

## Measuring Interactions

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Knowledge about causal interactions is not just of academic interest; it has important public-health implications. By identifying groups or settings in which interaction occurs, preventive actions can be more effective. Three examples illustrate how knowledge of causal interactions affects public health. First, influenza can lead to serious complications, but those at highest risk for complications are the young, the elderly, and people with heart and lung disorders. These groups can be targeted for influenza vaccination (but also see discussion of influenza vaccine efficacy in Chapter 7). Second, people who do get influenza are sometimes treated with aspirin. A rare but potentially deadly consequence of aspirin therapy is Reyes syndrome, which can also occur without aspirin use but is more likely to occur among youngsters who take aspirin for a viral illness. Rather than deter everyone from using aspirin, which is a useful drug with many indications in adults, epidemiologic knowledge of the interaction between aspirin and age has enabled preventive efforts to focus on discouraging aspirin use only in children. Third, one of the best-known efforts based on a causal interaction is the public-health campaign against drunk driving. Both driving and alcohol consumption are risk factors for injury, but their combination is a much more potent cause of injury than either alone.

## EFFECT-MEASURE MODIFICATION

In statistics, the term *interaction* is used to refer to a departure from additivity on the scale used in a statistical model. Because various statistical models use different scales, interaction does not have a consistent, universal meaning; statistical interaction in one model may be different from the interaction in another model based on a transformed scale, even with the same data. The arbitrariness of this concept of interaction has a counterpart in epidemiology in the term *effect-measure modification*, which refers to the common situation in which a measure of effect changes over values of some other variable.

Suppose, for example, that we are measuring the effect of an exposure and that the other variable is age. Consider the age-incidence curves in Figure 11-1. The rate of disease rises linearly with age among those who are unexposed. If it also rose linearly and with the same slope among those who are exposed, as depicted by the other solid line in Figure 11-1, the difference in incidence rate between exposed and unexposed people would be constant with age (ie, the two lines are parallel). In that case, we would say that age does not modify the rate difference measure of effect. Looking at the same two curves, however, we can see that the rate ratio measure of effect does change with age—that is, the ratio of the incidence rate among exposed versus unexposed people is large at younger ages and small at older ages, despite the constant rate difference. The reason that the rate ratio declines with age is the steady rise in rate among the unexposed with age.

Figure 11-1 also illustrates an alternative situation, in which the rate among the exposed increases linearly with age, so that the ratio of the rate in exposed

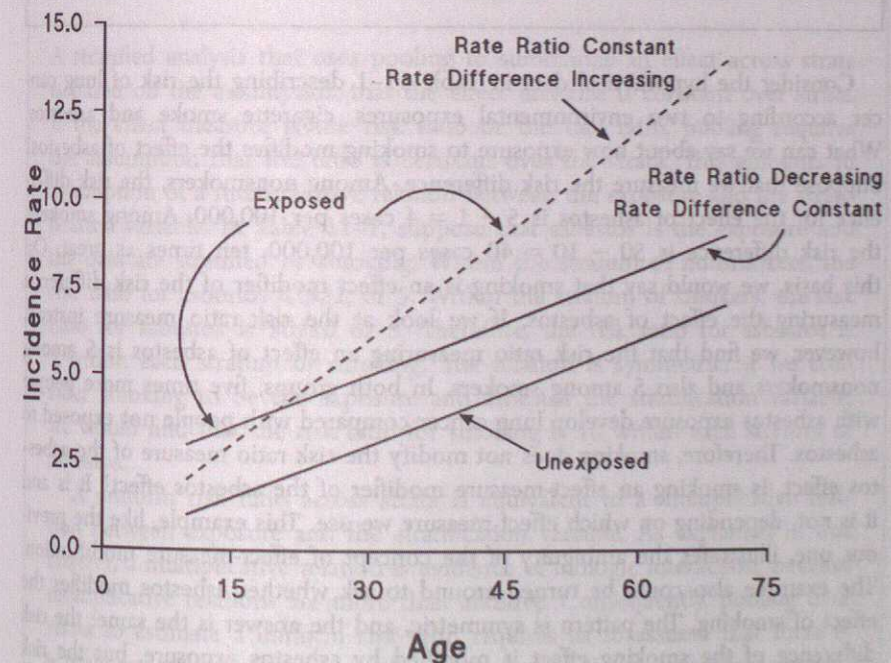


Figure 11-1 Age-incidence curves showing disease incidence increasing linearly with age for unexposed people and two possible linear relations with age for exposed people.



