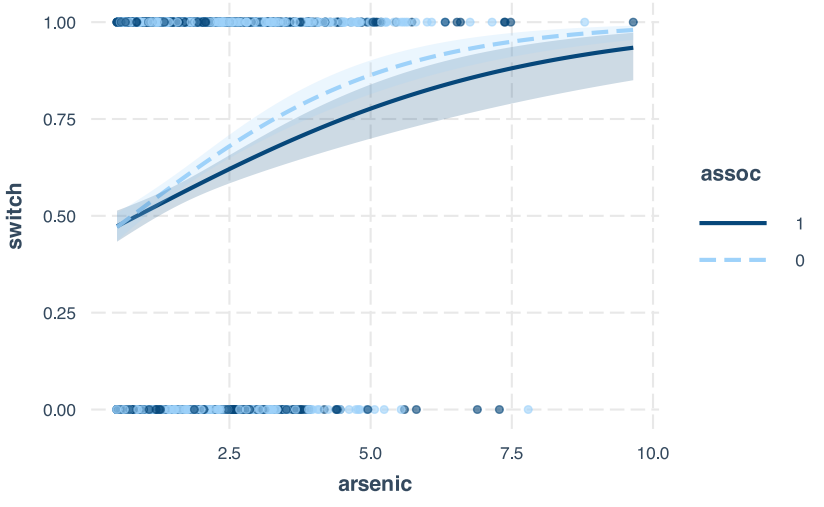
Example - Back to the unsafe wells in Bangladesh

```
##                   OR 2.5 % 97.5 %
## (Intercept)   0.71  0.59   0.86
## arsenic       1.55  1.40   1.72
## assoc         1.08  0.82   1.42
## arsenic:assoc 0.87  0.75   1.02
```

Measures of Interaction using `epiR`

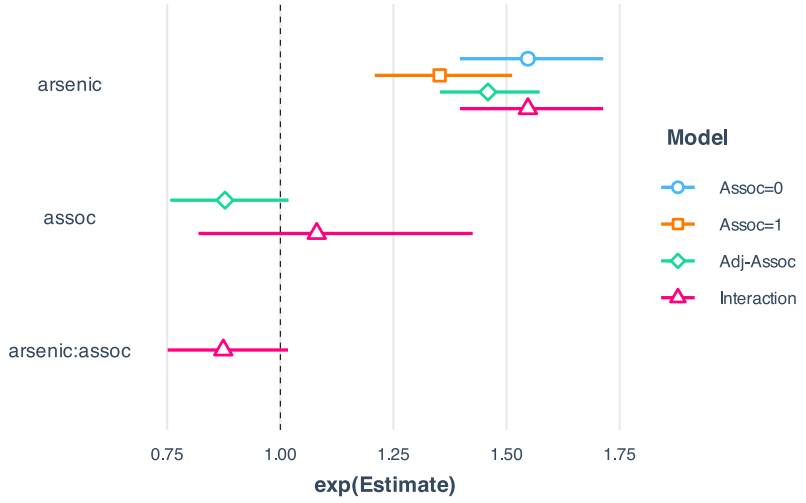
```
## $reri
##          est      lower     upper
## 1 -0.1668265 -0.3164641 -0.017189
##
## $apab
##          est      lower       upper
## 1 -0.1141958 -0.2096231 -0.01876857
##
## $s
##         est     lower     upper
## 1 0.7342288 0.5776462 0.9332563
##
## $multiplicative
##         est     lower    upper
## 1 0.8738788 0.7511418 1.017436
```

```
interact_plot(mod04, pred = arsenic, modx =
```

