

Interaction

Typical reasoning about effect modification/interaction

- Simple example of a study on the effect of vegetable intake on risk of H&N cancer
- Gender is a potential confounder as well as a potential effect modifier
- Let us assume a crude risk ratio (RR) for low vs. high vegetable intake of 2.0
- How do we typically assess presence of effect modification?

Typical reasoning about interaction/effect modification

To adjust for gender as a confounder we estimate the stratum-specific effects and then pool them

BUT, if strata specific estimates are different we say that there is effect modification

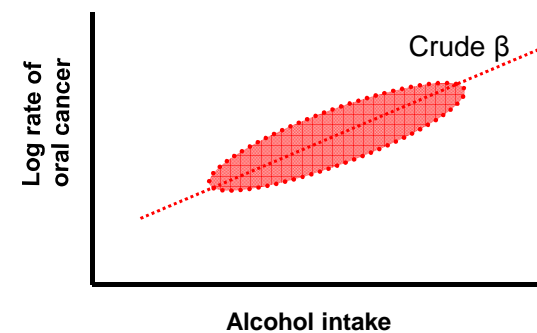
H&N cancer risk for vegetable intake (low vs. high)

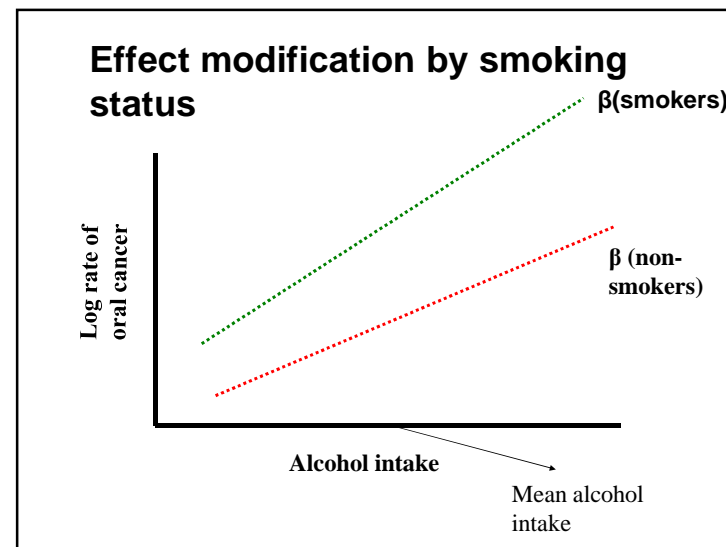
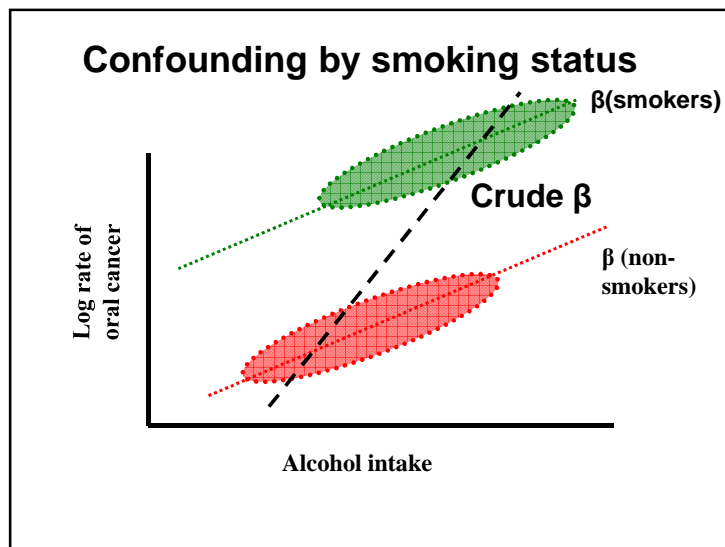
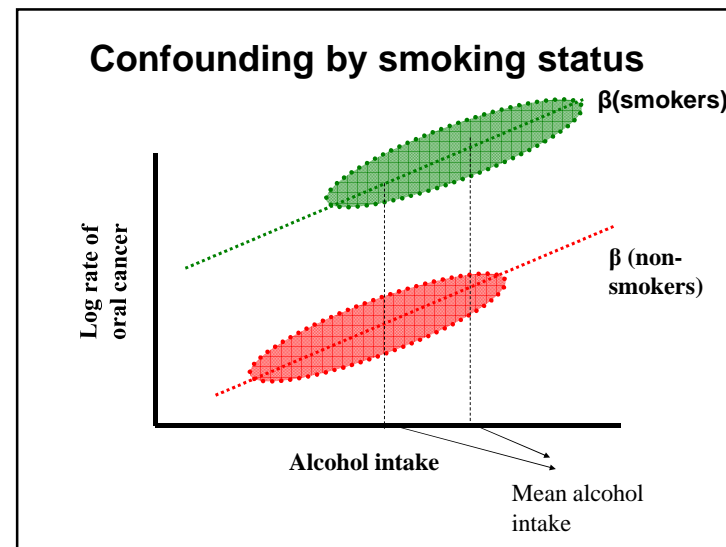
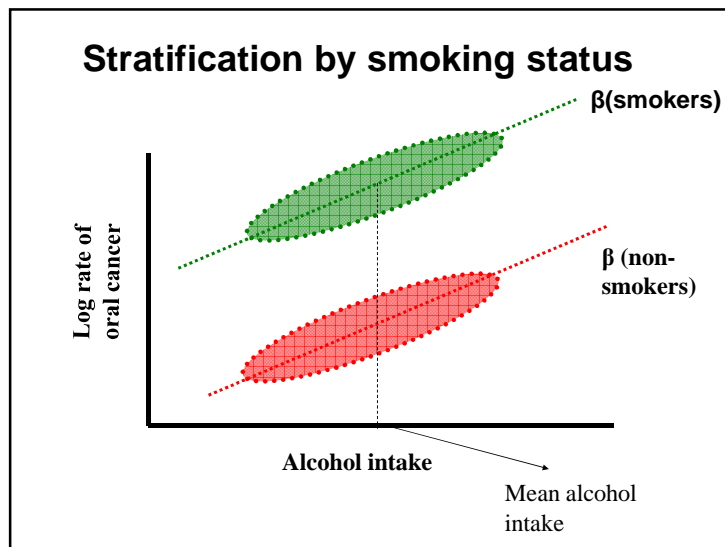
RR_{men}	= 1.5	RR_{men}	= 1.2
RR_{women}	= 1.4	RR_{women}	= 2.3