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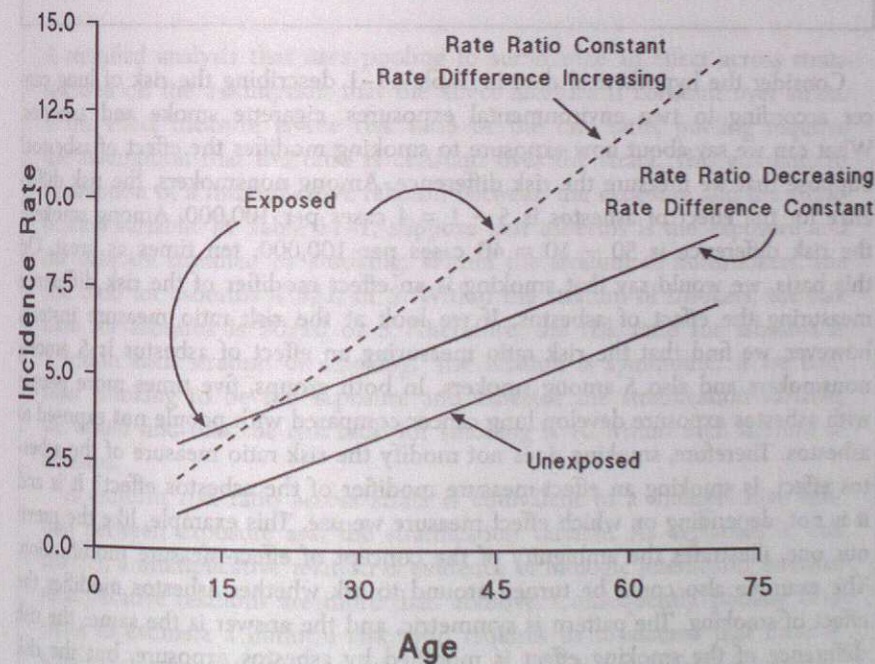


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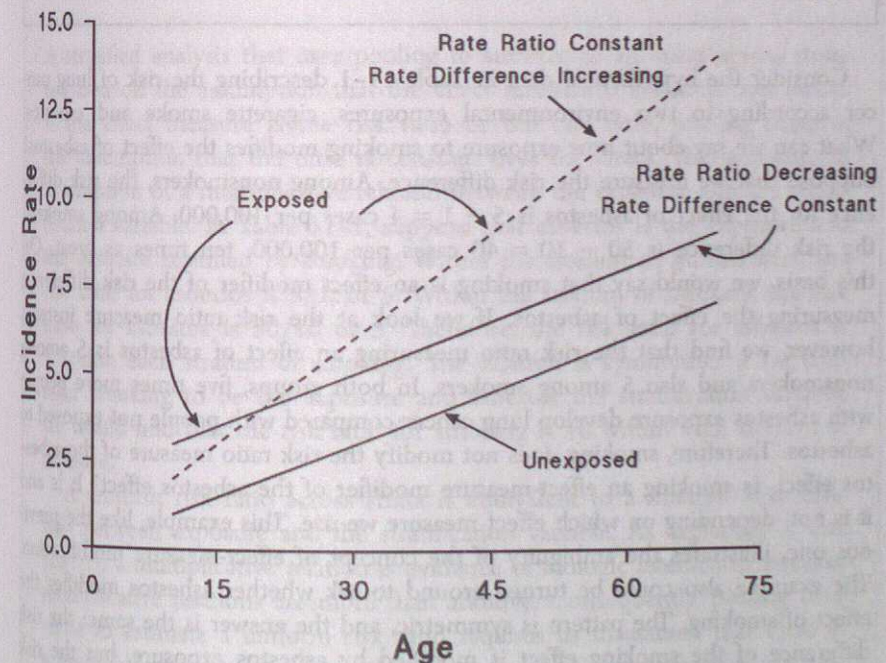


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versus unexposed people remains constant with increasing age; this alternative is depicted by the dashed line. In this situation, we would say that because the rate ratio is constant over age, age does not modify the rate ratio effect measure. The rate difference measure, however, does increase with age, as is evident from the increasing distance between the dashed line for exposed and the solid line for unexposed as age increases.

From these examples, it is easy to see that even in the unusual situation in which one of the effect measures is not modified by age, the other is likely to be modified. Therefore, we typically cannot make a blanket statement about the presence or absence of effect-measure modification, because the answer depends on which effect measure is under discussion.

