8 Designing an Observational Study: Cross-sectional and Case-control Studies

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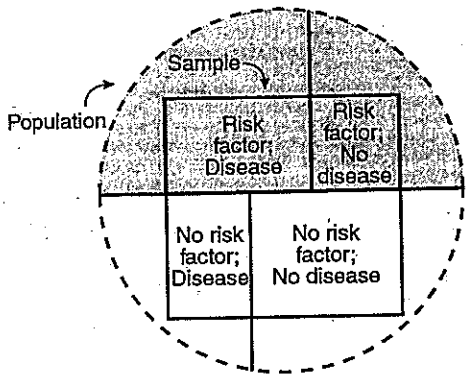
Chapter 7 dealt with cohort studies, in which the sequence of the measurements is the same as the chronology of cause and effect: first the predictor, then (after an interval of follow-up) the outcome. In this chapter we turn to two kinds of observational studies in which causal inference is not guided by this logical time sequence.

In a **cross-sectional** study, the investigator makes all of her measurements on a single occasion. She draws a sample from the population and looks at distributions of variables within that sample; she may then infer cause and effect from associations between variables she decides (using information from various sources) to designate as predictor and outcome. In a **case-control** study, the investigator works backward. She begins by choosing one sample from a population of patients with the outcome (the cases) and another from a population without it (the controls); then she compares the levels of the predictor variables in the two samples to see which ones are associated with the outcome.

■ CROSS-SECTIONAL STUDIES

Structure

The structure of a cross-sectional study is similar to that of a cohort study except that all the measurements are made at once, with no follow-up period (Fig. 8.1). Cross-sectional designs are very well suited to the goal of describing variables and their distribution patterns. In the National Health and Nutrition Examination Survey (NHANES), for example, a sample designed to represent the U.S. population is interviewed and examined. (Search for *NHANES* on the Web.) NHANES surveys have been carried out periodically, and a NHANES follow-up (cohort) study has been added to the original cross-sectional design. But each cross-sectional study is a major source of information about the health and habits of the U.S. population in the year it is carried out, providing estimates of such things as the prevalence of smoking in various demographic groups.



■ **FIGURE 8.1**

In a cross-sectional study, the investigator: (a) selects a sample from the population, and (b) measures predictor and outcome variables (e.g., presence or absence of a risk factor and disease).

Cross-sectional studies can also be used for examining associations, although the choice of which variables to label as predictors and which as outcomes depends on the cause-and-effect hypotheses of the investigator rather than on the study design. This choice is easy for constitutional factors such as age and race; these cannot usually be altered by other variables and therefore are predictors. For most variables, however, the choice is more difficult. For example, a cross-sectional finding in NHANES III is an association between childhood obesity and hours spent watching television (1,2). Is this because television viewing makes children obese or because obese children like to watch TV?

Example 8.1. Cross-Sectional Study

The research questions are, "What is the prevalence of chlamydia infection in women attending sexually transmitted disease (STD) clinics?" and, "Is it associated with the use of oral contraceptives?" To answer these questions in a cross-sectional study the investigator might

1. Select a sample of 100 women attending an STD clinic.
2. Measure the predictor and outcome variables by taking a history of oral contraceptive use and sending a cervical swab to the lab for chlamydia culture.

Note that there are several time elements in this study: The predictor variable addresses the use of oral contraceptives over the past year; the outcome variable is not available until several days later; and the investigator takes 6 months to examine all the women. The study is still cross-sectional, however, because the investigator makes all the measurements for each subject on a single occasion.

Suppose the findings are that 20 of the women report taking oral contraceptives and that four (20%) of these women have positive cultures, compared with eight of the 80 women (10%) not taking oral contraceptives. Then the overall prevalence of chlamydia infection in this sample of STD clinic attendees (who may not represent the general population) is 12 in 100 (12%) and there is an association between oral contraceptive use and chlamydia that has a relative prevalence of 20%/10% = 2.0. (See Appendix 8.A for the calculation.)

■ **TABLE 8.1**
Statistics for Expressing Disease Frequency in Observational Studies

Type of Study	Statistic	Definition
Cross-sectional	Prevalence	$\frac{\text{Number of people who } \textit{have} \text{ the disease at one point in time}}{\text{Number of people at risk at that point}}$
Cohort	Incidence	$\frac{\text{Number who } \textit{get} \text{ disease over a period of time}}{\text{Number of people at risk during that period}}$

Example 8.1 reveals an important descriptive statistic obtained from cross-sectional studies: prevalence. **Prevalence** is the proportion of the population who *have* a disease or condition at *one point in time* and is distinguished from **incidence** (the statistic obtained from a cohort study), which is the proportion who *get it over a period of time* (Table 8.1). Prevalence and incidence can also apply to variables other than diseases, so that prevalence of smoking, recent condom use, or any other attribute can be estimated. Prevalence is useful to the health planner who wants to know how many people have certain diseases so that she can allocate enough resources to care for them, and it is useful to the clinician who must estimate the likelihood that the patient sitting in her office has a particular disease.

