16

Association and Causation

Objectives Covered

41. Illustrate with one example the concept of multifactorial causation of disease.
42. Define the following types of association:
    a. Artifactual
    b. Noncausal
    c. Causal
43. Distinguish between association and causation, and list five criteria that support a causal inference.

Study Notes

Epidemiologic studies yield statistical associations between a disease and exposure. This is only the first step. We must interpret the meaning of these relationships. An association may be artifactual, noncausal, or causal.

An artifactual or spurious association may arise because of bias in the study. Sources of bias are discussed in Chapter 12. Noncausal associations occur in two ways:

1. The disease may cause the exposure (rather than the exposure causing the disease).
2. The disease and the exposure are both associated with a third (confounding) factor, *X,* known or unknown (see Figure 16–1). Here, in measuring exposure we are inadvertently measuring *X.*

An example of the second type of noncausal association follows. A positive statistical association between coronary heart disease (CHD) mortality rates and coffee drinking habits has been demonstrated. Let us assume the results shown in Table 16–1.

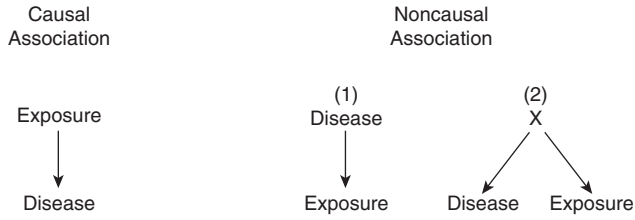

Figure 16–1 Causal and Noncausal Associations

However, it has been shown that people who drink coffee also tend to be cigarette smokers, and cigarette smoking is strongly associated with CHD mortality, as shown in Table 16–2.

Thus, to isolate the effect of coffee drinking, we cross-classify CHD mortality rates according to both variables (Table 16–3). Examination of Table 16–3 reveals that when cigarette consumption is held constant, the effect of coffee drinking disappears. Thus, the association between coffee drinking and CHD mortality is noncausal, mediated by the confounding factor of cigarette smoking (Figure 16–2). This means that if coffee drinking is varied independently of cigarette consumption, CHD mortality rates are unchanged.

Table 16–1

Coffee Consumption (Cups per Day)	*CHD Mortality in Males Aged 55–64 (Deaths per 1,000 per Year)*
0	6
1–5	8
6+	12

Table 16–2

Cigarette Consumption (Packs per Day)	*CHD Mortality in Males Aged 55–64 (Deaths per 1,000 per Year)*
0	4
1–2	10
3+	15

Table 16–3

CHD Mortality Rates

Coffee (Cups per Day)	*Cigarettes (Packs per Day)*			
	0	*1–2*	*3+*	*All*
0	4	9	15	6
1–5	6	10	13	8
6+	5	9	16	12
All	4	10	15	

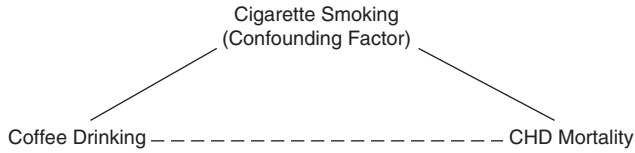

Figure 16–2 Noncausal Association between Coffee Drinking and CHD Mortality

Multiple Causation

When an outcome is affected by multiple variables, in order to examine the influence of a single one, it is necessary to adjust for the effects of the others. An earlier example is the use of age adjustment to control for the effects of age on mortality. A simple technique for isolating a specific effect due to one variable is to examine the outcome rates, at several levels of this variable, while holding the other variables constant. This technique is cross-classification. A sophisticated approach involves the use of multiple regression analysis to measure the effect of the relative contribution of each of a series of variables on an outcome.

Medicine offers numerous examples of multiple causation. Maternal mortality, for example, is affected positively by both age and parity (number of children born). It is necessary to study women of certain parity, for example, 1, 2–3, 4–5, and 6+, and in each of these four groups examine the relationship between age and maternal mortality. The result will be that the age effect persists in all parity groups, and the effect is very marked. If women in age groups < 20, 20–29, 30–39, and 40+ are classified according to parity within each of the age groups, it will be found that

increasing parity is associated with a small increase in maternal mortality, but not nearly as marked an effect as that of age.