CAN be pooled

EFFECT MODIFICATION

Continuous variable

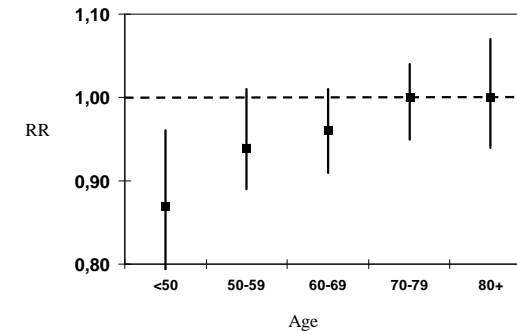




When are stratum-specific estimates different?

- Confounding is a bias that should be adjusted for, whereas effect modification is a real phenomenon that should be interpreted
- It is possible to carry out a test for homogeneity to evaluate if the estimates are constant over strata
- However, it is better to assume that the estimates can be pooled, unless there are a clear pattern of modification or some reasons to show the stratum-specific estimates
- Sometimes it is better to show both the stratum-specific and the pooled estimates

Effect of the introduction of the Italian smoking regulation on incidence of myocardial infarction. Piedmont Region



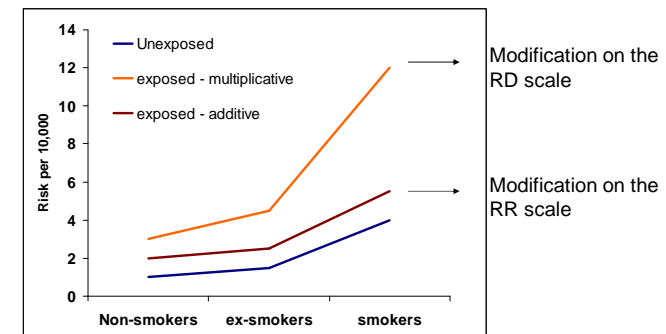
Barone-Adesi et al. Eu Heart J 2007

Note

- If there is effect modification (i.e. the effect measure is not the same in all the strata) the estimate obtained after pooling has no causal interpretation, while the stratum-specific estimates are interpretable
- Weights used for pooling have the main goal to reduce the variability of the pooled estimate
- Methods like standardization or IPW can estimate the average effect in the population, which it is not generalizable but has a causal interpretation for that population
- Let us suppose that adjustment for a variable L is necessary to obtain exchangeability but L is also an effect modifier. To obtain the average effect in the population we should use standardization