Example 8.1 also gives an example of an analytic statistic obtained from cross-sectional studies, the **relative prevalence.** This is the ratio of the prevalence of an outcome in subjects classified by their level of a predictor variable, the cross-sectional analog of relative risk.

Strengths and Weaknesses of Cross-Sectional Studies

A major strength of cross-sectional studies over cohort studies (and experiments) is that there is no waiting for the outcome to occur. This makes them fast and inexpensive, and it means that there is no loss to follow-up. A cross-sectional study can be included as the first step in a cohort study or experiment at little or no added cost. The results define the demographic and clinical characteristics of the study group at baseline and can sometimes reveal cross-sectional associations of interest. The cross-sectional design is the only one that gives the prevalence of a disease or risk factor.

Cross-sectional studies are convenient for examining **networks of causal links.** For example, the investigator in Example 8.1 could examine age as a predictor of the oral contraceptive use and then examine oral contraceptive use as a predictor of chlamydia infection.

A weakness of cross-sectional studies is the difficulty of establishing causal relationships from data collected in a cross-sectional time frame. Cross-sectional studies are also impractical for the study of rare diseases if the design involves collecting data on a sample of individuals from the general population. A cross-sectional study of stomach cancer in a general population of 45- to 59-year-old men, for example, would need about 10,000 subjects to find just one case.

Cross-sectional studies can be done on rare diseases if the sample is drawn from a population of diseased patients rather than from the general population. A case series of this sort is better suited to describing the characteristics of

the disease than to analyzing differences between these patients and healthy people, although informal comparisons with prior experience can sometimes identify very strong risk factors. Of the first 1,000 patients with AIDS, for example, 727 were homosexual or bisexual males and 236 were injecting drug users (3). It did not require a formal control group to conclude that these groups were at increased risk. Furthermore, within a sample of patients with a disease there may be associations of interest (e.g., the higher risk of Kaposi's sarcoma among AIDS patients who were homosexual than among those who were injecting drug users).

The fact that cross-sectional studies can only measure prevalence and not incidence limits the information they can produce on prognosis, natural history, and disease causation. To show causation, investigators need to demonstrate that the incidence of disease differs in those exposed to a risk factor. But cross-sectional studies can only show effects on prevalence, which is the product of disease incidence and disease duration. A factor that is associated with prevalence of disease may be a cause of the disease but could also be associated with duration of the disease, by affecting the course of the disease. For example, the prevalence of severe depression is affected not just by its incidence, but by the suicide rate and the responsiveness to medication of those affected.

Serial Surveys

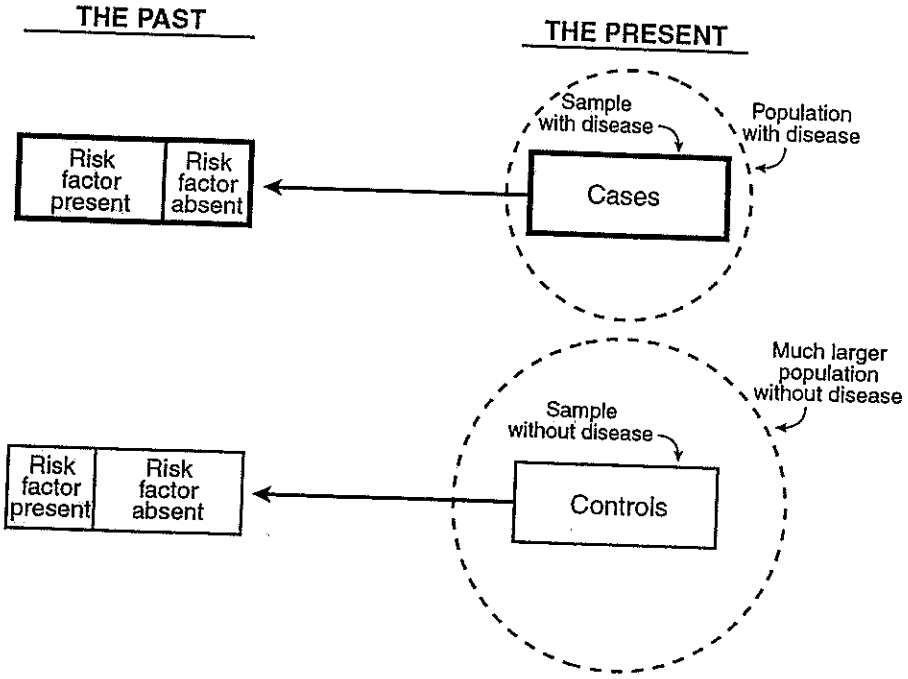
A series of cross-sectional studies of a single population observed at several points in time is sometimes used to draw inferences about changing patterns over time. A good example is the use of census data to characterize changes in the age structure of the U.S. population from one decade to the next. This is not a cohort design because it does not follow a single group of people over time; there are changes in the population through birth, death, and migration into and out of the United States.