Causal Association

Medicine is concerned with limiting or preventing disease. The search for etiology is pursued in the hope that, once the cause of a disease is found, prevention will follow. Causality is assumed when one factor is shown to contribute to the development of disease and its removal is shown to reduce the frequency of disease. This concept of causality is different from that applied in law or philosophy. In prevention, it is sufficient to identify an exposure without necessarily identifying the ultimate cause of the disease. For example, cigarette smoke has been identified as the contaminated substance that is associated with increased rates of lung and other cancers as well as heart and respiratory diseases. It is unnecessary to identify precisely which component in the smoke is the prime offender before instituting preventive measures.

Establishing Causation

Statistical methods alone cannot establish proof of a causal relationship in an association. Interpretation of such an association must be conducted in a systematic manner (Figure 16–3).

The advisory committee to the Surgeon General of the Public Health Service (Advisory Committee, 1964) defined five criteria that should be fulfilled to estab-

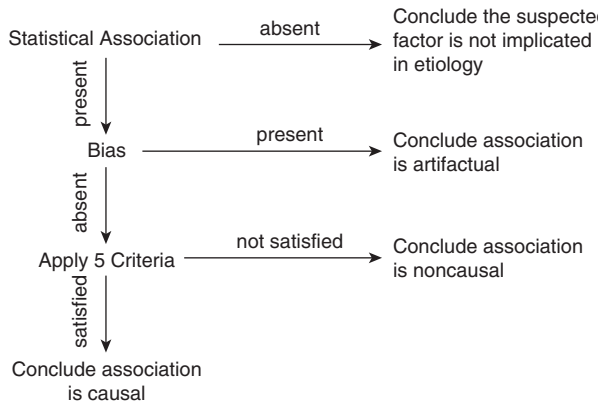

Figure 16–3 Interpretation of Results of an Epidemiological Study

lish a causal relationship. These five criteria have been generally adopted as a test of causation. They are

1. Consistency of the association
2. Strength of the association
3. Specificity of the association
4. Temporal relationship of the association
5. Coherence of the association

The definitions are summarized below:

1. Consistency means that different studies resulted in the same association, despite the fact that they employed different designs and were conducted on different populations, sometimes in different countries.
2. Strength refers to the size of the relative risk found. The greater the relative risk, the more convincing it is that the association is causal. Furthermore, if a dose-response gradient can be demonstrated, the likelihood that the exposure is causal increases. Such dose-response gradients may be recorded as the degree (e.g., the number of cigarettes smoked daily) or duration of exposure (e.g., the length of time oral contraceptives have been used).
3. Specificity measures the degree to which one particular exposure produces one specific disease. If the biological response to the exposure is variable, it is less likely to be causal.
4. Temporal relationship means exposure to the factor must precede development of the disease.
5. Coherence means biological plausibility, which may have been established in animal models.

The five criteria quoted above are the best guide to etiology in the absence of a controlled experiment, but they cannot be considered to be a substitute for the latter.

Propensity Scoring

A randomized clinical trial (Chapter 14) provides the strongest evidence of causation between an intervention and a health outcome. However, it is not always possible to implement such a trial and when an observational design must be used, propensity scoring represents a way to strengthen inferences (Chapters 12 and 13).

Random allocation of participants to intervention and control groups confers underlying similarity to the groups, thereby eliminating confounding bias. Propensity scoring is used in observational studies in an attempt to duplicate this feature of randomized trials. In some observational studies, the aim is to examine the effect of an intervention (bypass surgery, for example) while in others the effect to be examined relates to an exposure of some kind (workplace asbestos, for example). Below we shall use the term *intervention* to cover both cases.

The propensity score is the conditional probability that an individual belongs to the intervention group based on measured characteristics of that individual. Propensity scoring is implemented and used as follows:

1. A logistic equation is obtained that predicts membership in the intervention group from subject characteristics (such as age, for example).
2. The equation is applied to the characteristics of each subject to obtain their probability, or their propensity, of belonging to the intervention group.
3. All the subjects are then placed in strata according to their propensity scores, and comparisons between the intervention and control groups are made within strata of similar propensity.