#### EFFECT MODIFICATION VERSUS EFFECT-MEASURE MODIFICATION

Epidemiologists often use the term *effect modification* to mean what is described here as effect-measure modification. The addition of the word *measure* to the phrase is intended to emphasize the dependence of this phenomenon on the choice of the effect measure and its consequent ambiguity. One cannot speak in general terms about the presence or absence of effect modification, any more than one can speak in general terms about the presence or absence of clouds in the sky, without being more specific as to the details. For clouds in the sky, the details would include the geographic area, the time, and perhaps what is meant by a cloud. In the case of effect-measure modification, the details are in the choice of effect measure.

Consider the hypothetical data in Table 11-1 describing the risk of lung cancer according to two environmental exposures, cigarette smoke and asbestos. What can we say about how exposure to smoking modifies the effect of asbestos? Suppose that we measure the risk difference. Among nonsmokers, the risk difference for the effect of asbestos is  $5 - 1 = 4$  cases per 100,000. Among smokers, the risk difference is  $50 - 10 = 40$  cases per 100,000, ten times as great. On this basis, we would say that smoking is an effect modifier of the risk difference measuring the effect of asbestos. If we look at the risk ratio measure instead, however, we find that the risk ratio measuring an effect of asbestos is 5 among nonsmokers and also 5 among smokers. In both groups, five times more people with asbestos exposure develop lung cancer compared with people not exposed to asbestos. Therefore, smoking does not modify the risk ratio measure of the asbestos effect. Is smoking an effect-measure modifier of the asbestos effect? It is and it is not, depending on which effect measure we use. This example, like the previous one, illustrates the ambiguity of the concept of effect-measure modification. The example also could be turned around to ask whether asbestos modifies the effect of smoking. The pattern is symmetric, and the answer is the same: the risk difference of the smoking effect is modified by asbestos exposure, but the risk ratio is not.

The ambiguity of the concept of effect-measure modification corresponds directly to arbitrariness in the concept of *statistical interaction*. Some key statistical

Table 11-1 HYPOTHETICAL 1-YEAR  
RISK OF LUNG CANCER ACCORDING  
TO EXPOSURE TO CIGARETTE  
SMOKE AND EXPOSURE TO  
ASBESTOS (CASES PER 100,000)

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

models used in epidemiology are discussed in Chapter 12. If a 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 a statistical model is based on the multiplication of relative effects, as is the case for many popular statistical models used in epidemiologic applications (logistic regression is one example), the data in Table 11-1 would indicate no statistical interaction, because the relative effects of smoking and asbestos are multiplicative. That is, the risk ratio of smoking alone, 10, multiplied by the risk ratio of asbestos alone, 5, gives the risk ratio of 50 for those with both exposures compared with those with neither exposure.

#### POOLING AND A MULTIPLICATIVE RELATION

A stratified analysis that uses pooling to summarize an effect across strata is based on the assumption that the effect measure is constant over strata. If the effect measure is the risk ratio or the rate ratio, pooling requires the assumption that the ratio is constant over the strata. This amounts to assumption of a multiplicative relation between the exposure and the stratification variable. In Table 11-1, suppose that asbestos is the exposure and the data are stratified by smoking. Within the stratum of nonsmokers, the risk ratio for asbestos is  $5/1$ , or 5. Within the stratum of smokers, the risk ratio for asbestos is  $50/10$  or 5. Therefore, the risk ratio for asbestos is 5 within each stratum of smoking. The relation is symmetric: if we consider smoking to be the exposure and asbestos the stratification variable, we would find that the risk ratio for smoking is 10 within each stratum of asbestos.

A uniform risk ratio across strata is equivalent to a multiplicative relation between exposure and the stratification variable. As explained in this chapter, a multiplicative relation is evidence of biologic interaction, because multiplicative relations are more than additive. Consequently, pooling over strata to estimate a uniform risk ratio requires us to assume that there is a biologic interaction between the exposure and the stratification variable. This implicit assumption is not necessarily a problem with pooling, but it is a feature of stratified analysis worth keeping in mind.



These examples illustrate the arbitrariness in the terms "effect-measure modification" and "statistical interaction." Both depend on an arbitrary choice of measure or scale. In contrast, *biologic interaction* refers to a mechanistic interaction that either exists or does not exist. It is not a feature that can be turned off or on by the arbitrary choice of an effect measure or a statistical model. Statistical interaction, having an interpretation that is model dependent, cannot correspond to the specific concept of biologic interaction among component causes. For this reason, it is important not to confuse statistical with biologic interaction.<sup>1</sup> Unfortunately, when statistical interaction is discussed, it is usually described as simply "interaction" and is often confused with biologic interaction. Often, the only way to distinguish one from the other is by a careful reading of what is being reported or described. Here, we will use the terms *biologic interaction* and *statistical interaction* to keep these concepts separate.