The serial survey design is also useful when the investigator wants to characterize changes in a population over time but is concerned that in a cohort design the initial examination will produce a learning effect, influencing the responses to follow-up examinations. An example is the Stanford Five-City Project, which sampled the populations of five California cities over a number of years to observe trends in the prevalence of coronary heart disease (CHD) risk factors. Two kinds of samples were drawn in each city, one a true cohort of individuals in whom the factors predicting within-individual changes could be observed, and the other a series of independent samples of new individuals who had not been contaminated by the prior examination (4).

■ CASE-CONTROL STUDIES

Structure

To investigate the causes of all but the most common diseases, both cohort and cross-sectional studies of general population samples are expensive: Each would require thousands of subjects to identify risk factors for a rare disease like stomach cancer. A case series of patients with the disease can identify an obvious risk factor (such as, for AIDS, injection of illegal drugs), using prior knowledge of the prevalence of the risk factor in the general population. For most risk factors, however, it is necessary to assemble a reference group, so that the prevalence of the risk factor in subjects with the disease (cases) can be compared with the prevalence in subjects without the disease (controls).



■ **FIGURE 8.2**

In a case-control study, the investigator: (a) selects a sample from a population of people with the disease (cases), (b) selects a sample from a population at risk that is free of the disease (controls), (c) measures predictor variables.

The structure of a case-control study is shown in Fig. 8.2. Whereas cohort studies begin with people at risk and follow them forward in time to see who gets the disease and cross-sectional studies look at a single point in time, case-control studies are generally retrospective. They identify one group of subjects with the disease and another without it, then look backward in time to find differences in predictor variables that may explain why the cases got the disease and the controls did not.

Case-control studies began as epidemiologic studies to try to identify risk factors for diseases. Thus the outcome traditionally used to determine case-control status has been the presence or absence of the disease. For this reason and because it makes the discussion easier to follow, we often refer to "cases" as those with the disease. However, the case-control design can also be used to look at other outcomes, such as disability among those who already have a disease. In addition, when undesired outcomes are the rule rather than the exception, the cases in a case-control study may be the rare patients with a good outcome, such as smoking cessation or recovery from a usually fatal disease.

Case-control studies are the "house red" on the research design wine list: more modest and a little riskier than the other selections but much less expensive and sometimes surprisingly good. The design of a case-control study is challenging because of the increased opportunities for bias, but there are many examples of well-designed case-control studies that have yielded important results. These include the links between maternal diethylstilbestrol use and vaginal cancer in daughters (a classic study that provided a definitive conclusion based on just seven cases!) (5), and use of short-acting calcium channel blockers and increased risk of myocardial infarction (6).

Example 8.2. Case-Control Study

Since intramuscular (IM) vitamin K is given routinely to newborns in the United States, a pair of studies reporting a doubling in the risk of childhood cancer among those who had received IM vitamin K caused quite a stir (7,8). To investigate this association further, German investigators (9)

1. **Selected the sample of cases**—107 children with leukemia from the German Childhood Cancer Registry.
2. **Selected the sample of controls**—107 children matched by sex and date of birth and randomly selected from children living in the same town as the case at the time of diagnosis (from local government residential registration records).
3. **Measured the predictor variable**—reviewed medical records to determine which cases and controls had received intramuscular vitamin K in the newborn period.

The authors found 69 of 107 cases (64%) and 63 of 107 controls (59%) had been exposed to IM vitamin K, for an odds ratio of 1.2 (95% confidence interval [CI], 0.7 to 2.3). (See Appendix 8.A for the calculation.) Thus this study did not confirm the existence of an association between the receipt of IM vitamin K as a newborn and subsequent childhood leukemia, although the point estimate and upper limit of the 95% CI leave open the possibility of a clinically important increase in leukemia.*

Case-control studies cannot yield estimates of the incidence or prevalence of a disease because the proportion of study subjects who have the disease is determined by how many cases and how many controls the investigator chooses to sample, rather than by their proportions in the population. What case-control studies do provide is some descriptive information on the characteristics of the cases and, more important, an estimate of the strength of the association between each predictor variable and the presence or absence of the disease. These estimates are in the form of the odds ratio, which approximates the relative risk if the prevalence of the disease is not too high (Appendix 8.B).

