Chapter 11. Measuring Interactions

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Epidemiology (13)

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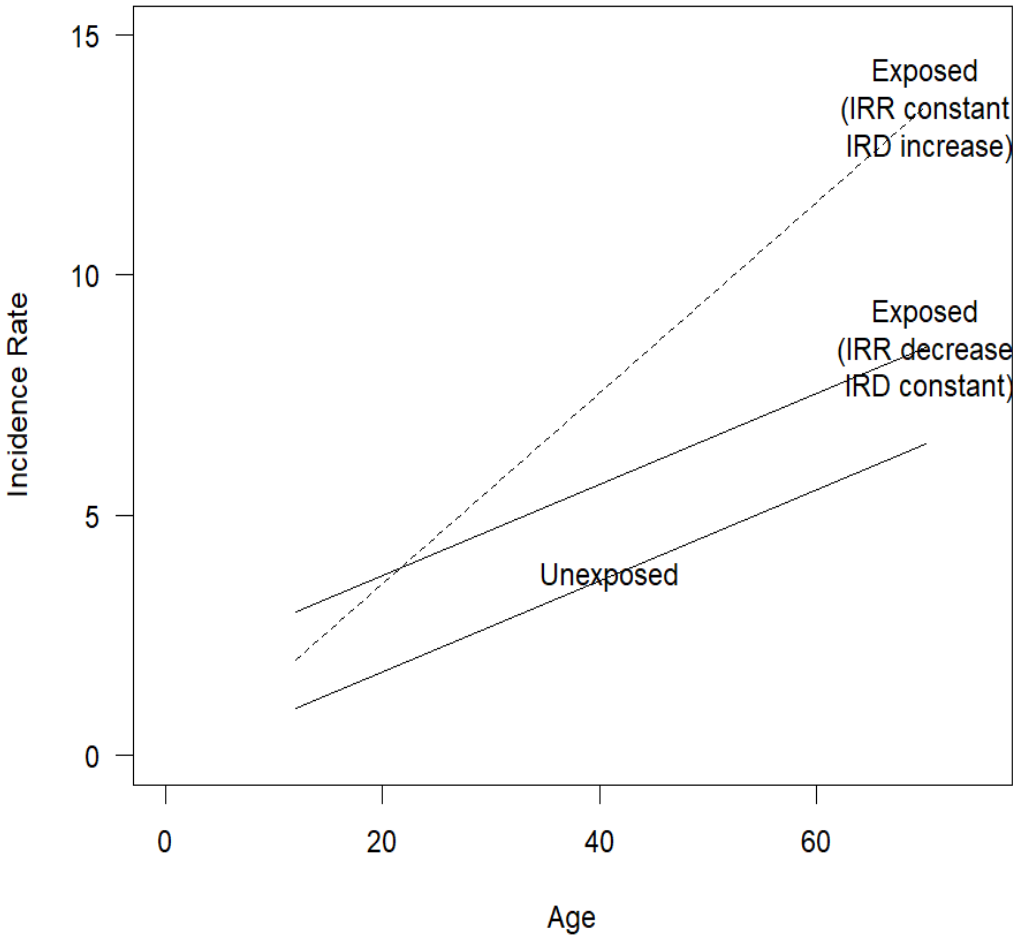
How to evaluate interaction

- Causal mechanisms are complex.
  - (eg.) Only 1 in 10 heavy smokers develops lung cancer. → Complementary causes for lung cancer acted in those 10% smokers → Those causes **biologically interacted** with smoking.
- Substantial confusion surrounding the evaluation of interaction: The term “interaction” has different mean in statistics and epidemiology.
  - Causal interaction has public health implication
    - (eg.1) Flu can lead serious complication. Highest risks are seen in youth, elderly, people with heart/lung disorders, and thus they are target of vaccination.
    - (eg.2) People got flu are sometimes treated with aspirin, which rarely causes Reyes syndrome (fatal complication, can also occur without aspirin, but more likely to occur with aspirin in youth). Knowing the interaction between the increased risk of Reyes syndrome by aspirin and age lead to discouraging aspirin use only in children.
    - (eg.3) One of the best known efforts based on causal interaction is the public health campaign against drunk driving. Driving and alcohol consumption are both risk for injury but the combined effects are more than additive.

EFFECT MEASURE MODIFICATION

- Statistics use the term “interaction” to refer to a departure from additivity on the scale used in a model.
- Different scale generates different statistical interaction.
- In epidemiology, “effect-measure modification” (NOT “effect modification”, see BOX) refers to the common situation in which a measure of effect changes over values of some other variable.
  - (eg.) Figure 11-1 shows it. If IRD is constant over age, age does not modify the IRD as a measure of effect, but IRR is large at younger ages and small at older ages (solid line of exposed). If IRR is constant over age, age does not modify IRR as a measure of effect, but IRD is small at younger ages and large at older ages (dashed line of exposed).