Presence of effect modification depends on the effect that we consider

Hypothetical occupational study on lung cancer



Moreover

Even on the same scale, if the underlying disease is not rare:

Absence of effect modification for a measure of association (say the OR)

implies

Presence of effect modification for another measure of association (say RR)

In a 2*2 Table: asbestos, smoking and lung cancer risk

		smoking	
		no	yes
Asbestos	no	2/1000	14/1000
	yes	4/1000	20/1000

■ Additivity: $R_{\text{yesyes}} - R_{\text{noyes}} = R_{\text{yesno}} - R_{\text{nono}}$
 $20/1000 - 4/1000 > 14/1000 - 2/1000$
 interaction coefficient: $R_{\text{yesyes}} - R_{\text{yesno}} - R_{\text{noyes}} + R_{\text{nono}}$

■ Multiplicativity $R_{\text{yesyes}}/R_{\text{noyes}} = R_{\text{yesno}}/R_{\text{nono}}$
 $20/4 < 14/2$

Modified from Rothman et al. Modern Epidemiology 2008

Further on the example

What is the population group that would benefit most from intervention of smoking prevention?

The answer to this question comes from the additive interaction

Also, if there is nonadditivity, the number of cases caused by asbestos depends on how many workers were smokers (interaction)

Risk nonadditivity has been thus considered as “public health interaction”.

Rothman et al. IJE 1980;112:467-70; Saracci AJE 1980;112:465-6

Using measures of association

Relative risks of lung cancer

		smoking	
		no	yes
Asbestos	no	1.0	7.0
	yes	2.0	10.0

Additive interaction: $(10-1) > (7-1)+(2-1)$

Multiplicative interaction: $10 < 7*2$

Measures of interaction

		smoking	
		no	yes
Asbestos	no	1.0	7.0
	yes	2.0	10.0

- RERI (relative excess risk for interaction) =
 $RR_{yes/yes} - RR_{yes/no} - RR_{no/yes} + 1 = 10 - 7 - 2 + 1 = 2$
 (perfect additivity is RERI=0)
- Synergy index =
 $(RR_{yes/yes} - 1) / (RR_{yes/no} - 1 + RR_{no/yes} - 1) = 9 / (6 + 1) = 1.29$
 (perfect additivity is Si=1)
- Ratio of RRs: $(10/7) / (2/1) = 0.71$
 (perfect multiplicativity is ratio=1)

Towards a clearer definition of interaction

- Difference between effect modification and interaction
- Use of causal frameworks
 - counterfactuals
 - sufficient-component causes
- How to report effect modifications and interactions

Effect modification vs. interaction

- Effect modification answers to questions like: “what is the subgroup of the populations who is going to benefit most (least) from the intervention?”
- interaction answers to questions like: “what is the effect of intervening on both exposures?”
- conditions necessary to identify the effects are different: e.g. for effect modification it is necessary that there is exchangeability for the exposure, in interaction analysis exchangeability is required for both exposures
- The effect modifier does not need to be a cause of the event, while in interaction both exposures should be causes

Eff Mod in the counterfactual framework

If the exposure E has two levels and the effect modifier Q has two levels, there is effect modification if:

$$E[Y^{e=1} | Q=1] - E[Y^{e=0} | Q=1] \neq E[Y^{e=1} | Q=0] - E[Y^{e=0} | Q=0]$$

“contrast between the counterfactual outcome under the exposure and the counterfactual outcome under no exposure differ over Q strata”

- The counterfactual outcomes are defined only considering the exposure E (and thus exchangeability is defined accordingly)
- The contrast can be derived on an additive or a multiplicative scale, etc: $(E[Y^{e=1} | Q=1] / E[Y^{e=0} | Q=1]) \neq (E[Y^{e=1} | Q=0] / E[Y^{e=0} | Q=0])$