Strengths of Case-Control Studies

Efficiency for Rare Outcomes. One of the major strengths of case-control studies is their high yield of information from relatively few subjects. Consider a study of the effect of circumcision on subsequent carcinoma of the penis. This cancer is very rare in circumcised men but is also rare in uncircumcised men: their lifetime cumulative incidence is about 0.16% (12). To do a cohort study with a reasonable chance (80%) of detecting even a very strong risk factor (say a relative risk of 50) would require more than 6,000 men, assuming that roughly equal proportions were circumcised and uncircumcised. A randomized clinical trial of circumcision at birth would require the same sample size, but the cases would occur at a median of 67 years after entry into the study. It would take three generations of epidemiologists to follow the subjects!

*Although most studies have found no evidence for an association between vitamin K and childhood cancer (10,11), a problem for policymakers is that leukemia is much more common than serious bleeding from vitamin K deficiency, so that even an odds ratio of 1.1 would mean more leukemias caused than episodes of serious bleeding prevented.

Now consider a case-control study of the same question. For the same chance of detecting the same relative risk, only 16 cases and 16 controls (and not much investigator time) would be required. For diseases that are either rare or have long latent periods between exposure and disease, case-control studies are far more efficient than the other designs. In fact, they are often the only feasible option.

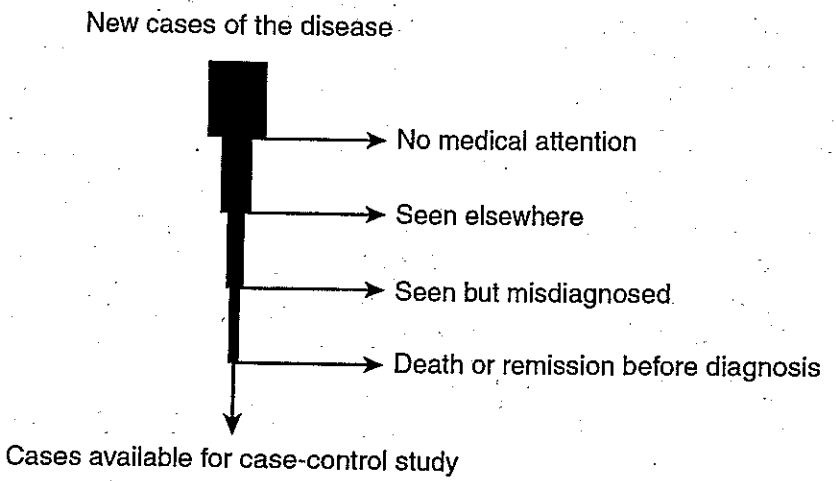
Usefulness for Generating Hypotheses. The retrospective approach of case-control studies, and their ability to examine a large number of predictor variables makes them useful for generating hypotheses about the causes of a new outbreak of disease. For example, a case-control study of an epidemic of acute renal failure in Haitian children (13) found an odds ratio of 52.7 for ingestion of locally manufactured acetaminophen syrup. Further investigation revealed that the renal failure was due to poisoning by diethylene glycol, which was found to contaminate the glycerine solution used to make the acetaminophen syrup.

Weaknesses of Case-Control Studies

Case-control studies have great strengths, but they also have major limitations. The information available in case-control studies is limited: There is no direct way to estimate the incidence or prevalence of the disease, nor the attributable or excess risk. There is also the problem that only one outcome can be studied (the presence or absence of the disease that was the criterion for drawing the two samples), whereas cohort and cross-sectional studies (and experiments) can study any number of outcome variables. But the biggest weakness of case-control studies is their increased susceptibility to bias. This bias comes chiefly from two sources: the separate sampling of the cases and controls, and the retrospective measurement of the predictor variables. These two problems and the strategies for dealing with them are the topic of the next two sections.

Sampling Bias and How to Control It. The sampling in a case-control study begins with the cases. Ideally, the sample of cases would be a random sample of everyone who develops the disease under study. An immediate problem comes up, however. How do we know who has developed the disease and who has not? In cross-sectional and cohort studies the disease is systematically sought in all the study participants, but in case-control studies the cases must be sampled from patients in whom the disease has already been diagnosed and who are available for study. This sample is not representative of all patients who develop the disease because those who are undiagnosed, misdiagnosed, or dead are less likely to be included (Fig. 8.3).

In general, sampling bias is important when the sample of cases is unrepresentative with respect to the risk factor being studied. Diseases that almost always require hospitalization and are relatively easy to diagnose, such as anencephaly and traumatic amputations, can be safely sampled from diagnosed and accessible cases. On the other hand, conditions that may not come to medical attention are not well suited to retrospective studies because of the selection that precedes diagnosis. For example, women seen in a gynecologic clinic with first-trimester spontaneous abortions would probably differ from the entire population of women experiencing spontaneous abortions because those with greater access to gynecologic care or with complications would be overrepresented. If a predictor variable of interest is associated with gynecologic care in the population (such as past use of an intrauterine device), sampling from the clinic could be an important source



■ **FIGURE 8.3**
Reasons that the cases in a case-control study may not be representative of all cases of the disease.

of bias. If, on the other hand, a predictor is unrelated to gynecologic care (such as blood type) there would be less likelihood of sampling bias.