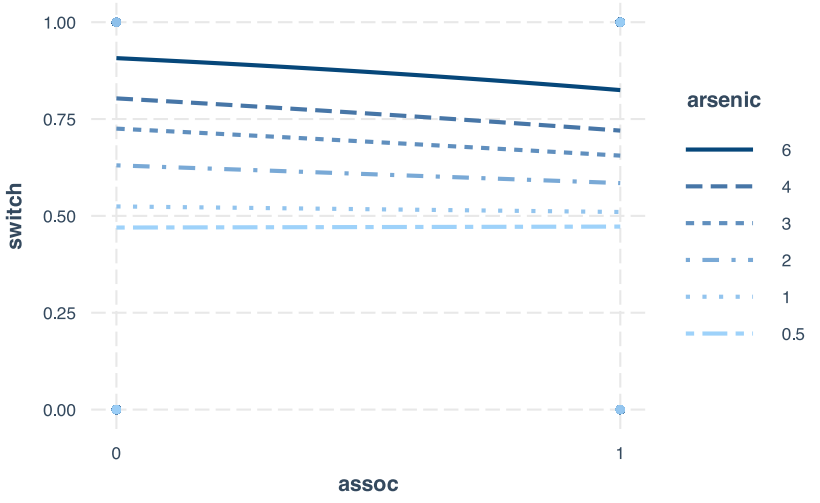



```
epi.interaction(model = mod04,
                param = "product",
                coef = c(2,3,4),
   conf.level = 0.95)
```

Example - back to the unsafe wells




```
interact_plot(mod04, pred = assoc, modx = a
                modx.values = c(0.5, 1, 2, 3
```



Example - Back to the unsafe wells in Bangladesh

```
table_object2 = interactionR(mod04, exposure_names = c("assoc", "arsenic"),
                             ci.type = "mover", ci.level = 0.95, em = F, recode = F)
#interactionR_table(table_object2); #table_object2$dframe[9:12,] #to obtain the estimates
```

Interaction of assoc and arsenic			
*	arsenic absent	arsenic present	Effect of arsenic within the strata of assoc
	OR [95% CI]	OR [95% CI]	OR [95% CI]
assoc absent	1 [Reference]	1.55 [1.4, 1.71]	1.55 [1.4, 1.71]
assoc present	1.08 [0.82, 1.43]	1.46 [1.17, 1.83]	1.35 [1.21, 1.51]
Effect of assoc within the strata of arsenic	1.08 [0.82, 1.43]	0.94 [0.8, 1.12]	
Multiplicative scale	0.87 [0.75, 1.02]		
RERI	-0.17 [-0.37, -0.04]		
AP	-0.11 [-0.22, -0.02]		
SI	0.73 [0.58, 0.93]		

Example - Back to the unsafe wells in Bangladesh

	Measures	Estimates	CI.ll	CI.ul	p
9	Multiplicative scale	0.87	0.75	1.02	0.08
10	RERI	-0.17	-0.37	-0.04	
11	AP	-0.11	-0.22	-0.02	
12	SI	0.73	0.58	0.93	

RERI and AP <0 and SI<1 = Less than additivity

- OR for multiplicative interaction (Measure of interaction on the multiplicative scale) = 0.87, less than multiplicative

QUESTIONS?

COMMENTS?

RECOMMENDATIONS?

Appendices

I. Examples

II. Theoretical Information for Causal Interaction from `H&R What if`?

	Definition	Interpretation	Assumptions
Additive interactions			
RERI (relative excess risk due to interaction)	$RR_{11} - RR_{01} - RR_{10} + 1$	Difference between the joint RR and the separate contributions by the two exposures	None when interpreted associationally; otherwise, NUCA for one or both exposures
Attributable proportion	$\frac{RERI}{RR_{11}}$	Proportion of outcome risk in the doubly exposed group attributable to interaction	None when interpreted associationally; otherwise, NUCA for one or both exposures
Proportion of joint effect due to interaction	$\frac{RERI}{RR_{11} - 1}$	Proportion of the joint effects that is attributable to interaction	None when interpreted associationally; otherwise, NUCA for one or both exposures
Mechanistic interactions			
Synergy	There exists an individual with $D_{11} = 1$ but $D_{01} = D_{10} = 0$.	Presence of a mechanism such that some individuals would experience the outcome under both exposures, but not under either exposure alone	NUCA; optionally monotonicity assumptions for less stringent tests
Compositional epistasis	There exists an individual with $D_{11} = 1$ but $D_{01} = D_{10} = D_{00} = 0$.	Presence of a mechanism such that some individuals would experience the outcome if and only if both exposures were present	NUCA; optionally monotonicity assumptions for less stringent tests
Other measures			
Proportion of joint effect due to exposure 1	$\frac{RR_{10}}{RR_{11} - 1}$	—	None when interpreted associationally; otherwise, NUCA for one or both exposures
Proportion of joint effect due to exposure 2	$\frac{RR_{01}}{RR_{11} - 1}$	—	None when interpreted associationally; otherwise, NUCA for one or both exposures

