Interaction and Effect-Measure Modification II

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Learning Objectives

Last week:

- Review statistical interaction
- Describe methods to assess statistical interaction:
  1. By stratification
  2. By comparing expected and observed joint effects
  3. By graphical assessment
  4. By estimating interaction magnitude
  5. By using statistical tests of interaction

Today:

- Explain the concept of biologic interaction
  - Defined under the sufficient cause approach
  - Defined under the counterfactual approach
    - Synergy vs. parallelism
- Learn how to estimate attributable fraction and other indices
- Discuss ways of presenting the results of analyses for interaction and for effect modification
- Practice data analysis using Stata

Biological interaction, cont'ed

II. Defined under the counterfactual approach and the sufficient cause approach

- 4 exposure categories for 2 binary variables=16 possible patterns of response types (given disease or no disease)
  - 10 categories can be considered interaction (interdependence) of some type (i.e., both of the 2 exposure types have an effect) and interaction contrast not equal 0

The counterfactual approach

Counterfactual = a "would be" response (1/0) under a given exposure

Examples of counterfactuals

	A=1 B=1	A=0 B=1	A=1 B=0	A=0 B=0
Ex 1	*Y=1 observed*	*Y=1 counterfactual*	*Y=0 counterfactual*	*Y=1 counterfactual*
Ex 2	*Y=0 counterfactual*	*Y=1 observed*	*Y=1 counterfactual*	*Y=0 counterfactual*

Possible response types for binary exposure

Person TYPE	Outcome (risk) Y for exposure combination				Interaction contrast (difference in risk differences) and causal type $IC = R_{11} - R_{01} - R_{10} + R_{00}$
	X=1 Z=1	X=0 Z=1	X=1 Z=0	X=0 Z=0	
	R_{11}	R_{01}	RR_{10}	R_{00}	
1	1	1	1	1	0=DOOMED (no effect for exposure combination)
2	1	1	1	0	-1=PARALLELISM (single + joint causation), factors compete to be INUS component causes in the same sufficient cause
3	1	1	0	1	1=RPEVENTIVE ANTAGONISM (z=1 blocks x=1 effect)
4	1	1	0	0	0=Z ONLY TYPE (z=1 is causal, x=1 is ineffective)
5	1	0	1	1	1=RPEVENTIVE ANTAGONISM (x=1 blocks z=1 effect)
6	1	0	1	0	0=X ONLY TYPE (x=1 is causal, z=1 is ineffective)
7	1	0	0	1	2=RPEVENTIVE ANTAGONISM (each factor prevents development of disease when the other is absent)
8	1	0	0	0	1=CAUSAL SYNERGISM (each factor causes disease only if the other is present)
9	0	1	1	1	-1=PREVENTIVE SYNERGISM (one factor prevents development of disease if the other is present)
10	0	1	1	0	-2=CAUSAL ANTAGONISM (each factor causes disease only if the other is absent)
11	0	1	0	1	0=(x=1 is preventive, z=1 is ineffective)
12	0	1	0	0	-1=CAUSAL ANTAGONISM (x=1 blocks z=1 effect)
13	0	0	1	1	0=(z=1 is preventive, x=1 is ineffective)
14	0	0	1	0	-1=CAUSAL ANTAGONISM (z=1 blocks x=1 effect)
15	0	0	0	1	1= (single + joint prevention), compete to be INUS partners in the same sufficient cause
16	0	0	0	0	0=IMMUNE (no effect for exposure combination)

Biological interaction, cont'ed

II. Defined under the counterfactual approach

- 4 exposure categories for 2 binary variables=16 possible patterns of response types (given disease or no disease)
- 10 categories can be considered interaction (interdependence) of some type (i.e., both of the 2 exposure types have an effect) and interaction contrast not equal 0
- If it is assumed the effect is causal, **Type 8 in the counterfactual approach is equivalent to causal or biological synergy. Each exposure only causes disease if the other is present.**

Interaction contrast

- Causal additivity = no causal interaction

$R_{11} - R_{00} = (R_{10} - R_{00}) + (R_{01} - R_{00}) =$ (p6+p13-p11-p13) + (p4+p11-p11-p13) =(0+0-0-0) + (0+0-0-0)=0