Vanderweele. Epidemiology 2009;20:863-71

Interaction in the counterfactual framework

If the exposure E has two levels and the exposure Q has two levels, there is interaction if:

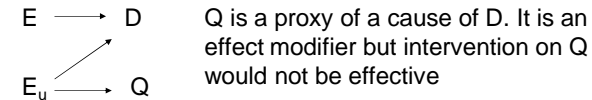
$$E[Y_{e=1,q=1}] - E[Y_{e=0,q=1}] \neq E[Y_{e=1,q=0}] - E[Y_{e=0,q=0}]$$

“contrast between the counterfactual outcomes under both exposures and under 1 of the two exposures differ from the contrast between the counterfactual outcomes under the other exposure and under no exposures”

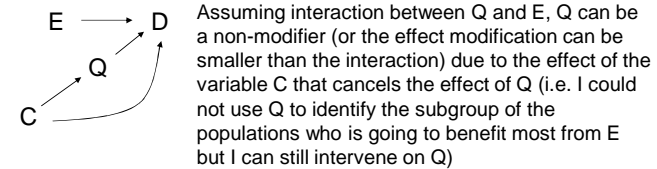
- The counterfactual outcomes are defined considering both E and Q
- The contrast can be derived on an additive or a multiplicative scale, etc: $E[Y_{e=1,q=1}] / E[Y_{e=0,q=1}] \neq E[Y_{e=1,q=0}] / E[Y_{e=0,q=0}]$

Interaction with no eff modification (and viceversa)

Effect modification with no interaction



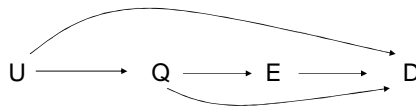
Interaction with no effect modification



Vanderweele. Epidemiology 2009;20:863-71; Vanderweele et al. Epidemiology 2007;18:561-8

Exchangeability (1)

- Since in interaction there are two exposures involved, exchangeability is required for both exposures
- It is possible that for a particular study exchangeability is met only for effect modification or for interaction



In this example, stratifying on Q (for assessment of effect modification) gives the causal effect of E on D, while analysis of the interaction between E and Q is confounded by U

Exchangeability (1)

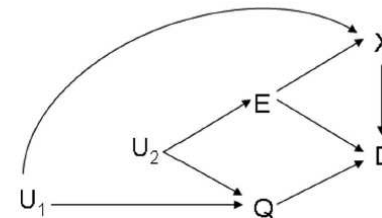


FIGURE 4. Identification of the joint effects of E and D without identification of effect modification of the effect of E on D by Q.

Vanderweele. Epidemiology 2009;20:863-71

More on counterfactuals

Let us consider a population of 10,000 individuals treated (or not treated) with two exposures (A and E) for a disease Y

Response types ($Y^{a,e}$) for joint intervention of E and A

Type	A_1E_1	A_0E_1	A_1E_0	A_0E_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

See

Hernan M, Robins J. Causal Inference. February 16, 2012

Greenland et al. Concepts of Interaction. In "Modern Epidemiology" 2008

Greenland et al. Scand J Work Environ Health 1988;14:125-9

Response types for joint intervention of E and A

Type	A_1E_1	A_0E_1	A_1E_0	A_0E_0	
1	1	1	1	1	Doomed: no effect regardless of the treatment
2	1	1	1	0	
3	1	1	0	1	If all the 10,000 individuals were of type 1 or 16 we would conclude that A and E have no causal effect on Y
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	Immune: no effect regardless of the treatment
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	

Response types for joint intervention of E and A

Type	A_1E_1	A_0E_1	A_1E_0	A_0E_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

For individual of these types the effect of one of the two exposures is the same regardless of the presence of the other exposure. Thus if all the 10,000 individuals were of these types, there would be no interaction between A and E

Response types for joint intervention of E and A

Type	A_1E_1	A_0E_1	A_1E_0	A_0E_0	For individual of these types there is interaction.
1	1	1	1	1	
2	1	1	1	0	Examples:
3	1	1	0	1	1) Type 8: they develop the outcome only if both treatments are present (synergism)
4	1	1	0	0	
5	1	0	1	1	2) Type 3: A_1 is preventive if E is not 1 (preventive antagonism)
6	1	0	1	0	
7	1	0	0	1	
8	1	0	0	0	
9	0	1	1	1	3) Type 11: co-presence of one exposure makes the other ineffective.
10	0	1	1	0	
11	0	1	0	1	
12	0	1	0	0	
13	0	0	1	1	4) Type 2: each factor has an effect on the outcome only if the other is not present (type of antagonism)
14	0	0	1	0	
15	0	0	0	1	
16	0	0	0	0	