RERI indicates relative excess risk due to interaction; D, binary outcome variable; E_1 and E_2, binary exposure variables; NUCA, no-unmeasured-confounding assumptions for one or both exposure–outcome relationships.[5] $RR_{ab} = \frac{P(D=1|E_1=a,\ E_2=b)}{P(D=1|E_1=0,\ E_2=0)}$, where $a, b \in \{0,1\}$, which can be replaced with an odds ratio as appropriate to study design. D_{ab} = potential outcome for D under an intervention setting $E_1 = a$ and $E_2 = b$.

EPIDEMIOLOGY

R Function for Additive Interaction Measures. Mathur, Maya B.; VanderWeele, Tyler J

Nice Examples:

Table 4. Logistic regression analyses for the interaction effects between chlamydia, gonorrhea, and syphilis (Factor 1) and prenatal care (PNC) utilization status (Factor 2) on preterm birth.

Factor 1	Factor 2	No Preterm Birth	Preterm Birth		*p* Value
		n	*n*	aOR (95%CI)	
Chlamydia (−)	PNC (−)	45,127	12,999	3.11 (3.05, 3.18)	<0.001
Chlamydia (−)	PNC (+)	3,034,729	260,730	1.00	
Chlamydia (+)	PNC (−)	1004	384	3.56 (3.15, 4.02)	<0.001
Chlamydia (+)	PNC (+)	56,962	6093	1.02 (0.99, 1.05)	0.229
Multiplicative Interaction				1.12 (1.01, 1.25)	0.054
Relative Excess Risk due to Interaction (RERI)				0.43 (0.32, 0.53)	<0.001
Attributable Proportion (AP)				0.12 (0.02, 0.22)	0.023
Synergy Index (SI)				1.20 (1.10, 1.31)	<0.001

Kondracki, A.J.; Li, W.; Bursac, Z.; Mokhtari, M.; Reddick, B.; Barkin, J.L. Interaction Effects of Maternal Sexually Transmitted Infections with Prenatal Care Utilization Status on Preterm Birth and Low Birthweight: U.S. National Data. J. Clin. Med. 2022, 11, 5184.

Other nice example

Risk Factor	n (%) with Outcome	RR (95% CI)	RERI (95% CI)*	AP (95% CI) (%)†	Adjusted RR (95% CI)*,‡	Adjusted RERI (95% CI)	Adjusted AP (95% CI) (%)†,‡
Any history of interpersonal violence before pregnancy							
No disability+no history of interpersonal violence	5,366 (0.4)	Ref	3.31 (2.42–4.25)	29.1 (23.2–35.6)	Ref	0.87 (0.47–1.29)	18.2 (10.8–25.5)
No disability+history of interpersonal violence	2,108 (4.6)	7.23 (6.55–7.98)			3.49 (3.24–3.77)		
Disability+no history of interpersonal violence	1,043 (0.5)	1.59 (1.49–1.71)			1.41 (1.32–1.52)		
Disability+history of interpersonal violence	759 (6.0)	11.41 (9.76–12.70)			4.78 (4.31–5.29)		
Recent history of interpersonal violence (less than 2 y before pregnancy)							
No disability+no history of interpersonal violence	6,434 (0.4)	Ref	9.59 (7.07–12.33)	40.0 (32.7–47.2)	Ref	1.61 (0.94–2.34)	26.5 (16.8–34.8)
No disability+history of interpersonal violence	1,040 (8.0)	13.51 (11.98–15.24)			4.06 (3.68–4.49)		
Disability+no history of interpersonal violence	1,389 (0.7)	1.59 (1.49–1.71)			1.40 (1.31–1.51)		
Disability+history of interpersonal violence	413 (11.8)	23.69 (20.32–27.63)			6.08 (5.34–6.93)		

RR, relative risk; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; Ref, referent.
* The RERI (also called the interaction contrast ratio) represents the excess risk due to interaction relative to the risk without exposure, derived as $RR_{11}-RR_{10}-RR_{01}+1$; RERI>0 indicates positive interaction.
† The AP represents the proportion of the outcome that is due to interaction among those with both exposures, derived as $RERI/RR_{11}$.
‡ Model adjusts for age, parity, neighborhood income quintile, rurality, stable and unstable chronic conditions, mental illness, and substance use disorders.