Although it is important to think about these issues, in actual practice the selection of cases is often straightforward because the accessible sources of subjects are limited. The sample of cases may not be entirely representative, but it may be all that the investigator has to work with. The more difficult decisions faced by an investigator designing a case-control study often relate to the more open-ended task of selecting the controls. The general goal is to sample controls from a population at risk for the disease that is otherwise similar to the cases. Four strategies for sampling controls follow:

1. ***Hospital- or clinic-based controls.*** One strategy to compensate for the possible selection bias caused by obtaining cases from a hospital or clinic is to select controls from the same facilities. For example, in a study of past use of an intrauterine device (IUD) as a risk factor for spontaneous abortion, controls could be sampled from a population of women seeking care for vaginitis at the same gynecologic clinic. Compared with a random sample of women from the same area, these controls would presumably better represent the population of women who, had they developed a spontaneous abortion, would have come to the clinic and become a case.

However, selection of an unrepresentative sample of controls to compensate for an unrepresentative sample of cases can be problematic. If the risk factor of interest also causes diseases for which the controls seek care, the prevalence of the risk factor in the control group will be falsely high, biasing the study results. If, for example, many women in the control group had vaginitis and use of an IUD increased the risk of vaginitis, there would be an excess of IUD users among the controls, masking a possible real association between IUD use and spontaneous abortion.

Because hospital-based and clinic-based control subjects are usually unwell and because their diseases may be positively or negatively associated with the risk factors being studied, the use of hospital- or clinic-based controls is not always successful in compensating for an unrepresentative sample of cases. Such control

groups are often used, however, because of another consideration in selecting controls: **convenience.** Clinical investigators work in clinics and hospitals, and the populations of control subjects most readily accessible to them are those that are in the hospital or clinic for other reasons. What the investigator must decide is whether the added convenience of hospital- or clinic-based controls is worth the possible threat to the validity of the study.

2. ***Matching.*** Matching is a simple method of ensuring that cases and controls are comparable with respect to major factors that are related to the disease but not of interest to the investigator. So many risk factors and diseases are related to age and sex, for example, that the study results may be meaningless unless the cases and controls are comparable with regard to these two variables. One approach to avoiding this problem is to choose controls that match the cases on these constitutional predictor variables. Matching does have its adverse consequences, however, particularly when modifiable predictors such as income or serum cholesterol level are matched. The reasons for this and the alternatives to matching are discussed in Chapter 9.

3. ***Using a population-based sample.*** Population-based case-control studies are now possible for many diseases, because of a rapid increase in the use of disease registries. In the San Francisco Bay Area, for example, there are registries of all new cases of cancer, birth defects, AIDS, and sudden infant death. Because cases obtained from such registries are generally representative of the general population of patients in the area with the disease, the choice of a control group is simplified: It should be a representative sample from the population living in the area covered by the registry. In Example 8.2, all residents of the town were registered with the local government, making such a sample straightforward. An alternative technique for generating a random sample is **random-digit dialing.**

Random-digit dialing can include a matching strategy by repeatedly dialing the same prefix as the case (thereby matching roughly on city district) until an age- and sex-matched individual is reached. There are some problems with random-digit dialing, however. First, because it requires that all controls live in a household with a telephone, cases with no telephones need to be excluded, potentially reducing the sample size and generalizability of the study. Second, a large and nonrandom portion of the controls might not consent to be in a study after being randomly dialed. Finally, as the number of telephone numbers per household proliferates, there is the problem that households with multiple telephone lines (which are not representative of all households) will be overrepresented.

When registries are available, population-based case-control studies are clearly the most desirable. As the disease registry approaches completeness and the population it covers approaches stability (i.e., no migration in or out), the population-based case-control study approaches a case-control study that is nested within a cohort study or clinical trial (Chapter 7). This design has the potential for eliminating sampling bias, because both cases and controls are selected from the same population. When designing the sampling approach for a case-control study, the **nested case-control** design is useful to keep in mind as the model to emulate.

4. ***Using two or more control groups.*** Because selection of a control group can be so tricky, particularly when the cases are not a representative sample of those with disease, it is sometimes advisable to use two or more control groups selected in different ways. The Public Health Service study of Reye's syndrome and medications (14), for example, used four types of controls: emergency room controls (seen in the same emergency room as the case), inpatient controls (admitted to

the same hospital as the case), school controls (attending the same school or day care center as the case), and community controls (identified by random-digit dialing). The odds ratios for salicylate use in cases compared with each of these control groups (in the order listed earlier) were 39, 66, 33 and 44, and each was statistically significant. The consistent finding of a strong association using control groups that would have a variety of sampling biases makes a convincing case for the inference that there is a real association in the population.