Biologic interaction between two causes occurs whenever the effect of one is partially or wholly dependent on the presence of the other. For example, being exposed to someone with an active measles infection is a causal risk factor for getting measles, but the effect of the exposure depends on another risk factor, lack of immunity. Someone who has been vaccinated or has already had measles will not experience any effect from being exposed to someone with an active measles infection. The effect is limited to people who lack immunity. Lack of immunity is sometimes referred to as *susceptibility*, a term that in its broadest sense refers to the condition of already having one of two interacting causes and therefore being predisposed to the effect of the other. (Other terms commonly used to describe aspects of biologic interaction include *predisposition*, *promotion*, *predisposing factor*, and *cofactor*.)

Another example of biologic interaction is the development of melanoma among those with high levels of exposure to ultraviolet light who also have fair skin. Dark skin protects against the adverse effects of ultraviolet light exposure, whereas those with fair skin experience a much greater increase in risk from ultraviolet light exposure. Many environmental causes of disease interact with genetic predisposing factors. People who carry the predisposing gene constitute a group that has high susceptibility to the environmental factor. For example, people who carry a gene that codes for faulty receptor sites for low-density lipoprotein ("bad cholesterol") have a greater risk for cardiovascular disease from a diet high in saturated fat than do those who do not carry the gene. For these genetically predisposed people, the effect of the dietary exposure to saturated fat interacts with the presence of the gene to cause disease.

#### A DEFINITION OF BIOLOGIC INTERACTION

How can we derive an unambiguous definition for biologic interaction? We have already described what we mean by interaction between causes in terms of the sufficient/component cause model (ie, coparticipation in a causal mechanism of two or more component causes). Interaction between causes A and B in a given instance corresponds to the occurrence of a case of disease in which A and B both played a causal role. It means that both A and B were part of the causal mechanism for that case, or, in terms of the model, both A and B were parts

of the same causal pie. Factors A and B can both be causes of the same disease without any direct interaction, but for that to happen they would have to operate through different mechanisms and would be causes of different cases, rather than acting together as causes of the same case. In other words, suppose that A plays a role in causal mechanisms in which B does not, and vice versa. Under those circumstances, some cases would occur as a result of causal mechanisms involving A, and others would occur from causal mechanisms involving B. In this situation, both factors would act independently as causes of the disease.

With regard to the interaction of factors A and B, there are four possible classes into which all causal mechanisms of the disease fall (Fig. 11-2). The first class (far left pie diagram in Fig. 11-2) comprises those mechanisms in which A and B interact in producing the disease. The piece of the causal pie labeled U refers to the unidentified complementary component causes that also interact with A and B to produce disease. Because U could represent many different combinations of component causes that act in concert with A and B through the same mechanism, we refer to the first pie as a set, or class, of causal mechanisms. Within this class of mechanisms, every specific causal mechanism includes both A and B as component causes. If either A or B were absent in a given person, that person could not get the disease through any mechanism in this class. Cases that occur through these mechanisms would not have occurred if either A or B had not been present. We can therefore say that these cases depend on the joint presence of both A and B.

The second and third diagrams in Figure 11-2 denote classes of causal mechanisms in which either A or B plays a causal role but the other does not. Again, U refers to unidentified complementary component causes other than A or B and could represent various combinations of complementary causes, explaining why each pie is an entire class of causal mechanisms.

The fourth class of mechanisms, often referred to as the *background occurrence*, consists of causal mechanisms that produce disease without either A or B playing any causal role. The solitary U in that pie represents all combinations of causal components that can cause the disease, with the proviso that these combinations include neither A nor B. This background occurrence represents disease mechanisms that are independent of the causal action of A or B.