Figure 11-1. Age-incidence curves



Hypothetical example

- Consider Table 11-1.
  - Among nonsmokers, RD for the effect of asbestos is 5-1=4 (/100000). Among smokers, RD for the effect of asbestos is 50-10=40 (/100000). → Smoking is an effect modifier of the RD measuring the effect of asbestos.
  - However, among nonsmokers, RR for the effect of asbestos is 5/1=5 and among smokers, RR is also 50/10=5. → Smoking does not modify the RR measure of the asbestos effect.
  - Whether smoking is an effect-measure modifier of asbestos or not depends on which effect measure is used. (Symmetrically, whether asbestos exposure is an effect-measure modifier of smoking or not depends on which effect measure is used.) → The concept of effect-measure modification is ambiguous.
  - The ambiguity of the effect-measure modification concept corresponds directly to arbitrariness in the concept of statistical interaction (For statistical models, see Chapter 12).

Table 11-1. Hypothetical 1-year risk of lung cancer according to exposure to cigarette smoke and exposure to asbestos (cases per 100000)

Smoke exposure	Asbestos exposure	
	No	Yes
Nonsmokers	1	5
Smokers	10	50

- "If the statistical model is based on additivity of effects, as an ordinary linear regression model is, the data in Table 11-1 would indicate the **presence of statistical interaction**, because the separate **effects** of smoking and asbestos **are not additive** when both are present."
- If model is based on multiplication of relative effects, as in logistic regression model, the data in Table 11-1 indicate **no statistical interaction**, because relative **effects** of smoking and asbestos **are multiplicative** (50 = (5/1) x (10/1)).

Pooling and a Multiplicative Relation (box)

- Stratified analysis uses pooling to summarize an effect across strata. It assumes the effect measure is constant over strata.
- If the effect measure is RR or IRR, pooling requires the assumption that the ratio is constant over the strata. That is multiplicative relation between exposure and the stratification variable.
  - In Table 11-1, when asbestos is exposure, smoking is stratification variable. And vise versa.
  - A uniform RR across strata is equivalent to a multiplicative relation between exposure and stratification variable.
  - As explained later, a multiplicative relation is evidence of biologic interaction, because multiplicative relations are more than additive.
- Consequently, pooling over strata to estimate a uniform RR or IRR requires to assume the biologic interaction between exposure and stratification variable.

Biologic interaction

- A mechanistic interaction that either exist or does not exist.
- Model-dependent interpretation cannot correspond to the specific concept of biologic interaction among component causes.
- Statistical interaction is often referred as simply “interaction”, but it should be distinguished from biologic interaction.
- **“Biologic interaction between 2 causes occurs whenever the effect of one is partially or wholly dependent on the presence of the other”**.
  - (eg.1) **Exposure** to measles patient and lack of immunity (***susceptibility***) are both causes of measles infection and have biologic interaction. → Susceptibility is the term for the condition of already having one of two interacting causes. Similar terms are predisposition, promotion, predisposing factor, and cofactor.
  - (eg.2) Exposure to ultraviolet light and having fair skin are both causes of melanoma and have biologic interaction. → Some genetic predisposing factors like fair skin biologically interact with environmental factors.
  - (eg.3) A carrier of a gene coding for faulty receptor sites for LDL have a higher risk of CVD from a diet high in saturated fat. → Fat rich diet biological interacts with such gene for the risk of CVD.

- Definition of biologic interaction using causal pie model (sufficient/component cause model).
  - Interaction between causes A and B corresponds to the case in which A and B both played a causal role (Far left pie in Fig.11-2). U is unidentified complementary component causes.
  - Second and third pies in Fig.11-2 denote class of causal mechanisms in which either A or B plays a causal role but the other does not (no interaction between A and B)
  - Fourth class (background occurrence) consists of causal mechanisms that produce disease without either A or B playing any causal role.
- There is no way to tell, by direct observation alone, which class of causal mechanism is responsible for an individual disease occurrence.

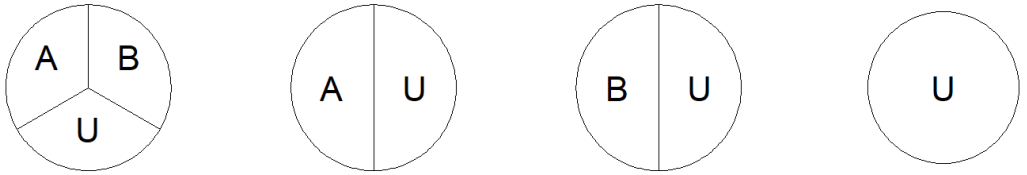


Figure 11-2. For classes of causal mechanisms.