- Interaction contrast=difference in risk differences

$IC = RD_{X,-} - RD_{-,Z} = (R_{11} - R_{01}) - (R_{10} - R_{00}) = (R_{11} - R_{10}) - (R_{01} - R_{00})$

$= R_{11} - R_{10} - R_{01} + R_{00} =$ (p3+p5+2p7+p8+p15) – (p2+p9+2p10+p12+p14)

Main risk factor (X)	Effect modifier (Z)	
	Yes	No
Yes	R_{11}	R_{10}
No	R_{01}	R_{00}

Necessary conditions for interaction

1. Departures from additivity can only occur when interaction causal types are present in the cohort
2. Absence of interaction does not imply absence of interaction types because sometimes different interaction types counterbalance each other's effect on the average risk
3. Definitions of response types depend on the definition of the outcome under study (if it changes, then response type can change too)

Departures from additivity

- Superadditivity: $RD_{11} > RD_{10} + RD_{01}$ – type 8 MUST be present
- Subadditivity: $RD_{11} < RD_{10} + RD_{01}$ – type 2 MUST be present
- However, presence of synergistic responders (type 8) or competitive responders (type 2) does not imply departures from additivity

- **If neither factor is ever preventive: IC = p8 –p2,**
  - i.e. synergism – parallelism = additive interaction

This is all good, but how do we know the response types?

population proportion	A=1 B=1	A=1 B=0	A=0 B=1	A=0 B=0	person type
p_{16}	0	0	0	0	"none"
p_1	1	1	1	1	"all"
p_6	1	1	0	0	"A only"
p_4	1	0	1	0	"B only"
p_8	1	0	0	0	"synergy"
=1	R_{11}	R_{10}	R_{01}	R_{00}	

Simplified assessment of synergy based on 5 response types

- **p8 = (R_{11} – R_{01}) – (R_{10} – R_{00})**
  - Effect of Z (effect modifier) when X=1 – Effect of Z when X=0
- Assumptions when only 5 types are used
  - **Effect measure is the Risk Difference, biologic interaction is then interaction for risk differences**
  - **p5 > 0, biologic interaction must be positive (although one can reparameterise the exposures X and Z to get a negative interaction)**
  - **Huge reduction of person types, from 16 to 5!**
  - **Keep in mind that this is a "biologic“ model**

Summary of R&G scheme under counterfactual theory

- The reduction from 16 person types to 5 makes it possible to get the p’s for the 5 types, by using the 4 observed probabilities, and the fact that the 4 R’s sum to 1.
- By solving the equations we get that the person type “synergy” is equal to additive interaction, with risk differences as measure of effect

Critique of R&G scheme

- Rothman and Greenland's model is simplistic.
- One reasonable person type is missing!

  p2 - Parallelism
- If A and B are both causal, then it is reasonable to think that some individuals in the population will develop the disease when exposed to only A, only B or both A and B.

Darroch, J. “Biologic Synergism and Parallelism”, AmJEpi 1997; 145:7 page 661-668

- John Darroch discusses an expansion of the ideas by Rothman and Greenland. He assumes 6 person types, including "parallelism".
- By using 6 person types he covers all the possible person types if A and B are directly causal in their effect on disease.

population proportion	A=1 B=1	A=1 B=0	A=0 B=1	A=0 B=0	person type
p_{16}	0	0	0	0	"none"
p_1	1	1	1	1	"all"
p_6	1	1	0	0	"A only"
p_4	1	0	1	0	"B only"
p_8	1	0	0	0	"synergy"
p_2	1	1	1	0	"parallelism"
=1	R_{11}	R_{10}	R_{01}	R_{00}	

Simplified assessment of synergy based on 6 response types

- **$p8 - p2 = (R_{11} - R_{01}) - (R_{10} - R_{00})$**
  - Effect of Z (effect modifier) when X=1 – Effect of Z when X=0
- This means you will not be able to specify the biologic interaction (p8) exactly from the 4 known probabilities, but you can find the boundaries.