One way to measure the interaction between A and B would be to measure the risk of developing disease that was caused by mechanisms in which both A and B played a role—in other words, the risk of disease caused by mechanisms in the first class in Figure 11-2. Unfortunately, there is no way to tell, by direct observation alone, which class of causal mechanisms is responsible for an individual

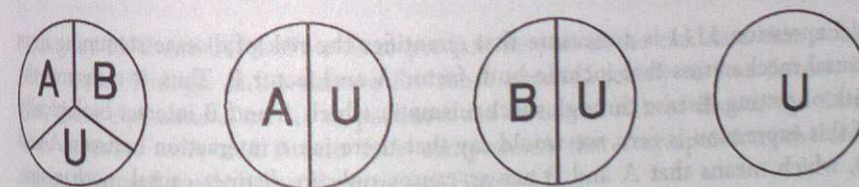


Figure 11-2 Four classes of causal mechanisms involving component causes A and B. U refers to unidentified complementary component causes other than A or B.



case. Even if a person were exposed to both A and B and developed the disease, the disease might have been caused by a causal mechanism in any of the classes in Figure 11-2, and one or both of the exposures to A and B might have been just an incidental characteristic rather than a factor that played a causal role for that case of disease. We can, however, indirectly estimate the risk of becoming a case through mechanisms involving both A and B. We start by measuring the risk among people exposed to both factor A and factor B. Cases of disease among people exposed to both A and B will include cases occurring from all four classes of mechanisms in Figure 11-2. We narrow these down to the first class of mechanisms in Figure 11-2 by subtraction. For simplicity, we assume that all risks are low, and we ignore competing risks.

Let us define  $R_{AB}$  as the risk of disease among those with exposure to both A and B. People exposed to both A and B will get disease through all four classes of mechanisms in Figure 11-2. Let us now subtract that component of the total risk for those with exposure to A and B that corresponds to the risk of getting disease from mechanisms that include factor A but not factor B. We can estimate this component by measuring the disease risk among people exposed to A but not to B. We will call this risk  $R_A$ . People exposed to A but not B cannot get disease from any causal mechanism that involves B. Therefore, the first and third classes of mechanisms in Figure 11-2 do not occur among these people. They can get disease through mechanisms that involve A but not B and through mechanisms that involve neither A nor B (the background). Therefore, of the original four classes of causal mechanisms, the expression  $R_{AB} - R_A$  removes cases stemming from two of those classes and leaves two others: the class of causal mechanisms involving biologic interaction between A and B and the class of causal mechanisms involving factor B without factor A. (For this subtraction of risks to be valid, we have to assume that there was no confounding, which we must always assume when we use the risk or rate in one group to estimate what would happen in another group under counterfactual circumstances.)

Next, to eliminate the class of mechanisms that involve B without A, so that we are left with just the class of mechanisms that include both A and B, we subtract the risk of disease among those with exposure B who lack exposure A. We will designate this risk  $R_B$ . This subtraction removes disease mechanisms that involve B without A, but it also subtracts disease mechanisms that involve neither B nor A (the background). Because the background was already subtracted once when we subtracted  $R_A$ , if we subtract it a second time with  $R_B$  we need to add it back again. We then have the following equation:

$$\text{Interaction Risk} = R_{AB} - R_A - R_B + R_U \quad [11-1]$$

Expression 11-1 is a measure that quantifies the risk of disease stemming from causal mechanisms that include both factor A and factor B. Thus, it measures the risk of getting disease through mechanisms in which A and B interact biologically. If this expression is zero, we would say that there is no interaction between A and B, which means that A and B act as causes only in distinct causal mechanisms, rather than acting together in the same mechanism. By setting Equation 11-1 equal to zero, which corresponds to no biologic interaction, we can derive an

expression that gives the relation among the risks if A and B are biologically independent:

$$\begin{aligned} \text{Interaction Risk} = 0 &= R_{AB} - R_A - R_B + R_U \\ R_{AB} &= R_A + R_B - R_U \\ (R_{AB} - R_U) &= (R_A - R_U) + (R_B - R_U) \end{aligned} \quad [11-2]$$

Equation 11-2 expresses the relation between the risks under conditions of biologic independence. This equation says that the risk difference between those with joint exposure to A and B and those with exposure to neither A nor B is equal to the sum of the risk differences for the effect of exposure to A in the absence of B and the effect of exposure to B in the absence of A, both compared with the risk among those who lack exposure to both factors (ie, the background risk). In short, the risk differences are additive under independence. (Technically, the converse is not strictly true: although independence implies additivity of risk differences, additivity does not guarantee complete independence between the two causes, because there may be two or more types of biologic interactions that cancel each other and produce, on balance, additivity. Nevertheless, when there is additivity of risk differences, the net effect of the two causes on a population is equivalent to what occurs under biologic independence. For a more detailed discussion, see Chapter 5 in *Modern Epidemiology*.<sup>2</sup>)

