

Statistical Interaction vs. Biological Interaction.

Statistical Interaction

- Refers to effect measure modification when no bias present.
- Refers to associations whether causal or not.
- Scale dependent.

Biological Interaction (Causal or sufficient cause interaction).

- Interaction within a causal framework.

- Biological Interaction has a causal interpretation: It is about two or more factors within a sufficient cause working together to cause disease (i.e. identifying synergy).
- public health impact

Determine which scale we are interested in (the additive scale).

① Assume No Interaction type

P	X=1 Z=1	X=0 Z=1	X=1 Z=0	X=0 Z=0	IC*	Description
1	1	1	1	1	0	Doomed
2	1	1	1	0	-1	Single, plus joint
3	1	1	0	1	1	Z is preventive, Z blocks
4	1	1	0	0	0	Z causal, X ineffective
5	1	0	1	1	1	Z is preventive, X blocks
6	1	0	1	0	0	X causal, Z ineffective
7	1	0	0	1	2	Mutual blockage preventive ant.
8	1	0	0	0	1	Causal synergism
9	0	1	1	1	-1	Preventive synergism
10	0	1	1	0	-2	Causal antagonism
11	0	1	0	1	0	X preventive, Z ineffective
12	0	1	0	0	-1	X blocks Z, causal antagonism
13	0	0	1	1	0	Z preventive, X ineffective
14	0	0	1	0	-1	Z blocks X, causal antagonism
15	0	0	0	1	1	Single plus joint prevention
16	0	0	0	0	0	Immune

$$*IC = R_{11} - R_{10} - R_{01} + R_{00}$$

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4	1	1	0	0	Z causal, X ineffective
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13	0	0	1	1	Z preventive, X ineffective
16	0	0	0	0	Immune

$$R_{11} = p_1 + p_2 + p_3 + p_4 + p_5 + p_6 + p_7 + p_8 = p_1 + p_4 + p_6$$

$$R_{01} = p_1 + p_2 + p_3 + p_4 + p_5 + p_10 + p_11 + p_12 = p_1 + p_4 + p_{11}$$

$$R_{10} = p_1 + p_2 + p_3 + p_4 + p_5 + p_6 + p_10 + p_{13} + p_{14} = p_1 + p_6 + p_{13}$$

$$R_{00} = p_1 + p_2 + p_3 + p_4 + p_5 + p_6 + p_7 + p_8 + p_{11} + p_{13} + p_{15} = p_1 + p_{11} + p_{13}$$

Additive Interaction?

Let's use the stratified assessment:

Let's compare R10-R00 to R11-R01:

$$R_{10} - R_{00} \stackrel{?}{=} R_{11} - R_{01}$$

$$R_{10} - R_{00} =$$

$$=$$

$$R_{11} - R_{01} =$$

$$=$$

No additive interaction.

But do we have multiplicative interaction?

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

$$R_{11} = p_1 + p_4 + p_6$$

$$R_{01} = p_1 + p_4 + p_{11}$$

$$R_{10} = p_1 + p_6 + p_{13}$$

$$R_{00} = p_1 + p_{11} + p_{13}$$

$$\frac{p_1 + p_4 + p_6}{p_1 + p_{11} + p_{13}} = \left(\frac{p_1 + p_6 + p_{13}}{p_1 + p_{11} + p_{13}} \right) \left(\frac{p_1 + p_4 + p_{11}}{p_1 + p_{11} + p_{13}} \right)$$

$$\frac{\left(\frac{p_1 + p_{11} + p_{13}}{p_1 + p_6 + p_{13}} \right) \left(\frac{p_1 + p_4 + p_{11}}{p_1 + p_{11} + p_{13}} \right)}{\left(\frac{p_1 + p_{11} + p_{13}}{p_1 + p_6 + p_{13}} \right) \left(\frac{p_1 + p_4 + p_{11}}{p_1 + p_{11} + p_{13}} \right)} \neq 1$$

But we do appear to have multiplicative interaction even though there are no interacting subtypes

↓
Now we know additive scale is more important.
↓

How can we assess biologic interaction?

↓
What simplifying assumption can we make?
What if X and Z can not prevent disease?
(Monotonicity)?

$$IC = R_{11} - R_{01} - R_{10} + R_{00}$$

$$= p_8 - p_2$$

Antagonistic
Responders.

Causal synergism Single, plus joint causation.

$X=1$	$X=0$	$Z=1$	$Z=0$	Description	Intervention
$\frac{1}{2}$	1	1	1	○	Single, plus joint/whelpetitive
8	1	0	0	○	Causal synergism.

Competitive interaction: Each factor will cause disease when the other is absent, but neither factor can have an effect on the outcome under study once the other is present.

Causal synergism: Each factor causes disease if and only if the other factor is present.

↓
single plus joint causation (issue of redundancy).

↓.

$IC > 0$ (Supraadditivity)
plus no prevention implies that synergistic responders (type 8) must be present

$IC < 0$ (Subadditivity)
plus no prevention implies that whelpetitive responders (type 2) must be present.

↓
What if $IC = p_8 - p_2 = 0$

There is no Additive Intervention

There is perfect balance of p_8 and p_2 in our population.

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Biologic vs. Statistical Intervention.

① Risk ratio homogeneity - often overlooked that this means

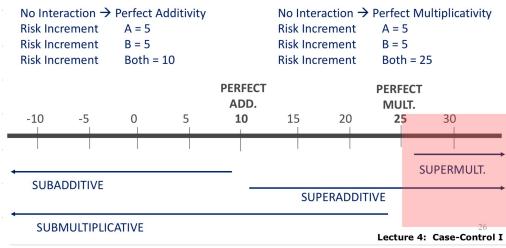
The absence of Biological Interaction

- ④ But presence of Biological Interaction depends on the risk nonadditivity = additive interaction is present.
- ⑤ Need information on types of Biologic interactions
e.g. if neither risk-factor is preventive, risk ratio homogeneity implies superadditivity.

From Epi 2

Relationship between additive and multiplicative interaction

- If neither factor is preventive, both perfect multiplicativity (RR homogeneity) and supermultiplicativity imply superadditivity



Lecture 4: Case-Control I

Additive Scale \rightarrow Public Health Impact.

- ① Cancer is the # of cases occurring in a population and the proportional contribution of each cause

② Departures from additivity are important.

- ③ Predict public health impact of removing or introducing only one of them.

Why Do we usually address modification only on Multiplicative scale?

- ① Very useful
- ② If modification on multiplicative scale is present, modification on additive scale present.