Note

- Presence of interaction implies that at least one of these response types is present
- Absence of interaction may imply perfect cancellation of the different interactive response types
- It is possible to define specific forms of interaction of interest (e.g. Type 8).
- If we calculate the interaction coefficient ($R_{11} - R_{01} - R_{10} + R_{00}$), the same result, say $IC=1$, is obtained for, say, Type 3 (1 1 0 1) and Type 8 (1 0 0 0) individuals.
 → In type 3 there is preventive antagonism (the preventive effect of one exposure is blocked by the other)
 → in type 8 there is causal synergism: presence of the two exposures cause the event

No interaction

Type	A_1E_1	A_0E_1	A_1E_0	A_0E_0	p (proportion of individuals with that response type)
1	1	1	1	1	p1
4	1	1	0	0	p4
6	1	0	1	0	p6
11	0	1	0	1	p11
13	0	0	1	1	p13
16	0	0	0	0	p16

Average population Risks

$R_{11} = p1 + p4 + p6$ (individuals who develop the disease when $A=1$ and $E=1$)

$R_{01} = p1 + p4 + p11$; $R_{10} = p1 + p6 + p13$; $R_{00} = p1 + p11 + p13$

$R_{11} - R_{01} = p6 - p11$

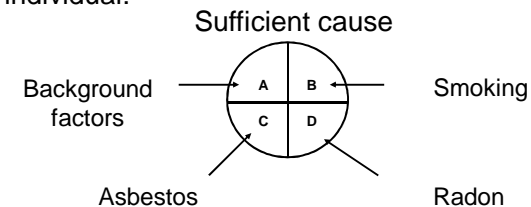
$R_{01} - R_{00} = p6 - p11$

THUS

$$R_{11} - R_{01} = R_{01} - R_{00}$$

The sufficient-component causes model

Causal mechanism for lung cancer in an individual:



Each factor is a component cause. Each factor is not sufficient to determine the disease

Sufficient causes for two exposures

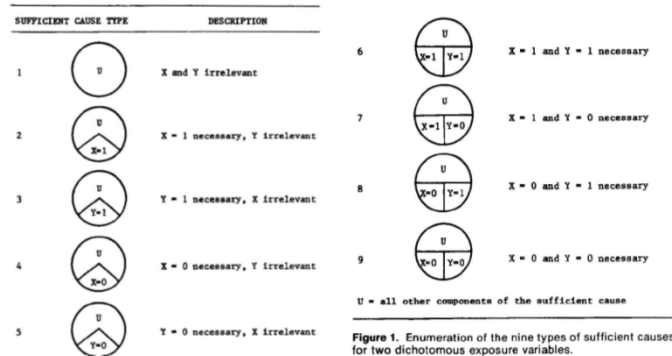


Figure 1. Enumeration of the nine types of sufficient causes for two dichotomous exposure variables.

Greenland et al. SJWEH 1988

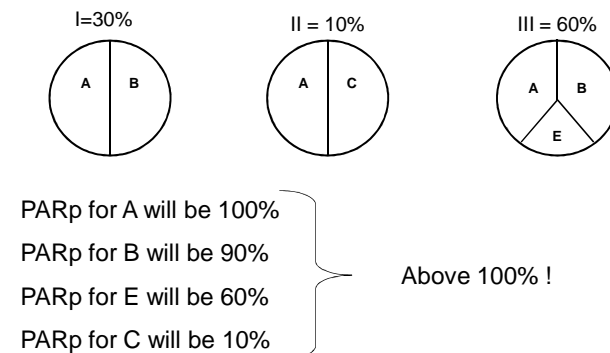
Note

There is correspondence between response types and sufficient-component causes

For example the type 1 pie of previous slide corresponds to Type 1 response. However correspondence is not always 1:1

Each person can be at risk for more than 1 pie, but only 1 pie can be responsible for an individual's disease