Because Equation 11-2 involves absolute risks, it appears to be useful only for cohort studies, in which risks can be measured. Is there an analogous expression for case-control studies, from which risk ratios can be estimated but risks and risk differences are not obtainable? To derive an equivalent expression for risk ratios, we need only divide each term in Equation 11-2 by the background risk,  $R_U$ :

$$(RR_{AB} - 1) = (RR_A - 1) + (RR_B - 1) \quad [11-3]$$

In Equation 11-3,  $RR_{AB}$  denotes the risk ratio for those exposed jointly to A and B compared with those exposed to neither factor (for whom the risk is  $R_U$ );  $RR_A$  denotes the risk ratio for those exposed to A but not B compared with  $R_U$ ; and  $RR_B$  denotes the risk ratio for those exposed to B but not A compared with  $R_U$ . All of the risk ratios in Equation 11-3 can be obtained from a case-control study that measures the effect of factors A and B.

#### PARTITIONING THE RISK AMONG THOSE WITH JOINT EXPOSURE

Equations 11-2 and 11-3 allow us to predict the risk or the risk ratio that would occur under biologic independence for those exposed jointly to two factors. In fact, these equations allow us to partition the observed risk of disease for those with exposure to A and B into four components that correspond to the four classes of causal mechanisms depicted in Figure 11-2.

As an illustration, let us partition the risk in Table 11-1 for people jointly exposed to cigarette smoke and asbestos into its four components. The value of



the risk for those with joint exposure is 50 cases per 100,000. From Table 11-1, the risk among those who are nonsmokers and are not exposed to asbestos is 1 per 100,000. This value is the background risk, which is equal to the background component in the partitioning of the risk among those with joint exposure. It means that for every 50 cases of lung cancer occurring among those who were exposed to both smoke and asbestos, an average of 1 of those cases would be expected to have occurred from background causes that involve neither smoking nor asbestos. How many cases would we expect from smoking acting in the absence of asbestos? The risk difference for smokers who are not exposed to asbestos is  $10 - 1 = 9$  cases per 100,000. Therefore, among every 50 cases with exposure to both smoking and asbestos, we would expect 9 cases to have occurred from smoking through causal mechanisms that do not involve asbestos. Similarly, from the risk difference for asbestos alone, we would expect 4 of the cases to have occurred from mechanisms involving asbestos but not smoking. These three components add to  $1 + 9 + 4 = 14$  cases.

We have so far accounted for 14 cases of every 50 that occur among those with joint exposure. If smoking and asbestos acted independently of one another, we would expect the risk among those with both exposures to be 14 per 100,000. This is the value if there is no biologic interaction. All of the excess above 14 cases in every 50 corresponds to the effect of biologic interaction between smoking and asbestos. This excess is 36 cases out of 50. Therefore, most of the risk among people with both exposures is attributable to biologic interaction between asbestos and smoking. Every 50 cases among those with both exposures can be partitioned into those resulting from the effect of background (1 case), the effect of smoking alone (9 cases), the effect of asbestos alone (4 cases), and the biologic interaction between smoking and asbestos (36 cases). Thus, the data in Table 11-1 show considerable biologic interaction; quantitatively, we can say that  $36/50$  or 72% of the cases occurring among people with joint exposure are attributable to causal mechanisms in which both factors play a causal role, which is to say that 72% of the cases are attributable to biologic interaction.

As another example, let us consider the risk ratio data in Table 11-2, which reports on the interaction between oral contraceptives and hypertension in the causation of stroke. These data come from a case-control study, but we can use the same approach as we used for the lung cancer data in Table 11-1 to evaluate interaction. The idea, once again, is to partition the effect measure for those with joint exposure into four parts: the background effect, the effects relating to each of the two exposures in the absence of the other (ie, the independent effects of the two risk factors), and the effect attributable to the biologic interaction. The risk ratio for those who are hypertensive and who also use oral contraceptives is 13.6. The background component is 1.0 out of 13.6, because the value of 1.0 for the risk ratio is by definition the value among those with neither exposure. How do we determine the effect of oral contraceptives in the absence of hypertension?