What happens if the control groups give conflicting results? Luckily, this happens less often than one might expect, and when it does it may be helpful, revealing inherent fragility to the case-control method for the research question at hand. If possible, the investigator should seek additional information to try to determine the magnitude of potential biases from each of the control groups. In any case, it is better to have inconsistent results and conclude that the answer is not known than to have just one control group and draw the wrong conclusion.

Differential Measurement Bias and How to Control It. The second particular problem of case-control studies is bias that affects one group more than the other caused by the retrospective approach to measuring the predictor variables. Case-control studies of birth defects, for example, are hampered by differential recall bias: Parents of babies with birth defects may be more likely to recall drug exposures than parents of normal babies, because they will already have been worrying about what caused the defect. Differential recall bias cannot occur in a cohort study because the parents are asked about exposures before the baby is born.

In addition to the strategies set out in Chapter 4 for controlling biased measurements (standardizing the operational definitions of variables, choosing objective approaches, supplementing key variables with data from several sources, etc.), there are two specific strategies for avoiding bias in measuring risk factors in case-control studies:

1. **Use data recorded before the outcome occurred.** It may be possible, for example, to examine the prenatal records in a case-control study of birth defects. This excellent strategy is limited to the extent that recorded information about the risk factor of interest is available and of satisfactory reliability. Bias can still occur, however, if the investigator searches the medical records for evidence of past habits more vigorously in the cases than in the controls.
2. **Use blinding.** The general approach to blinding was discussed in Chapter 4, but there are some issues that are specific to designing interviews in case-control studies. Because both observers and study subjects could be blinded both to the case-control status of each subject and to the risk factor being studied, four types of blinding are possible (Table 8.2)

Ideally, neither the study subjects nor the investigators should know which subjects are cases and which are controls. If this can be done successfully, differential bias in measuring the predictor variable is eliminated. In practice, this is often difficult. The subjects know whether they are sick or well, so they can be blinded to case-control status only if controls are drawn from patients who are also ill with diseases that they believe might be related to the risk factors being studied. (Of course, if the disease of any of the controls is related to the risk factor being studied, it will cause sampling bias.) Efforts to blind interviewers are hampered

■ **TABLE 8.2**
Approaches to Blinding Interview Questions in a Case-Control Study

Person Blinded	Blinding Case-control Status	Blinding Risk Factor Measurement
Subject	Possible if both cases and controls have diseases that could plausibly be related to the risk factor.	Include "dummy" risk factors and be suspicious if they differ between cases and controls. May not work if the risk factor for the disease has already been publicized.
Observer	Possible if cases are not externally distinguishable from controls, but subtle signs and statements volunteered by the subjects make it difficult.	Possible if interviewer is not the investigator, but may be difficult to maintain.

by the obvious nature of some diseases (an interviewer can hardly help noticing if the patient is jaundiced or has had a laryngectomy), and by the clues that interviewers may discern in the patient's responses.

Blinding to the specific risk factor being studied is usually easier than blinding as to case-control status. Both the study subjects and the interviewer can be kept in the dark about the study hypotheses by including "dummy" questions about plausible risk factors not associated with the disease. For example, if the specific hypothesis to be tested is whether honey intake is associated with increased risk of infant botulism, equally detailed questions about jelly, yogurt, and bananas could be included in the interview. This type of blinding does not actually prevent differential bias, but it allows an estimate of whether it is a problem: If the cases report more exposure to honey but no increase in the other foods, then differential measurement bias is less likely. This strategy would not work if the association between infant botulism and honey had previously been widely publicized or if some of the dummy risk factors turned out to be real risk factors.

Blinding the observer to the case-control status of the study subject is a particularly good strategy for laboratory measurements such as blood tests and x-rays. Blinding under these circumstances is easy and should always be done: Someone other than the individual who will make the measurement simply applies coded identification labels to each specimen. Its importance is illustrated by 15 case-control studies comparing measurements of bone mass between hip fracture patients and controls; much larger differences were formed in the studies that used unblinded measurements than in the blinded studies (15).

■ CHOOSING AMONG OBSERVATIONAL DESIGNS

The pros and cons of the main observational designs presented in the last two chapters are summarized in Table 8.3. We have already described these issues in detail and will make only one final point here. Among all these designs, none is best and none is worst; each has its place and purpose, depending on the research question and the circumstances.