Disease pattern in a given population



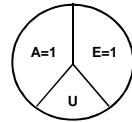
Sufficient cause interaction (1)

There is interaction between A and E in a population if they appear together in a sufficient cause in that population

Vanderweele and Robins derived conditions for identification of synergism under the sufficient component cause framework → see next slide

Vanderweele et al. Epidemiology 2007;18:329-39; Vanderweele Epidemiology 2009;20:6-13

Thus



- Sufficient cause interaction between A and E implies co-presence of A and E in the pie
- This implies response types 7 and/or 8

Type	A_1E_1	A_0E_1	A_1E_0	A_0E_0
7	1	0	0	1
8	1	0	0	0

- Thus

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

Identification (1)

Assuming that A and E are two binary exposures:

→ if $R_{11} - R_{10} - R_{01} > 0$, there is synergism between A_1 and E_1 and individuals with a response type 7 or 8 should exist. (note: type 7 and 8 differ only for the potential outcome in A_0E_0 that is =0 in type 7 and =1 in type 8 → no information on R_{00} needed)

Analogously

- If $R_{10} - R_{11} - R_{00} > 0$ there is synergism between A_1 and E_0 and individuals with response type 10 or 14 must exist
- If $R_{01} - R_{11} - R_{00} > 0$ there is synergism between A_0 and E_1 and individuals with response type 10 or 12 must exist
- If $R_{00} - R_{01} - R_{10} > 0$ there is synergism between A_0 and E_0 and individuals with response type 7 or 15 must exist

Identification (2): Assuming monotonic effects

Monotonic effect: the direction of the effect of an exposure on the outcome is the same for all individuals regardless of the other exposure → either always beneficial or neutral or always harmful or neutral

→ If A and E both have a positive monotonic effect and $R_{11} - R_{10} - R_{01} + R_{00} > 0$, there is synergism between A_1 and E_1 and individuals with a response type 8 should exist

Analogously

It is possible to derive the analogous statements for negative monotonic effects and for combinations of $A_{0\text{and}1}$ and $E_{0\text{and}1}$

Identification (2): Assuming monotonic effects

Monotonic effect: the direction of the effect of an exposure on the outcome is the same for all individuals regardless of the other exposure → either always beneficial or neutral or always harmful or neutral

→ If A and E have a positive monotonic effect and $R_{11} - R_{10} - R_{01} + R_{00} > 0$, there is synergism between A_1 and E_1 and individuals with a response type 8 should exist

NOTE this is what is defined as interaction coefficient

Analogously

It is possible to derive the analogous statements for negative monotonic effects and for combinations of $A_{0\text{and}1}$ and $E_{0\text{and}1}$

Example

		smoking	
		no	yes
Asbestos	no	2/1000	14/1000
	yes	4/1000	20/1000

- $20/1000 - 14/1000 - 4/1000 > 0$ there should be some **sufficient cause** with both asbestos and smoking
- assuming (sensibly) monotonic effects for smoking and asbestos, as $20/1000 - 14/1000 - 4/1000 + 2/1000 > 0$ there should be **somebody in the cohort who would not have developed lung cancer** without concomitant presence of both smoking and asbestos (Type 8)

RR scale

		smoking	
		no	yes
Asbestos	no	1.0	7.0
	yes	4.0	10.0

$$RERI = RR_{yes/yes} - RR_{yes/no} - RR_{no/yes} + 1 > 0$$

→ Under monotonic effects, testing for sufficient interaction implies

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

$$RR_{yes/yes} - RR_{yes/no} - RR_{no/yes} + 1 = RERI > 0 \rightarrow \text{RERI} > 0$$

→ Without assumption of monotonic effects

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

$$RR_{yes/yes} - RR_{yes/no} - RR_{no/yes} = (RERI - 1) > 0 \rightarrow \text{RERI} > 1$$

Log-linear or logistic models

$$\blacksquare S = RR_{11} / (RR_{10} \cdot RR_{01})$$

If monotonic effects are assumed, there is sufficient interaction if $S > 1$ (i.e. the interaction coefficient in a log-linear or logistic model is > 0)

If no monotonic effects are assumed there is sufficient interaction if

- $S > 2$ (i.e. the interaction coefficient in a log-linear or logistic model is $> \log(2)$) AND $RR_{01} > 0$ and $RR_{10} > 0$
- $S > 1$ (i.e. the interaction coefficient in a log-linear or logistic model is > 0) AND $RR_{10} > 2$ and $RR_{01} > 2$