VanderWeele 2015

Table 10-12. CONCLUSIONS ABOUT THE PRESENCE OF RESPONSE TYPES UNDER VARIOUS MONOTONICITY ASSUMPTIONS AND SUPERADDITIVITY OR SUBADDITIVITY

Assumption	Superadditivity	Subadditivity
No monotonicity assumption	3, 5, 7, 8, or 15	2, 9, 10, 12, or 14
G positive monotonic	5 or 8	2 or 14
G negative monotonic	3 or 15	9 or 12
E positive monotonic	3 or 8	2 or 12
E negative monotonic	5 or 15	9 or 14
G positive, *E* positive	8	2
G positive, *E* negative	5	14
G negative, *E* positive	3	12
G negative, *E* negative	15	9

 VanderWeele2015, Ch. 10

Summary notes on synergy and parallelism

1. **Can only be partially determined from the data at hand**
2. **Example of synergy (assuming the factors are causal): if the gene and environment factors acted together, infants would only get the congenital disorder if exposed to both gene and environment**
3. **Example of parallelism (assuming the factors are causal): infants would only get the congenital disorder if exposed to either gene or environment but would not get the congenital disorder if exposed to neither.**
4. **If synergy - parallelism or R(AB) - R(AB) - R(A) - R(B) + R is a positive number the result is consistent with the presence of more synergy than parallelism in the population studied**
   - The public health approach would be to prevent exposure to either genes or environment

Summary notes on synergy and parallelism, cont'ed

5. **Greater than an additive relationship is consistent with superadditivity and multiplicativity but inconsistent with the single hit model of disease causation**
6. **If synergy – parallelism or R(AB) - R(A) - R(B) + R is a negative number it is an indication that there is more parallelism than synergy in the population**
7. **Less than an additive relationship is consistent with subaddivitity and inconsistent with the no hit and multistage models of disease**
   - The public health approach would be to prevent exposure to both genes and environment.
8. **If there is no additive interaction there may be no synergism or the proportion of individuals for whom the exposures work synergistically may be the same for whom the exposures work in a parallel manner**

Example from Darroch 1997

Study by Hertz-Picciotto et al. *"Synergism between occupational arsenic exposure and smoking in the induction of lung cancer" Epidemiology 1992;3:23-31*

RR	B=0 arsenic=no	B=1 arsenic=yes
A=0 smoking=no	*1.0* **R_{00}**	*5.1* **R_{01}**
A=1 smoking=yes	*7.2* **R_{10}**	*20.7* **R_{11}**

Darroch vs. R&G

Synergism p_8	B only p_4	$R_{11} - R_{10}$
A only p_6	Parallelism p_2	$R_{10} - R_{00}$
$R_{11} - R_{01}$	$R_{01} - R_{00}$	$R_{11} - R_{00}$

R&G counterfactual theory:

$p8 = (R_{11} - R_{01}) - (R_{10} - R_{00})$

Darroch's model using marginals:

$p8 - p2 = (R_{11} - R_{01}) - (R_{10} - R_{00})$

$p8 = (R_{11} - R_{01}) - (R_{10} - R_{00})$

R&G counterfactual model of interaction:

$p8 = (20.7 - 5.1) - (7.2 - 1) = 9.4 > 0$ - superadditivity

$R_{00} = R$ (baseline risk) $R_{01} = 5.1\ R$

$R_{10} = 7.2\ R$ $R_{11} = 20.7\ R$

Darroch's model of interaction:

Synergism $9.4\ R < p_8 < 13.5\ R$	B only $p_4 < 4.1\ R$	$R_{11} - R_{10}$ $20.7\ R - 7.2\ R = 13.5\ R$
A only $2.1\ R < p_6 < 6.2\ R$	Parallelism $p_2 < 4.1\ R$	$R_{10} - R_{00}$ $7.2\ R - R = 6.2\ R$
$R_{11} - R_{01}$ $20.7\ R - 5.1\ R = 15.6\ R$	$R_{01} - R_{00}$ $5.1\ R - R = 4.1\ R$	$R_{11} - R_{00}$ $20.7\ R - R = 19.7\ R$