Among those without hypertension, oral contraceptive users had a risk ratio of 3.1, which means that oral contraceptive use increased the risk ratio from 1.0 to 3.1. The difference, 2.1, is the effect of oral contraceptives in the absence of hypertension. Similarly, the effect of hypertension in the absence of oral contraceptive use was  $6.9 - 1.0 = 5.9$ . That gives us three of the four components of

Table 11-2 RISK RATIO 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 Collaborative Group for the Study of Stroke in Young Women.<sup>3</sup>

the 13.6 cases: 1.0 for the background, 2.1 for oral contraceptives alone, and 5.9 for hypertension alone. The remainder, 4.6 cases, represents the part of the risk ratio that is attributable to the biologic interaction between oral contraceptive use and hypertension in the causation of stroke. We can describe the amount of biologic interaction by estimating the proportion of stroke cases, among women with hypertension who also use oral contraceptives, that is attributable to the biologic interaction of these two causes. This proportion is  $4.6/13.6 = 34\%$ . The proportion would be zero if the two causes were biologically independent; the fact that about one third of all cases result from biologic interaction between the two causes indicates that the interaction is considerable.

The data in Table 11-2 provide an interesting contrast between the evaluation of biologic interaction and that of statistical interaction. A purely statistical approach to these case-control data would ordinarily fit a multiplicative model to the data, because such models are typically used for the analysis of case-control data (see Chapter 12). Using such a model, we would find that there is a statistical interaction in the data in Table 11-2, but it goes in the opposite direction to the biologic interaction that we have just described. A multiplicative model would predict a value of the risk ratio for women who use oral contraceptives and are hypertensive by multiplying the product of the individual risk ratios for each risk factor alone. The predicted risk ratio for joint exposure in this case would be  $3.1 \times 6.9 = 21.4$ , whereas the observed risk ratio for the group with joint exposure was 13.6. Therefore, evaluation of statistical interaction based on a multiplicative model indicates that those with joint exposure exhibit a smaller effect than would be predicted from the separate effects of the two causes. This conclusion is strikingly different from the interpretation that emerges from an evaluation of biologic interaction, as previously shown.

The evaluation of statistical interaction means only that the effect in those with joint exposure is less than multiplicative; it has no biologic implication. The data in this example demonstrate how misleading it can be to examine statistical interaction when the interest is in the biologic interaction between two causes. Use of multiplicative models as the baseline from which to measure (statistical) interaction will lead to an estimate of interaction that is smaller than an evaluation based on departures from additivity of risk differences. In the worst-case scenario, such as in this example of stroke, the two approaches can be so different that they point in opposite directions.



### ASSESSING BIOLOGIC INTERACTION WITH PREVENTIVE FACTORS

The approach to measuring biologic interaction described in this chapter involves partitioning the cases that have simultaneous exposure to two factors into four subsets, according to the types of causal mechanisms involved. The method assumes that both factors are causes, rather than preventives. If both factors are preventives, or if one is a cause and the other is a preventive, the assessment can be more complicated. It is possible to avoid the complication of preventive factors, however, if one chooses the high-risk category of both factors to be the "exposed" category for that factor, making the group with the lowest risk, considering the combination of the two risk factors, the referent category for comparisons.<sup>4</sup> This technique changes a preventive factor into a causal factor by considering lack of the preventive to be the cause. For example, suppose that a vaccine prevents disease. We could say that being unvaccinated is a cause of disease. Similarly, if regular exercise reduces the risk of cardiovascular disease, we could just as well say that the absence of regular exercise increases the risk. By defining the exposure category so that each factor is viewed as a cause of disease, rather than a preventive, one can avoid the problem of dealing with preventive factors or a combination of causes and preventives in assessing biologic interaction.

Why is it that biologic interaction should be evaluated as departures from additivity of effect? Perhaps the easiest way to understand the connection between additivity and biologic independence is to reflect on the derivation of Equation 11-2, which establishes additivity as the definition of biologic independence. This derivation depends on the concept that we can partition the cases occurring among those with joint exposure to two factors into the four causal subsets depicted in Figure 11-2. Partitioning of a set of objects implies classifying them into subsets that are mutually exclusive and collectively exhaustive, and this is the case for the subsets in Figure 11-2. This partitioning process would not make much sense if one were to invoke scale transformations first. For example, you can partition a collection of colored marbles into subsets by color or by size, but it makes less sense to consider partitioning the logarithm of the number of marbles into equivalent subsets. Multiplicative models typically involve logarithmic transformations of the original scale for which partitioning into the four biologically distinct causal subsets is sensible. It is because the partitioning into subsets can be easily understood only on the original scale in which the cases are enumerated that the definition of biologic interaction is linked logically to that original scale. Because of this linkage, biologic independence is inherently linked to the additivity of risk differences. A more thorough discussion of this topic is given in Chapter 5 of *Modern Epidemiology*.<sup>2</sup>

Although multivariable modeling is not discussed until the next chapter, it is worth noting here that most of the multivariable models in common use for epidemiologic data employ logarithmic transformations. As a result, attempting to evaluate interaction from these models using the conventional statistical