Monotonic effects

$$\log(P(D = 1 | X_1 = x_1, X_2 = x_2)) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

$IC > 0$ implies

$$p_{11} - p_{10} - p_{01} + p_{00} = e^{\beta_0 + \beta_1 + \beta_2 + \beta_3} - e^{\beta_0 + \beta_1} - e^{\beta_0 + \beta_2} + e^{\beta_0} > 0$$

$RERI > 0$ implies

$$e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_1} - e^{\beta_2} + e^{\beta_0} > 0$$

if $\beta_1 \geq 0$ we can write

$$e^{\beta_1} (e^{\beta_2 + \beta_3} - 1) - (e^{\beta_2} - 1) > 0 \quad [1]$$

if also $\beta_3 > 0$ follows that:

$$e^{\beta_1} (e^{\beta_2 + \beta_3} - 1) \geq (e^{\beta_2 + \beta_3} - 1) > (e^{\beta_2} - 1) \text{ and thus condition [1] is met}$$

for symmetry the same applies if $\beta_2 \geq 0$

Thus testing for $\beta_3 > 0$ implies $RERI > 0$

No monotonic effects

$$p_{11} - p_{10} - p_{01} = e^{\beta_0 + \beta_1 + \beta_2 + \beta_3} - e^{\beta_0 + \beta_1} - e^{\beta_0 + \beta_2} > 0$$

$RERI > 1$ implies

$$e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_1} - e^{\beta_2} > 0$$

can be written as:

$$\left(\frac{1}{2}\right)e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_1} + \left(\frac{1}{2}\right)e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_2} > 0$$

or as:

$$e^{\beta_1} \left\{ \left(\frac{1}{2}\right)e^{\beta_2 + \beta_3} - 1 \right\} + e^{\beta_2} \left\{ \left(\frac{1}{2}\right)e^{\beta_1 + \beta_3} - 1 \right\} > 0 \quad [10]$$

if $e^{\beta_1} \left\{ \left(\frac{1}{2}\right)e^{\beta_2 + \beta_3} - 1 \right\} > 0$ and $e^{\beta_2} \left\{ \left(\frac{1}{2}\right)e^{\beta_1 + \beta_3} - 1 \right\} > 0$ then condition [10] is met

the 2 conditions can be rewritten as

$$e^{\beta_3} > 2e^{-\beta_1} \text{ and } e^{\beta_3} > 2e^{-\beta_2} \text{ or } \beta_3 > \log(2) - \beta_1 \text{ and } \beta_3 > \log(2) - \beta_2$$

Thus, there is mechanistic interaction if:

- 1) $\beta_3 > 0$ and $\beta_1 \geq \log(2)$ and $\beta_2 \geq \log(2)$
- 2) $\beta_3 > \log(2)$ and $\beta_1 \geq 0$ and $\beta_2 \geq 0$

OR

Summary: how to report effect modifications

Table 2 Example—modification of the effect of antidepressant use on diabetes by chronic disease score

	No antidepressant use		Antidepressant use		RRs (95% CI) for antidepressant use within strata of chronic disease score
	N with/without diabetes	RR (95% CI)	N with/without diabetes	RR (95% CI)	
Chronic disease score of 0	243/24195	1.0	153/15470	1.16 (0.95–1.42); $P=0.150$	1.16 (0.95–1.42); $P=0.150$
Chronic disease score of 1 or more	338/11260	1.55 (1.30–1.84); $P<0.001$	246/8611	2.07 (1.73–2.47); $P<0.001$	1.34 (1.13–1.58); $P=0.001$

Measure of effect modification on additive scale: $RERI$ (95% CI) = 0.36 (–0.003–0.73); $P=0.052$.
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI) = 1.15 (0.89–1.49); $P=0.282$.
RRs are adjusted for age, sex and benzodiazepine use.