$p8 - p2 = (20.7 - 5.1) - (7.2 - 1) = 9.4$; $p8 = 9.4 + p2 = 9.4 + 4.1 = 13.5$

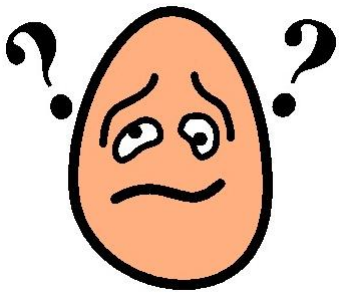
Synergism is between $9.4\ R < p_8 < 13.5\ R$

Biological interaction, cont'ed

III. Defined under an additive model with a "twist"

- Additive model with a "twist" allows the best representation of synergy
- An additive model assumes that risks add in their effects
- Positive deviations from additivity (superadditivity) indicates the presence of synergy
- The "twist" is that risks do something slightly less than add (parallelism – some individuals can develop disease from either one of the two exposures under study)
- What we see as the combined effect of two exposures reflects the balance of synergy and parallelism
- In summary, although superadditivity indicates synergy, a failure to find superadditivity does not imply the absence of synergy

My head is spinning! Please help!



IV. Assessing interaction by estimating interaction magnitude
(Estimating synergy in epi studies)

- **Problems:**
  - We generally analyze our data according to multiplicative models such as logistic regression. This practice poses a dilemma for the assessment of synergy if we think that synergy should be assessed under an additive model
  - Assessment of interaction by entering a product term into the linear or logistic regression model leads to different interpretation of the regression coefficient. In linear regression analysis the regression coefficient of the product term means departure from additivity, whereas in logistic regression (and in Cox regression) the regression coefficient of the product term estimates departure from multiplicativity
  - Biologic interaction means that two causes are both needed to cause disease; the two causes are component causes in the same causal model. Rothman has argued that when biologic interaction is examined, we should focus on interaction as departure from additivity rather than departure from multiplicativity. In etiologic epidemiologic research, we are interested in biologic interaction rather than in statistical interaction. However, by adding a product term to a logistic model, interaction is (unknowingly) estimated as departure from multiplicativity.

IV. Assessing interaction by estimating interaction magnitude
(Estimating synergy in epi studies)

- **If there is positive interaction on the multiplicative scale, there will be positive interaction on the additive scale (supermultiplicativity implies superadditivity)**
- **We can assess interaction on the additive scale from the multiplicative model by calculating:**
  - Interaction contrast (IC) and interaction contrast ratio (ICR)
  - Relative excess risk due to interaction (RERI) – for multivariate models or models with continuous exposures
  - Attributable proportion (AP)
  - Synergy index

In a 2x2 table

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

- **IC=0.33-0.17-0.10+0.10=0.16 >0 ⇨ synergy**

Dunedin Child-Development Study, Caspi et al. 2002, 2003

Estimation of IC and ICR

- **Cohort studies**
  - Intercept provides the baseline risks of disease
  - Use Interaction Contrast (IC), same as RERI
- **Case-controls studies**
  - Intercept may be biased
  - Odds for those exposed to both factors: 0.33/0.67; odds for those exposed to life events only: 0.17/0.83; odds for those with short allele only: 0.10/0.90; odds exposed to neither: 0.10/0.90
  - Additive ICR=$OR_{both/neither} - OR_{life\ events/neither} - OR_{short\ allele/neither}$ + baseline
  - Multiplicative: ICR=$OR_{both/neither}$ / [$OR_{life\ events/neither}$ * $OR_{short\ allele/neither}$]
  - ICR / $OR_{both/neither}$

4+ Stressful life events	Genotype with short allele	
	Yes	No
Yes	0.33/0.67	0.17/0.83
No	0.10/0.90	0.10/0.90

ICR = [(0.33/0.67)/(0.10/0.90)] – [(0.17/0.83)/(0.10/0.90)] –
–[(0.10/0.90)/(0.10/0.90)] + 1 = 4.4 – 1.8 – 1 + 1 = 2.6 – INDICATIONS OF POSITIVE ADDITIVE INTERACTION ON ADDITIVE SCALE (Larger than IC=0.20 estimated in a cohort study, see slide #25)

ICR = [(0.33/0.67)/(0.10/0.90)] / ([(0.17/0.83)/(0.10/0.90)] * [(0.10/0.90)/(0.10/0.90)] = 4.4 / (1.8 * 1) = 2.4 – INDICATIONS OF POSITIVE MULTIPLICATIVE INTERACTION. Different from ICR of 1.07 in the cohort study. WHY? Not a rare disease! Odds exposed to neither is 0.10 / 0.90 = 0.11. In the VanderWeele2015 tutorial (page 6), IC from a cohort study closely matches ICR from a case-control study because odds of disease with neither exposure is 0.02.