OBSTETRICS & GYNECOLOGY

Brown H.K., et al. Disability and Interpersonal Violence in the Perinatal Period. Obstetrics & Gynecology: October 6, 2022 - Volume - Issue - 10.1097/AOG.0000000000004950

H&R What if? 5.5 Sufficient cause interaction

The colloquial use of the term "interaction between treatments **X** and **E**" evokes the existence of some causal mechanism by which the two treatments work together (i.e., "interact") to produce certain outcome.

- The definition of interaction within the counterfactual framework **does not require any knowledge about those mechanisms**.
- We said that there is an interaction between the treatments **X** and **E** if the causal effect of **X** when everybody receives **E** is different from the causal effect of **X** when nobody receives **`E`**.

Interaction is defined by the contrast of counterfactual quantities, and can therefore be identified by conducting an ideal randomized experiment in which the conditions of exchangeability, positivity, and consistency hold for both treatments **X** and **E**.

- There is no need to contemplate the causal mechanisms (physical, chemical, biologic, sociological...) that underlie the presence of interaction.

H&R What if? 5.5 Sufficient cause interaction

Rothman (1976) described the concepts of synergism and antagonism within the sufficient-component cause framework.

- This concept of interaction is not based on counterfactual contrasts but rather on `sufficient-component causes`, and thus we refer to it as interaction within the sufficient-component-cause framework or, "sufficient cause interaction."
- Sufficient cause interaction is defined as the joint presence of treatments **X and E** in the same causal mechanism, that is, in the same sufficient cause. [2]
- For example, suppose some individuals with background factors U5 = 1 will develop the outcome when jointly receiving `X` and `E`, but not when receiving only one of the two treatments.
- That is, these individuals have counterfactual responses $Y^{a=1,e=1} = 1$ and $Y^{a=0,e=1} = Y^{a=1,e=0} = 0$.
- Then there must exist some causal mechanism that requires the joint presence of both treatments **X** and **E**.

[2] See extra notes on sufficient causes or background causes in appendices for this lecture.

H&R What if? 5.5 Sufficient cause interaction

Sufficient cause interactions can be synergistic or antagonistic.

- There is synergism between treatment `X` and treatment `E` when `X=1` and `E=1` are present in the `same sufficient cause`,
- Antagonism between treatment `X` and treatment `E` when `X=1` and `E=0` (or `X=0 and E=1`) are present in the same sufficient cause.
- Alternatively, one can think of antagonism between `X` and `E` as synergism between treatment `X` and no treatment `E` (or between no treatment `X` and treatment `E`). [3]
- Unlike the counterfactual definition of interaction, sufficient cause interaction makes explicit reference to the causal mechanisms involving the treatments `X` and `E`.
- One could then think that identifying the presence of sufficient cause interaction requires detailed knowledge about these causal mechanisms.

It turns out that this not always the case: sometimes we can conclude that sufficient cause interaction exists even if we lack any knowledge whatsoever about the sufficient causes and their components.

[3] See extra notes on synergism and sufficient causes in appendices.

H&R What if? Fine Point 5.1

The classification of individuals by counterfactual response types makes it easier to consider specific forms of interaction.

$Pr[Y^{x=1,e=1} = 1] - Pr([Y^{x=0,e=1} = 1] + [Y^{x=1,e=0} = 1]) > 0$ or equivalently

$Pr[Y^{x=1,e=1} = 1] - Pr[Y^{x=0,e=1} = 1] > Pr[Y^{x=1,e=0} = 1]) > 0$

Some intuition:

- Synergism implies some individuals will develop the outcome when receiving both treatments $X = 1$ and $E = 1$, but not when receiving only one of the two.

- Synergism implies there are individuals with counterfactual responses $Y^{x=1,e=1} = 1$ and $Y^{x=0,e=1} = Y^{x=1,e=0} = 0$.