- 1) There is a single reference category: excess risk can be estimated. However, stratum-specific estimates only for the exposure of interest (antidepressant use) are given in the last column
- 2) Estimates of effect modification on relative and multiplicative scale are reported
- 3) Models are adjusted for confounders of the antidepressant use – diabetes association

Knol et al. *int J Epidemiol* 202;41:514-20

Interaction

Table 4 Example—interaction between XRCC1 codon 399 genotype and dietary vitamin E intake on the risk of prostate cancer

	XRCC1 codon 399 genotype				OR (95% CI) for Arg/Arg within strata of vitamin E
	Arg/Gln + Gln/Gln		Arg/Arg		
	N cases/controls	OR (95% CI)	N cases/controls	OR (95% CI)	
High vitamin E intake	17/46	1.0	14/44	1.04 (0.42–2.60); P = 0.93	1.04 (0.42–2.60); P = 0.93
Low vitamin E intake	22/57	1.22 (0.53–2.82); P = 0.65	24/33	2.40 (1.02–5.63); P = 0.04	1.97 (0.89–4.41); P = 0.10
ORs (95% CI) for vitamin E within strata of genotype		1.22 (0.53–2.82); P = 0.65		2.30 (0.93–5.74); P = 0.07	

Measure of interaction on additive scale: $RERI$ (95% CI) = 1.14 (–0.57 to 2.85); $P=0.19$.
Measure of interaction on multiplicative scale: ratio of ORs (95% CI) = 1.89 (0.56 to 6.34); $P=0.30$.
ORs are adjusted for age, ethnicity, first-degree relative with prostate cancer, education, ever been a farmer, BMI, total energy intake, total fat intake and intake of other antioxidants.

- Stratum-specific estimates are provided for both exposure
- Models are adjusted for confounders for both exposures

$$\log(P(D = 1|X_1 = x_1, X_2 = x_2))$$

Saturated log-linear model

$$= \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$$

$$p_{11} - p_{10} - p_{01} + p_{00} = e^{\beta_0 + \beta_1 + \beta_2 + \beta_3} - e^{\beta_0 + \beta_1} - e^{\beta_0 + \beta_2} + e^{\beta_0} > 0$$

$$e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_1} - e^{\beta_2} + 1 > 0$$

$RERI > 0$

$$e^{\beta_3}(e^{\beta_2 + \beta_3} - 1) - (e^{\beta_2} - 1) > 0$$

If $\beta_1 \geq 0$ we can write

$$e^{\beta_3}(e^{\beta_2 + \beta_3} - 1) - (e^{\beta_2} - 1) > 0$$

If $\beta_3 > 0$ we can write

$$e^{\beta_3}(e^{\beta_2 + \beta_3} - 1) \geq (e^{\beta_2 + \beta_3} - 1) > (e^{\beta_2} - 1)$$

This condition is satisfied and thus there is mechanistic interaction

The same applies if $\beta_2 \geq 0$, which is always true if monotonic effects are assumed. Thus $\beta_3 > 0 \rightarrow$ implies mechanistic interaction

No monotonic effects

$$p_{11} - p_{10} - p_{01} = e^{\beta_0 + \beta_1 + \beta_2 + \beta_3} - e^{\beta_0 + \beta_1} - e^{\beta_0 + \beta_2} > 0$$

$$e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_1} - e^{\beta_2} > 0 \quad \text{RERI} > 1$$

$$(1/2)e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_1} + (1/2)e^{\beta_1 + \beta_2 + \beta_3} - e^{\beta_2} > 0 \quad \text{Can be written as}$$

$$e^{\beta_1} \{ (1/2)e^{\beta_2 + \beta_3} - 1 \} + e^{\beta_2} \{ (1/2)e^{\beta_1 + \beta_3} - 1 \} > 0. \quad \text{Or as (cond 10)}$$

Clearly if $(1/2)e^{\beta_2 + \beta_3} - 1 > 0$ and $(1/2)e^{\beta_1 + \beta_3} - 1 > 0$ then condition 10 will be satisfied. These 2 conditions we can rewrite as $e^{\beta_3} > 2e^{-\beta_2}$ and $e^{\beta_3} > 2e^{-\beta_1}$ or as $\beta_3 > \log(2) - \beta_2$ and $\beta_3 > \log(2) - \beta_1$. We have thus established the following

Thus there is mechanistic interaction if

1) $\beta_3 > 0$ and $\beta_1 \geq \log(2)$ and $\beta_2 \geq \log(2)$

or

2) $\beta_3 > \log(2)$ and $\beta_1 \geq 0$ and $\beta_2 \geq 0$