TABLE 8.3
Advantages and Disadvantages of the Major Observational Designs

Design	Advantages	Disadvantages*
Cohort		
All	Establishes sequence of events Can study several outcomes Number of outcome events grows over time Yields incidence, relative risk, excess risk	Often requires large sample sizes Less feasible for rare outcomes
Prospective	More control over selection of subjects More control over measurements Avoids bias in measuring predictors	More expensive Longer duration
Retrospective	Less expensive Shorter duration	Less control over selection of subjects Less control over measurements
Multiple cohort	Useful when distinct cohorts have different or rare exposures	Potential for bias and confounding from sampling several populations
Cross-Sectional		
	May study several outcomes Relatively short duration A good first step for a cohort study Yields prevalence, relative prevalence	Does not establish sequence of events Not feasible for rare predictors or rare outcomes Does not yield incidence or true relative risk
Case-Control		
	Useful for studying rare conditions Short duration Relatively inexpensive Relatively small Yields odds ratio (usually a good approximation of relative risk unless the outcome is common)	Potential for bias and confounding from sampling two populations Does not establish sequence of events Potential survivor bias Limited to one outcome variable Does not yield prevalence, incidence, or excess risk
Combination Designs		
Nested case-control	Advantages of a retrospective cohort design, only much more efficient	Sometimes requires banked samples stored until outcomes occur
Nested case-cohort	Can use a single control group for multiple studies	

*All these observational designs have the disadvantage (compared with experiments) of being susceptible to the influence of confounding variables.

■ SUMMARY

1. In a **cross-sectional** study, the variables are all measured at a single point in time, with no structural distinction between predictors and outcomes. Cross-sectional studies are valuable for providing **descriptive** information about **prevalence**; they also have the advantage of avoiding the time, expense, and dropout problems of a follow-up design.
2. Cross-sectional studies yield **weaker evidence for causality** than cohort studies, however, because the predictor variable is not shown to precede the outcome. A further weakness is the need for a large sample size (compared with that of a case-control study) when studying the prevalence of uncommon diseases and variables in the general population. The cross-sectional design can be used for an uncommon disease in a **case series** of patients with that disease, and it often serves as the first step of a cohort study or experiment.
3. In a **case-control study,** the prevalence of risk factors in a sample of subjects who have a disease or other outcome of interest (the cases) is compared with that in a sample who do not (the controls). This design, in which people with and without the disease are sampled separately, is relatively **inexpensive** and uniquely **efficient** for studying **rare diseases.**
4. One problem with case-control studies is their susceptibility to **sampling bias.** The likelihood of sampling bias depends on both the disease and risk factor in question. Four approaches to reducing sampling bias are (a) to sample controls and cases in the same (admittedly unrepresentative) way; (b) to **match** the cases and controls; (c) to do a population-based study; and (d) to use **several** control groups, sampled in different ways.
5. The other major problem with case-control studies is their retrospective design, which makes them susceptible to **differential measurement bias** (between cases and controls). Such bias can be reduced by obtaining **past measurements** of the predictor variable and by **blinding** the subjects and observers.

EXERCISES

1. The research question is, "How much does a family history of ovarian cancer increase the risk for ovarian cancer?" You plan a case-control study to answer this question.
   a. How would you pick the cases?
   b. How would you pick the controls?
   c. Comment on potential sources of bias in the sampling of cases and controls.
   d. How would you measure "family history of ovarian cancer" as the predictor variable of interest? Comment on the sources of bias in this measurement.
   e. What measure of association would you use, and what test of statistical significance?
   f. Do you think the case-control method is an appropriate approach to this research question? Discuss the advantages and disadvantages of the case-control design relative to other possibilities for this research question.

2. The research question is, "Does maternal height or weight predict infant

birth weight?" During a 12-month period an investigator assembles data on consecutive newborns in a large maternity hospital. The study is limited to term newborns as defined by delivery 38 to 42 weeks after the mother's last menstrual period. In the maternity ward, the investigator measures each infant's birth weight and the mother's height and weight. Based on the data obtained, the investigator concludes that birth weight is strongly dependent on both maternal height and weight.

a. What kind of study is this?

b. Explain why you agree or disagree with the investigator's conclusions?

References

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■ APPENDIX 8.A

Calculating Measures of Association

Cross-Sectional Studies. The research questions for Example 8.1 were, "What is the prevalence of chlamydia infection in women attending STD clinics." and "Is it associated with the use of oral contraceptives?" The hypothetical findings are that 20 of the women report taking oral contraceptives and that four of these women have positive cultures, compared with eight of the 80 women not taking oral contraceptives. A two-by-two table of these findings is as follows:

	Outcome Variable: Cervical Culture Results		
Predictor Variable: Contraceptive History	**Chlamydia Present**	**Chlamydia Absent**	**Total**
Users of oral contraceptives (OCs)	4(a)	16(b)	20($a + b$)
Nonusers of OCs	8(c)	72(d)	80($c + d$)
Total	12($a + c$)	88($b + d$)	100 ($a + b + c + d$)