ICR / $OR_{both/neither}$ = 2.6/4.4 0.59 – the proportion of disease among those with both risk factors that is attributable to interaction.

Conclusion: 59% of the disease among those with 4 or more stressful life events and the susceptible genotype is attributable to interaction between these factors.

RG Ch 16, VanderWeele tutorial 2015

Additional indices of additive interaction

- **S, AP, Rothman's I** $S = \frac{RR_{11} - 1}{(RR_{10} - 1) + (RR_{01} - 1)}$ $AP = \frac{RR_{11} - RR_{10} - RR_{01} + 1}{RR_{11}}$

I = R11 - R01 - R10 + R00 = (R11 - R01) – (R10 - R00) = (R11 - R10) – (R01 - R00);

- **Terminology:**
  - RERI - departure from additivity of effects on a relative scale
  - ICR – could assess departure from additivity and multiplicativity using a relative scale, both for cohort and control studies

V. Assessing interaction by using statistical tests of interaction

- **Observed heterogeneity within categories of the third variable may be due to:**
  - Random variability
    - Typical scenario: no a priori subgroup analyses were planned and after null overall findings, the researcher decides to pursue subgroup analyses. Sample size inevitably decreases with such testing, making it likely that heterogeneity will be observed due to chance alone.
  - Confounding effects
    - If confounding is only present in one group of the third variable, it can explain the apparent heterogeneity of effect estimates within strata of the third variable
  - Bias
    - Differential bias across strata
  - Differential intensity of exposure
    - Apparent heterogeneity of effects could be due to differential intensity of exposure of some other variable

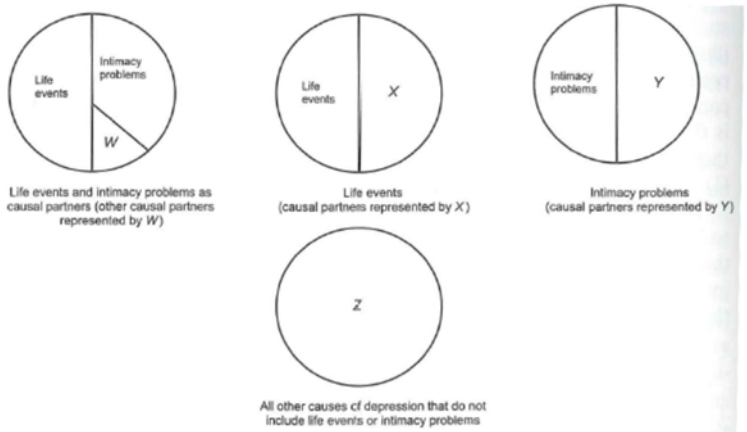
Summary

- There is a distinct difference between biological interaction and statistical effect modification
- In Epidemiology, we are interested in biological interaction on an additive scale
- Various methods exist to evaluate biological interaction and to estimate the magnitude of interaction
- Additional steps are needed to evaluate biological interaction in typical regression models

Bringing it all together:

From synergy to its mathematical representation

Causes of depression:
Theory about life events and their interaction with intimacy problems



Brown and Harris 1978

Assessing interaction between life events and intimacy problems

"Type" Person Is:	CAUSAL PARTNERS PERSON HAS	CAUSE PERSON IS SUSCEPTIBLE TO	DISEASE EXPERIENCE IF EXPOSED TO: LIFE EVENTS	INTIMACY PROBLEMS	BOTH	NEITHER
SYNERGYSTIC	W	Life events / Intimacy problems W	No disease	No disease	D+	No disease
LIFE EVENT susceptible	X	Life events X	D+	No disease	D+	No disease
INTIMACY PROBLEM susceptible	Y	Intimacy problems Y	No disease	D+	D+	No disease
DOOMED	Z	Z	D+	D+	D+	D+
IMMUNE		NONE	No disease	No disease	No disease	No disease
PARALLEL	X / Y	Life events OF Intimacy problems X / Y	D+	D+	D+	No disease