Biologic interaction (cont'd)

- Let R_{AB} as the risk of disease among those with exposure to both A and B, R_A as the risk with exposure to A but not to B, R_B as the risk with exposure to B but not to A, R_U as the risk without exposure A nor B
- People who exposed both A and B may develop disease at the risk of R_{AB} by one of all four classes in Fig.11-2.
- $R_{AB} - R_A$ removes cases stemming from the second and fourth classes. $(R_{AB} - R_A) - R_B$ removes cases stemming from the third and fourth cases. Since the fourth cases are removed doubly, by adding R_U, **interaction risk** (the first class) to quantify the risk of disease stemming from causal mechanisms that include both factors A and B can be obtained.
  - Interaction risk = $R_{AB} - R_A - R_B + R_U$ [11-1]
  - By dividing all terms of [11-1] by R_U, Interaction risk ratio = $RR_{AB} - RR_A - RR_B + 1$ [11-1']
- When **<u>no biologic interaction</u>** (biologic independence)
  - Interaction risk = $0 = R_{AB} - R_A - R_B + R_U$
  - $R_{AB} = R_A + R_B - R_U$
  - $(R_{AB} - R_U) = (R_A - R_U) + (R_B - R_U)$ [11-2]
  - [RD between those with joint exposure to A and B and those with exposure to neither A nor B] = [Sum of RD for the effect of exposure to A in the absence of B and RD for the effect of exposure to B in the absence of A, each compared to the lack of exposure to both].
  - **<u>RD is additive under independence</u>**.
    - Additivity does not guarantee complete independence.
  - By dividing all terms of [11-2] by R_U,
    - $(RR_{AB} - 1) = (RR_A - 1) + (RR_B - 1)$ [11-3]
    - RR_{AB} denotes the risk ratio for those exposed jointly to A and B compared with those exposed to neither factor.
    - All of RRs (as ORs) in [11-3] can be obtained from a case-control study to measure the effect of A and B.

Partitioning the risk among those with joint exposure

- Using [11-2] and [11-3], under biologic independence, risk and risk ratios can be predicted from either exposure.
- From Table 11-1, risk in joint exposure is 50. Risk in exposed to smoking but not to asbestos is 10. Risk in exposed to asbestos but not to smoking is 5. Risk in exposed neither is 1.
- Using [11-1], interaction risk is
  50 – 10 – 5 + 1 = 36 (/100000).
  36/50 (=72%) of the cases among the people with joint exposure are attributable to causal mechanisms in which both factors play a causal role. Thus 72% of the cases are attributable to biologic interaction.
- Assessing biologic interaction with preventive factors (Box in p.208)
  - If both exposures are or either one of the exposures is not the cause but the preventive factor, it's possible to consider interaction in the same way, because "exposure to preventive measure" can be regarded as "the lack of exposure to cause".
- Independence is not a model (Box in p.209)
  - Some wrote relation among variables is multiplicative under certain circumstances but additive under other circumstances and insisted the usefulness of different model selection for flexibility. → It's flawed. Confusion between the goal of modeling and the goal of measuring biologic interaction.
  - The reference point for measuring biologic interaction must be the additivity of risk differences. Even if the 2 causes have multiplicative relation, the amount of biologic interaction in the data can be measured by taking the excess over additivity of effects.

Table 11-2. RR (OR) of stroke by exposure to oral contraceptives and presence or absence of hypertension.

Oral contraceptive use	Hypertension	
	No	Yes
Nonusers	1.0	6.9
Users	3.1	13.6

Data from CGSS (1975)
https://www.ncbi.nlm.nih.gov/pubmed/1172861

- Another example using Table 11-2.
  - This is case-control study, but apply same approach with Table 11-1.
  - Using [11-1'], interaction risk ratio is
    13.6 – 3.1 – 6.9 + 1.0 = 4.6.
    4.6/13.6 (34%) of the cases among the people with joint exposure are attributable to causal mechanisms in which both factors play a causal role. **Biological interaction (34%) is considerable**.
  - Attributable fraction by hypertension is (13.6 – 3.1)/13.6 and by oral contraceptive use is (13.6 – 6.9)/13.6.
- Purely statistical approach usually fit a multiplicative model and thus expected RR (OR) in joint exposure is 3.1 x 6.9 = 21.4, which is larger than 13.6. This result is misleading, in which joint exposure looks to show a smaller effect than predicted from the separate effects of the two causes.