Prevalence of chlamydia infection in users = $a/(a + b) = 4/20 = 20\%$.
Prevalence of chlamydia infection in nonusers = $c/(c + d) = 8/80 = 10\%$.
Prevalence of chlamydia infection overall = $(a + c)/(a + b + c + d) = 12/100 = 12\%$.

$$\text{Relative prevalence}^* = \frac{\text{Prevalence of chlamydia in OC users}}{\text{Prevalence of chlamydia in nonusers}} = \frac{a/(a+b)}{c/(c+d)} = \frac{4/20}{8/80} = 2.0$$

$$\text{Excess prevalence}^* = \frac{a}{a+b} - \frac{c}{c+d} = \frac{4}{20} - \frac{8}{80} = 10\%$$

Thus the prevalence of chlamydia infection in this population of STD clinic patients is 20% among oral contraceptive users, 10% among nonusers, and 12% overall. There is an association between oral contraceptive use and chlamydia infection that is characterized by a relative prevalence of 2.0 and by an excess prevalence of 10%.

Case-Control Studies. The research question for Example 8.2 was whether there is an association between intramuscular vitamin K and risk of childhood leukemia. The findings were that 69/107 leukemia cases and 63/107 controls had received intramuscular vitamin K. A two-by-two table of these findings is as follows:

	Outcome Variable: Diagnosis	
Predictor Variable: Medication History	**Childhood Leukemia**	**Control**
IM vitamin K	69(a)	63(b)
No IM vitamin K	48(c)	54(d)
Total	107	107

$$\text{Relative risk} \approx \textit{odds ratio} = \frac{ad}{bc} = \frac{69 \times 54}{63 \times 48} = 1.2$$

Because the disease (leukemia in this instance) is rare, the odds ratio provides a good estimate of the relative risk.

*Relative prevalence and excess prevalence are the cross-sectional analogs of relative risk and excess risk.

APPENDIX 8.B

Why the Odds Ratio Can Be Used as an Estimate for Relative Risk in a Case-Control Study

The data in a case-control study represent two samples: The cases are drawn from a population of people who have the disease and the controls from a population of people who do not have the disease. The predictor variable is measured, and the following two-by-two table produced:

	Disease	No Disease
Risk factor present	a	b
Risk factor absent	c	d

If this two-by-two table represented data from a cohort study, then the incidence of the disease in those with the risk factor would be $a/(a + b)$ and the relative risk would be simply $[a/(a + b)]/[c/(c + d)]$. However, it is not appropriate to compute either incidence or relative risk in this way because the two samples are not drawn from the population in the same proportions. Usually, there are roughly equal numbers of cases and controls in the study samples but many fewer cases than controls in the population. Instead, relative risk in a case-control study can be approximated by the odds ratio, computed as the cross-product of the two-by-two table, ad/cb.

The basis for this extremely useful fact cannot be understood intuitively, but is relatively easy to demonstrate algebraically. Consider the situation for the full population, represented by a', b', c', and d'.

	Disease	No Disease
Risk factor present	a'	b'
Risk factor absent	c'	d'

Here it is appropriate to calculate the risk of disease among people with the risk factor as $a'/(a' + b')$, the risk among those without the risk factor as $c'/(c' + d')$, and the relative risk as $[a'/(a' + b')]/[c'/(c' + d')]$. We have already discussed the fact that $a'/(a' + b')$ is not equal to $a/(a + b)$. However, if the disease is relatively uncommon (as most are), then a' is much smaller than b', and c' is much smaller than d'. This means that $a'/(a' + b')$ is closely approximated by a'/b' and that $c'/(c' + d')$ is closely approximated by c'/d'. Thus the relative risk of the population can be approximated as follows:

$$\frac{a'/(a' + b')}{c'/(c' + d')} \approx \frac{a'/b'}{c'/d'}$$

The latter term is the odds ratio of the population (literally, the ratio of the odds of disease in those with the risk factor, a'/b', to the odds of disease in those without the risk factor, c'/d'). This can be rearranged as the cross-product:

$$\left(\frac{a'}{b'}\right)\left(\frac{d'}{c'}\right) = \left(\frac{a'}{c'}\right)\left(\frac{d'}{b'}\right)$$

However, a'/c' in the population equals a/c in the sample if the cases are representative of all cases in the population (i.e., have the same prevalence of the risk factor). Similarly, b'/d' equals b/d if the controls are representative.

Thus the population parameters in this last term can be replaced by the sample parameters, and we are left with the fact that the odds ratio observed in the sample, ad/bc, is a close approximation of the relative risk in the population, $[a'/(a' + b')]/[c'/(c' + d')]$, provided that the disease is rare and sampling error (systematic as well as random) is small.