

6

Overview of Epidemiologic Study Designs

LEARNING OBJECTIVES

By the end of this chapter, the reader will be able to:

- Distinguish between experimental and observational studies.
- Describe the key characteristics of experimental, cohort, case-control, cross-sectional, and ecologic studies regarding subject selection, data collection, and analysis.
- Identify the design of a particular study.
- Discuss the factors that determine when a particular design is indicated.

Introduction

As described in Chapter 1, epidemiology is the study of the distribution and determinants of disease frequency in human populations and the application of this study to control health problems.^{1(p1),2(p55)} The term *study* includes both *surveillance*, whose purpose is to monitor aspects of disease occurrence and spread that are pertinent to effective control,^{3(p507)} and *epidemiologic research*, whose goal is to harvest valid and precise information about the causes, preventions, and treatments for disease. The term *disease* refers to a broad array of health-related states and events including diseases, injuries, disabilities, and death.

Epidemiologic research encompasses several types of study designs, including experimental studies and observational studies such as cohort and case-control studies. Each type of epidemiologic study design simply represents a different way of harvesting information. The selection of one design over another depends on the particular research question, concerns

about validity and efficiency, and practical and ethical considerations. For example, experimental studies, also known as trials, investigate the role of some factor or agent in the prevention or treatment of a disease. In this type of study, the investigator assigns individuals to two or more groups that either receive or do not receive the preventive or therapeutic agent. Because experimental studies closely resemble controlled laboratory investigations, they are thought to produce the most scientifically rigorous data of all the designs.

However, because experimental studies are often infeasible because of difficulties enrolling participants, high costs, and thorny ethical issues, most epidemiologic research is conducted using observational studies. Observational studies are considered “natural” experiments because the investigator lets nature take its course. Observational studies take advantage of the fact that people are exposed to noxious and/or healthy substances through their personal habits, occupation, place of residence, and so on. The studies provide information on exposures that occur in natural settings, and they are not limited to preventions and treatments. Furthermore, they do not suffer from the ethical and feasibility issues of experimental studies. For example, although it is unethical to conduct an experimental study of the impact of drinking alcohol on the developing fetus by assigning newly pregnant women to either a drinking or non-drinking group, it is perfectly ethical to conduct an observational study by comparing women who choose to drink during pregnancy with those who decide not to do so.

The two principal types of observational studies are cohort and case-control studies. A classical cohort study examines one or more health effects of exposure to a single agent. Subjects are defined according to their exposure status and followed over time to determine the incidence of health outcomes. In contrast, a classical case-control study examines a single disease in relation to exposure to one or more agents. Cases who have the disease of interest and controls who are a sample of the population that produced the cases are defined and enrolled. The purpose of the control group is to provide information on the exposure distribution in the population that gave rise to the cases. Investigators obtain and compare exposure histories of cases as well as controls.

Additional observational study designs include cross-sectional studies and ecologic studies. A cross-sectional study examines the relationship between a disease and an exposure among individuals in a defined population at a point in time. Thus, it takes a snapshot of a population and measures the exposure prevalence in relation to the disease prevalence. An ecologic study evaluates an association using the population rather than the individual as the unit of analysis. The rates of disease are examined in relation to factors described on the population level. Both the cross-sectional and ecologic designs have important limitations that make them

less scientifically rigorous than cohort and case-control studies. These limitations are discussed later in this chapter.

An overview of these study designs is provided in Table 6–1. The goal of all these studies is to determine the relationship between an exposure and a disease with validity and precision using a minimum of resources. *Validity* is defined as the lack of bias and confounding. *Bias* is an error committed by the investigator in the design or conduct of a study that leads to a false association between the exposure and disease. *Confounding*, on the other hand, is not the fault of the investigator but rather reflects the fact that epidemiologic research is conducted among free-living humans with unevenly distributed characteristics. As a result, epidemiological studies that try to determine the relationship between an exposure and disease are susceptible to the disturbing influences of extraneous factors known as confounders. *Precision* is the lack of random error, which leads to a false association between the exposure and disease just by “chance,” an uncontrollable force that seems to have no assignable cause.^{4(p309)} Bias, confounding, and random error are covered in greater detail in Chapters 10 through 12.