It is important to recognize that, while a randomized trial provides similarity on all subject characteristics, those that are measured and those that are not, the propensity scoring method can only assure similarity regarding measured characteristics.

Exercises

1. Tables 16–4, 16–5, and 16–6 give the results of a study of the factors associated with response to a cervical cancer screening program. From these data it would be correct to infer that
   a. Married women respond better.
   b. No inferences can be drawn from these tables because the marital status of high and low social class people is not shown.

Table 16–4 Response to Program by Social Class

Social Class	*Percent Population Responding*
High social class	75
Low social class	46
All social classes	53

Table 16–5 Response to Program by Marital Status

Marital Status	*Percent Population Responding*
Married	82
Single	68
Widowed and divorced	43
All marital status	53

Table 16–6 Percent of Persons in Each Subgroup (Social Class by Marital Status) Responding to Program

Social Class	*Married*	*Single*	*Widowed and/or Divorced*	*All Marital Status*
High social class	83	67	43	75
Low social class	81	69	43	46
All social classes	82	68	43	53

c. Married people have a higher response rate than do the single or widowed because more of them are in a high social class.

d. No inference can be drawn from these tables because it is not known if this is a cohort or case-control study.

2. Table 16–7 shows the data obtained in a cross-sectional study of obesity and blood pressure.

Table 16–7 Relationship of Obesity to Level of Blood Pressure (Expressed as Numbers of People)

	Low Blood Pressure	*Intermediate Blood Pressure*	*High Blood Pressure*	*Total*
Obese	50	50	100	200
Normal weight	170	30	100	300
Thin (nonobese)	380	20	100	500
Total	600	100	300	1,000

From these data, which of the following conclusions may be correct:

a. 50/100 = 50% of those with intermediate blood pressure are obese.

b. 100/1,000 = 10% of those with high blood pressure are obese.

c. 50/200 = 25% of the obese have low blood pressure.

d. 100/500 = 20% of those with high blood pressure are thin.

3. The association between cigarette smoking and lung cancer has been subjected to considerable scrutiny. Which of the following statements both strengthen the association between cigarette smoking and lung cancer and move the evidence toward the direction of a causal relationship?

a. The risk of lung cancer increases as the daily consumption of cigarettes increases and/or as the duration of smoking lengthens.

b. Ex-smokers have lung cancer incidence rates intermediate between those of nonsmokers and current smokers.

   c. **Animal experiments have shown an increased incidence of precancerous lesions following tobacco smoke inhalation.**
   d. **Prospective studies agree with retrospective studies about the presence and direction of the association.**
4. **Retrospective studies have shown a higher level of stress reported by survivors than reported by controls in the year prior to a heart attack. Can it be concluded from this study that stress causes heart attacks?**
5. **Cross-sectional studies (surveys) reveal that a higher proportion of Arizona residents have respiratory disease than residents of other states. Can it be concluded from this that living in Arizona causes respiratory disease?**
6. **A study of stillbirths and congenital malformations revealed that a higher proportion of mothers of such children had taken steroids during pregnancy than a control group of mothers of normal children. From this information, may we conclude that taking steroids during pregnancy causes stillbirths and congenital malformations?**

Reference

Advisory Committee to the Surgeon General of the Public Health Service. (1964). *Smoking and health* (pp. 182–189). P.H.S. Publication No. 1103. Washington, DC: Public Health Service.

Recommended Readings

Gordis, L. (2008). *Epidemiology* (4th ed.). Philadelphia: W. B. Saunders. Chapter 13 discusses association and causation and the evidence that can be used to support a causal argument.

Hennekens, C. H., & Buring, J. E. (1987). *Epidemiology in medicine.* S. L. Mayrent (Ed.). Boston, Little, Brown, & Co. Chapter 8 provides an overview of association and causation with an excellent example using smoking and lung cancer.

Susser, M. (1977). *Causal thinking in the health sciences: Concepts and strategies in epidemiology.* New York: Oxford University Press. The entire book is devoted to the concept of causality and the principles of establishing cause in epidemiological investigations.