### INDEPENDENCE IS NOT A MODEL

Some writers have pointed out that under certain circumstances we should expect to see variables that have a multiplicative relation, and under other circumstances we should expect to see an additive relation. They have used this observation to argue in favor of flexibility for choosing different types of models in epidemiologic analysis. The argument is flawed, however, if it is used to suggest that we should be flexible about which model to use as a starting point for measuring interaction. The main problem is confusion between the goal of modeling, which is to find a succinct mathematical expression to explain the patterns in the data, and the goal of measuring biologic interaction, which requires that we know the reference point from which we are measuring the interaction. The reference point for measuring biologic interaction is additivity of risk differences, as has been shown in this chapter. Taking this reference point as the definition of biological independence is not the same thing as applying an additive model; in fact, it is not modeling at all.

It may be that two causes have a multiplicative relation, as they do in Table 11-1. Nevertheless, even then, the amount of biologic interaction in the data is measured by taking the excess over additivity of effects. Doing so does not amount to the application of an additive model, or of any model, but rather the application of a specific definition of biologic independence. It is important to avoid confusion between modeling, on the one hand, and defining the relation specified by biologic independence, on the other hand. We can be flexible in modeling, but there is less room for arbitrariness when defining biologic independence. In short, evaluating interaction is not the same as choosing a statistical model.

approaches (ie, inclusion of "product terms" in the model) amounts to the evaluation of departures from a multiplicative model rather than departures from additivity. Therefore, statistical evaluation of interaction using these models will not yield an appropriate assessment of biologic interaction. It is possible, however, to use multivariable models to assess biologic interaction appropriately; in fact, it is straightforward. The method for doing so is given in the next chapter.

### QUESTIONS

1. Explain why the mere observation that not every cigarette smoker gets lung cancer implies that cigarette smoking interacts with other factors in causing lung cancer.
2. From the data in Table 11-2, estimate the proportion of stroke cases among hypertensive women who use oral contraceptives that is attributable to the causal role of oral contraceptives.



3. In an analysis of the effect of oral contraceptives on stroke based on the data in Table 11-2, suppose that you were interested in the oral-contraceptive effect and wished only to control for possible confounding by hypertension using stratification. What would be the stratum-specific risk ratio estimates for oral contraceptive use for the two strata of hypertension? In an ordinary stratified analysis, why is there a separate referent category in each stratum?

4. Show that if there is an excess over a multiplicative effect among those with joint exposure to two causes, there will also be an excess over an additive effect.

5. The investigators of the study described in Table 11-2 claimed that women who faced increased risk from one risk factor ought to avoid additional risk from another risk factor, regardless of whether the two factors interacted in the causation of the disease. Does this suggestion make sense? What would it imply about seat belt use for women who take oral contraceptives?

6. List reasons why the study of biologic interaction is more difficult than the study of the effects of single factors.

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## Using Regression Models in Epidemiologic Analysis

The straight line depicted in Figure 12-1 is an example of a simple mathematical model. It is a model because we use the mathematical equation for the straight line that is fitted to the data as a way of describing the relation between the two variables in the graph, in this case cigarette smoking and laryngeal cancer mortality. Models in epidemiology are used for various purposes, the two primary ones being to make predictions and to control for confounding. Prediction models are used to estimate risk (or other epidemiologic measures) based on information from risk predictors. For example, an equation can be used to estimate a person's risk of heart attack during a 10-year period based on information about the person's age, sex, family history, blood pressure, smoking history, weight, height, exercise habits, and medical history. Values for each of these predictors could be inserted into an equation that predicts the risk of heart attack from the combination of risk factors. The model must have terms in it for all the risk factors listed.

In contrast to the goal of risk prediction for specific people, much of epidemiologic research is aimed at learning about the causal role of specific factors for disease. In causal research, regression models are used to evaluate the causal role of one or more factors while simultaneously controlling for possible confounding effects of other factors. Because this use of multivariable regression models differs from the use of models to obtain estimates of risk for people, there are different considerations that apply to the construction of multivariable models for causal research. Unfortunately, many courses in statistics do not distinguish between the use of regression models for prediction of individual risk and the use of such models for causal inference.

The data in Figure 12-1 illustrate an almost perfect linear relation between the number of cigarettes smoked per day and the age-standardized mortality rate of laryngeal cancer. Seldom do epidemiologic data conform to such a striking linear pattern. The line drawn through the data points is a *regression line*, meaning that