Several factors help epidemiologists determine the most appropriate study design for evaluating a particular association, including the hypothesis being tested, state of knowledge, the frequency of the exposure and the disease, and the expected strength of the association between the two. This chapter provides: (1) an overview of five epidemiologic study designs—experimental, cohort, case-control, cross-sectional, and

TABLE 6–1 Main Types of Epidemiologic Studies

<i>Type of study</i>	<i>Characteristics</i>
Experimental	Studies preventions and treatments for diseases; investigator actively manipulates which groups receive the agent under study.
Observational	Studies causes, preventions, and treatments for diseases; investigator passively observes as nature takes its course.
Cohort	Typically examines multiple health effects of an exposure; subjects are defined according to their exposure levels and followed for disease occurrence.
Case-control	Typically examines multiple exposures in relation to a disease; subjects are defined as cases and controls, and exposure histories are compared.
Cross-sectional	Examines relationship between exposure and disease prevalence in a defined population at a single point in time.
Ecological	Examines relationship between exposure and disease with population-level rather than individual-level data.

ecological designs—and (2) a description of the settings in which the three main study designs—experimental, cohort, and case-control—are most appropriate. Chapters 7 through 9 describe these three study designs in more detail.

Overview of Experimental Studies

Definitions and Classification

An experimental study, also known as a trial, investigates the role of some agent in the prevention or treatment of a disease. In this type of study, the investigator assigns individuals to two or more groups that either receive or do not receive the preventive or therapeutic agent. The group that is allocated the agent under study is generally called the treatment group, and the group that is not allocated the agent under study is called the comparison group. Depending on the purpose of the trial, the comparison group may receive no treatment at all, an inactive treatment such as a placebo, or another active treatment.

The active manipulation of the agent by the investigator is the hallmark that distinguishes experimental studies from observational ones. In the latter, the investigator acts as a passive observer merely letting nature take its course. Because experimental studies more closely resemble controlled laboratory investigations, most epidemiologists believe that experimental studies produce more scientifically rigorous results than do observational studies.

Experimental studies are commonly classified by their objective—that is, by whether they investigate a measure that prevents disease occurrence or a measure that treats an existing condition. The former is known as a preventive or prophylactic trial, and the latter is known as a therapeutic or clinical trial. In preventive trials, agents such as vitamins or behavioral modifications such as smoking cessation are studied to determine if they are effective in preventing or delaying the onset of disease among healthy individuals. In therapeutic trials, treatments such as surgery, radiation, and drugs are tested among individuals who already have a disease.

Selection of Study Population

During the recruitment phase of an experimental study, the study population—which is also called the experimental population—is enrolled on the basis of eligibility criteria that reflect the purpose of the trial, as well as scientific, safety, and practical considerations. For example, healthy or high-risk individuals are enrolled in prevention trials, while individuals with specific diseases are enrolled in therapeutic trials. Additional inclusion and exclusion criteria are used to restrict the study population by factors such as gender and age.

The study population must include an adequate number of individuals in order to determine if there is a true difference between the treatment and comparison groups. An investigator determines how many subjects to include by using formulas that take into account the anticipated difference between the groups, the background rate of the outcome, and the probability of making certain statistical errors.^{5(pp142–146)} In general, smaller anticipated differences between the treatment and comparison groups require larger sample sizes.

Consent Process and Treatment Assignment

All eligible and willing individuals must give consent to participate in an experimental study. The process of gaining their agreement is known as *informed consent*. During this process, the investigator describes the nature and objectives of the study, the tasks required of the participants, and the benefits and risks of participating. The process also includes obtaining the participant's oral or written consent.

Individuals are then assigned to receive one of the two or more treatments being compared. Randomization, "an act of assigning or ordering that is the result of a random process,"^{6(p220)} is the preferred method for assigning the treatments because it is less prone to bias than other methods and because it produces groups with very similar characteristics, if the study size is sufficient. Random assignment methods include flipping a coin, using a random number table (commonly found in statistics textbooks), and using a computerized random number generator.

Treatment Administration

In the next phase of a trial, the treatments are administered according to a specific protocol. For example, in a therapeutic trial participants may be asked to take either an active drug or an inactive drug known as a placebo. The purpose of placebos is to match as closely as possible the experience of the comparison group with that of the treatment group. The principle underlying the use of placebos harkens back to laboratory animal experiments where, except for the test chemical, all important aspects of the experimental conditions are identical for all groups. Placebos permit study participants and investigators to be masked—that is, to be unaware of the participant's treatment assignment. Masking of subjects and investigators helps prevent biased ascertainment of the outcome, particularly when end points involve subjective assessments.