The inequality is a sufficient condition for these individuals to exist.

II- Theoretical information.

1 - Note on:H&R What if? 5.2 Identifying interaction within the counterfactual framework

In chapter 4, H&R used the notation M (rather than E) for variables for which one was not willing to make exchangeability, positivity, or consistency assumptions.

- In Chapter 4, the effect of transplant A was modified by nationality M, but we never required any identifying assumptions for the effect of M. We also found that nationality M did not have a causal effect on any individual's Y.
- That M does not act on the outcome implies that it does not interact with A–no action, no interaction. Yet M is a modifier of the effect of A on Y because M is correlated with (e.g., it is a proxy for) an unidentified variable that actually has an effect on Y and interacts with A.
- Thus there can be modification of the effect of A by another variable without interaction between A and that variable.

1b - Technical Point 5.2. Monotonicity of causal effects.

Consider a setting with a dichotomous treatment A and outcome Y.

- The value of the counterfactual outcome Y a=0 is greater than that of Y a=1 only among individuals of the “helped” type.
- For the other 3 types, Y a=1 ≥ Y a=0 or, equivalently, an individual’s counterfactual outcomes are monotonically increasing (i.e., non decreasing) in a.
- Thus, when the treatment cannot prevent any individual’s outcome (i.e., in the absence of “helped” individuals), all individuals’ counterfactual response types are monotonically increasing in a.
- We then simply say that the causal effect of A on Y is monotonic.
- The concept of monotonicity can be generalized to two treatments A and E.

2 - Note on: 5.4 H&R What if? Sufficient causes

Consider those individuals who were actually treated. Some of them died and some of them didn't, which implies that treatment alone is insufficient to bring about the outcome.

- As an oversimplified example, suppose that heart transplant A = 1 only results in death in subjects allergic to anesthesia or with a heightened immunological response. We refer to the smallest set of background factors that, together with A = 1, are sufficient to inevitably produce the outcome as U1. The simultaneous presence of treatment (A = 1) and these background factors (U1 = 1) is a sufficient cause of the outcome Y.

Now consider individuals who were not treated. Again some of them died and some of them didn't, which implies that lack of treatment alone is insufficient to bring about the outcome. As an oversimplified example, suppose that no heart transplant A = 0 only results in death if subjects have an ejection fraction less than 20%. We refer to the smallest set of background factors that, together with A = 0, are sufficient to produce the outcome as U2. The simultaneous absence of treatment (A = 0) and presence of these background factors (U2 = 1) is another sufficient cause of the outcome Y. By definition of "background" factors, U cannot be affected by treatment A.

2 - Note on: 5.4 H&R What if? Sufficient causes

Finally, consider those (“doomed”) individuals that would have developed the outcome whether they had been treated or untreated.

- The existence of these individuals implies that there are some other background factors that are themselves sufficient to bring about the outcome.
- As an oversimplified example, suppose that all subjects with pancreatic cancer at the start of the study will die.
- We refer to the smallest set of background factors that are sufficient to produce the outcome regardless of treatment status as U0. The presence of these factors (U0 = 1) is another sufficient cause of the outcome Y.

3 - Note on: 5.4 H&R What if? Sufficient causes and synergism

Specifically, if the inequality:

$Pr[Y^{a=1,e=1} = 1] - Pr([Y^{a=0,e=1} = 1] + [Y^{a=1,e=0} = 1]) > 0$ or equivalently

$Pr[Y^{a=1,e=1} = 1] - Pr[Y^{a=0,e=1} = 1] > Pr[Y^{a=1,e=0} = 1]) > 0$

holds, then there exists synergism between A and E.

- This implies that one can conduct an experiment in which treatments A and E are randomly assigned, compute the three counterfactual risks in the above inequality, and empirically check that synergism is present without ever giving any thought to the causal mechanisms by which A and E work together to bring about the outcome.
- This result is not that surprising because of the correspondence between counterfactual response types and sufficient causes, and because the above inequality is a sufficient but not a necessary condition, i.e., the inequality may not hold even if synergism exists.
    - In fact this sufficient condition is so strong that it may miss most cases of synergism.