Brown and Harris 1978

Relationship between observed risk and unobserved types

Disease risk	Among those exposed to both life events and intimacy problems	Among those exposed only to life events	Among those exposed to intimacy problems	Among those exposed to neither life events nor intimacy problems
Observation	Proportion diseased among those exposed to both	Proportion diseased in those exposed only to life events	Proportion diseased in those exposed to only intimacy problems	Proportion diseased among those exposed to neither
Numeric representation	R_{12}	R_1	R_2	R
Types contributing to this risk	Synergistic, doomed, life even: susceptible, intimacy problem susceptible, parallel	Doomed, life event susceptible, parallel	Doomed, intimacy problem susceptible, parallel	Doomed

Relationship Between Observed Risk and Unobserved Types

$R_{12} - R_1 - R_2 + R =$ [Synergistic, doomed, life event susceptible, intimacy problem susceptible, parallel] − [Doomed, life event, susceptible, parallel] − [Doomed, intimacy problem susceptible, parallel] + [Doomed]

= Synergy – parallelism

Mathematical model representing conceptual model for interaction

Stressful life events	Intimacy problems	
	Yes	No
Yes	32%	10%
No	3%	1%

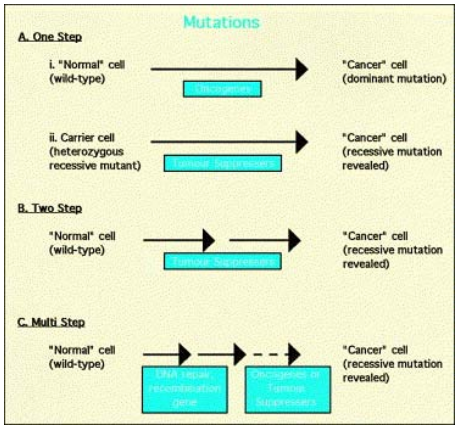
- **Synergy – parallelism = p8 – p2 = ($R_{11} - R_{01}$) – ($R_{10} - R_{00}$)**
- **Synergy – parallelism = 0.32 – 0.10 – 0.03 + 0.01 = 0.20**
- **Conclusion:**
  - Stressful life events and intimacy problems work in a synergistic manner to produce depression for at least some people
  - **The estimate of the proportion of people who developed disease because of synergy is underestimate because of parallelism**
  - Among the group with both risk factors, there may be some people for whom either risk factor alone would be sufficient to complete a sufficient cause for the disease
  - Parallel types are likely to occur when social forces, such as SES, are linked to disease through multiple pathways

Final notes on interaction

- Superadditivity implies synergy, absence of superadditivity does not imply absence of synergy
- In the presence of contravening effects (parallelism, antagonism), synergy will be difficult to detect
- Darroch's method using an "additive model with a twist," through interaction contrasts, helps to detect synergy that usual approaches based on multiplicative models would miss (they can only detect synergy that produces such large deviations from additive effects that they are also greater than multiplicativity)
- Fits into the larger picture of causal theory: identification of causal partners of the exposure under study specifies the conditions under which the exposure will and will not have an effect.

Relationship to single-hit (1), no-hit (2) or multistage (3) models of carcinogenesis

- model 1 incorporates the restriction that there is no synergism and models 2 and 3 the restriction that there is no parallelism.
- model 1 must be false if the additive interaction is positive, and models 2 and 3 must be false if the additive interaction is negative.