Maintenance and Assessment of Compliance

All experimental studies require the active involvement and cooperation of participants. Although participants are apprised of the study

requirements when they enroll, many fail to follow the protocol exactly as required as the trial proceeds. The failure to observe the requirements of the protocol is known as noncompliance, and this may occur in the treatment group, the comparison group, or both. Reasons for not complying include toxic reactions to the treatment, waning interest, and desire to seek other therapies. Noncompliance is problematic because it results in a smaller difference between the treatment and comparison groups than truly exists, thereby diluting the real impact of a treatment.

Because good compliance is an important determinant of the validity of an experimental study, many design features are used to enhance a participant's ability to comply with the protocol requirements.⁷ These include designing an experimental regimen that is simple and easy to follow, enrolling motivated and knowledgeable participants, presenting a realistic picture of the required tasks during the consent process, maintaining frequent contact with participants during the study, and conducting a run-in period before enrollment and randomization. The purpose of the run-in period is to ascertain which potential participants are able to comply with the study regimen. During this period, participants are placed on the test or comparison treatment to assess their tolerance and acceptance and to obtain information on compliance.^{6(p143)} Following the run-in period, only compliant individuals are enrolled in the trial.

Ascertaining the Outcomes

During the follow-up stage of an experimental study, the treatment and comparison groups are monitored for the outcomes under study. If the study's goal is to prevent the occurrence of disease, the outcomes may include the precursors of disease or the first occurrence of disease (that is, incidence). If the study is investigating a new treatment among individuals who already have a disease, the outcomes may include disease recurrence, symptom improvement, length of survival, or side effects. The length of follow-up depends on the particular outcome under study. It can range from a few months to a few decades.

Usually, all reported outcomes under study are confirmed in order to guarantee their accuracy. Confirmation is typically done by masked investigators who gather corroborating information from objective sources such as medical records and laboratory tests. High and comparable follow-up rates are needed to ensure the quality of the outcome data. Follow-up is adversely affected when participants withdraw from the study (these individuals are called dropouts) or cannot be located or contacted by the investigator (these individuals are termed lost to follow-up). Reasons for dropouts and losses include relocation, waning interest, and adverse reactions to the treatment.

Analysis

The classic analytic approach for an experimental study is known as an intent-to-treat or treatment assignment analysis. In this analysis, all individuals who were randomly allocated to a treatment are analyzed, regardless of whether they completed the regimen or received the treatment.⁸ An intent-to-treat analysis gives information on the effectiveness of a treatment under everyday practice conditions. The alternative to an intent-to-treat analysis is known as an efficacy analysis, which determines the treatment effects under ideal conditions, such as when participants take the full treatment exactly as directed.

Overview of Cohort Studies

Definitions

A cohort is defined as a group of people with a common characteristic or experience. In a cohort study, healthy subjects are defined according to their exposure status and followed over time to determine the incidence of symptoms, disease, or death. The common characteristic for grouping subjects is their exposure level. Usually two groups are compared, an “exposed” and “unexposed” group. The unexposed group is called the *referent group* or *comparison group*.

Cohort study is the term that is typically used to describe an epidemiologic investigation that follows groups with common characteristics. Other expressions that are used include *follow-up*, *incidence*, and *longitudinal study*. There are several additional terms for describing cohort studies that depend on the characteristics of population from which the cohort is derived, whether the exposure changes over time, and whether there are losses to follow-up. The term *fixed cohort* is used when the cohort is formed on the basis of an irrevocable event such as undergoing a medical procedure. Thus, an individual’s exposure in a fixed cohort does not change over time. The term *closed cohort* is used to describe a fixed cohort with no losses to follow up. In contrast, a cohort study conducted in an *open population* is defined by exposures that can change over time such as cigarette smoking. Cohort studies in open populations may also experience losses to follow-up.