Attributable fraction:

Taking the estimation of interaction effects one step further

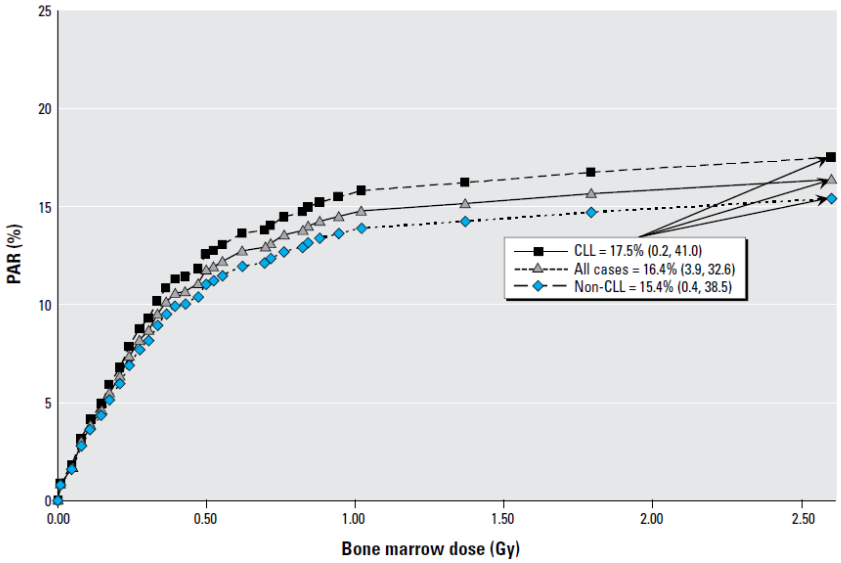
- **What proportion of cases is attributable to the interaction of two factors?**
- **AF = RERI / R11 (RGL2009)**
- **(0.32 – 0.10 – 0.03 + 0.01) / 0.32 = 0.20 / 0.32 = 62.5%**

Stressful life events	Intimacy problems	
	Yes	No
Yes	32%	10%
No	3%	1%

- **Recent update: AF = RERI / (RR11 – 1) = ? (VanderWeele and Tchetchgen Tchetchgen 2014)**

General principles of attributable fraction estimation

- **AF = (RR – 1) / RR**
- **PAR = population attributable risk**
  - PAR={ ∑k* Pk* (RRk – 1) } / (∑k* Pk* RRk)
  - where k = 0, 1, .. 100, and where Pk and RRk are the proportion and relative risk at the kth dose level
  - Confidence limits for PAR could be calculated by using the substitution method (Daly 1998)
  - Risk estimate*mean dose of kth class*weight of the kth class in the population (represented by controls)



Zablotska et al. 2013

Presentation of results

- An important assumption when generalizing results from a study is that the study population should have an "average" susceptibility to the exposure under study with regard to a given outcome
- Results cannot be "adjusted," need to present heterogeneous effect estimates
- When we select a risk factor to study, we can introduce a particular confounder; effect modifiers exist independently of any particular study design or study group

Presentation of results for effect modification

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 Step 3	153/15470 Step 1	1.16 (0.95–1.42); P 0.150	1.16 (0.95–1.42); P 0.150 Step 2
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. Present RRs, ORs or RDs with CIs for each stratum of A and X with a single reference category (possibly taken as the stratum with the lowest risk of D).
2. Present RRs, ORs or RDs with CIs for A within strata of X.
3. Present measures of effect modification on both additive (e.g. RERI) and multiplicative scales with CIs and P-values.
4. List the confounders for which the relation between A and D was adjusted. If A has more than two levels, additional columns could be added

Knol and VanderWeele 2012

Presentation of results for 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 Step 1	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	Step 2	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. Step 3
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.

1. Present RRs, ORs or RDs with CIs and P–values for each stratum of A and B with a single reference category (possibly taken as the stratum with the lowest risk of D).
2. Present RRs, ORs or RDs with CIs and P-values of the effect of A on D in strata of B and of B on D in strata of A.
3. Present measures of effect modification on both additive (e.g. RERI) and multiplicative scales with CIs and P-values.
4. List the confounders for which the relation between A and D and for which the relation between B and D were adjusted

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Summary

- There is a distinct difference between biological interaction and statistical effect modification
- In Epidemiology, we are interested in biological interaction on an additive scale
- Various methods exist to evaluate biological interaction and to estimate the magnitude of interaction
- Additional steps are needed to evaluate biological interaction in typical regression models