Timing of Cohort Studies

Three terms are used to describe the timing of events in a cohort study: prospective, retrospective, and ambidirectional. In a *prospective cohort study*, participants are grouped on the basis of past or current exposure and are followed into the future in order to observe the outcomes of interest. When the study commences, the outcomes have not yet developed and the

investigator must wait for them to occur. In a *retrospective cohort study*, both the exposures and outcomes have already occurred when the study begins. Thus, this type of investigation studies only prior outcomes and not future ones. An *ambidirectional cohort study* has both prospective and retrospective components. The decision to conduct a retrospective, prospective, or ambidirectional study depends on the research question, practical constraints such as time and money, and the availability of suitable study populations and records.

Selection of the Exposed Population

The choice of the exposed group in a cohort study depends on the hypothesis being tested, the exposure frequency, and feasibility considerations such as the availability of records and ease of follow-up. Special cohorts are used to study the health effects of rare exposures such as uncommon workplace chemicals, unusual diets, and uncommon lifestyles. Special cohorts are often selected from occupational groups (such as rubber workers) or religious groups (such as Mormons) where the exposures are known to occur. General cohorts are typically assembled for common exposures such as cigarette smoking and alcohol consumption. These cohorts are often selected from professional groups such as nurses or from well-defined geographic areas in order to facilitate follow-up and accurate ascertainment of the outcomes under study.

Selection of Comparison Group

There are three sources for the comparison group in a cohort study: an internal comparison group, the general population, and a comparison cohort. An internal comparison group consists of unexposed members of the same cohort. An internal comparison group should be used whenever possible, because its characteristics will be most similar to the exposed group. The general population is used for comparison when it is not possible to find a comparable internal comparison group. The general population comparison is based on preexisting population data on disease incidence and mortality. A comparison cohort consists of members of another cohort. It is the least desirable option because the comparison cohort, while not exposed to the exposure under study, is often exposed to other potentially harmful substances and so the results can be difficult to interpret.

Sources of Information

Cohort study investigators typically rely on many sources for information on exposures, outcomes, and other key variables. These include medical

and employment records, interviews, direct physical examinations, laboratory tests, biological specimens, and environmental monitoring. Some of these sources are preexisting, and others are designed specifically for the study. Because each type of source has advantages and disadvantages, investigators often use several sources to piece together all of the necessary information.

Health care records are used to describe a participant's exposure history in studies of possible adverse health effects stemming from medical procedures. The advantages of these records include low expense and a high level of accuracy and detail regarding a disease and its treatment. Their main disadvantage is that information on many other key characteristics, apart from basic demographic characteristics, is often missing.

Employment records are used to identify individuals for studies of occupational exposures. Typical employment record data includes job title, department of work, years of employment, and basic demographic characteristics. Like medical records, they usually lack details on exposures and other important variables.

Because existing records such as health care and employment records often have limitations, many studies are based on data collected specifically for the investigation. These include interviews, physical examinations, and laboratory tests. Interviews and self-administered questionnaires are particularly useful for obtaining information on lifestyle characteristics (such as use of cigarettes or alcohol), which are not consistently found in records.

Whatever the source of information, it is important to use comparable procedures for obtaining information on the exposed and unexposed groups. Biased results may occur if different sources and procedures are used. Thus, all resources used for one group must be used for the other. In addition, it is a good idea to mask investigators to the exposure status of a subject so that they make unbiased decisions when assessing the outcomes. Standard outcome definitions are also recommended to guarantee both accuracy and comparability.

Approaches to Follow-Up

Loss to follow-up occurs either when the participant no longer wishes to take part or when he or she cannot be located. Because high rates of follow-up are critical to the success of a cohort study, investigators have developed many methods to maximize retention and trace study participants.⁹ For prospective cohort studies, strategies include collection of information (such as full name, Social Security number, and date of birth) that helps locate participants as the study progresses. In addition, regular contact is recommended for participants in prospective studies. These contacts might involve requests for up-to-date outcome information or

newsletters describing the study's progress and findings.⁹ The best strategy to use when participants do not initially respond is to send additional mailings.

When participants are truly lost to follow-up, investigators employ a number of strategies.⁹ These include sending letters to the last known address with "Address Correction Requested"; checking telephone directories, directory assistance, newly available Internet resources such as the "White Pages," vital statistics records, driver's license rosters, and voter registration records; and contacting relatives, friends, and physicians identified at baseline.

Analysis

The primary objective of the analysis of cohort study data is to compare the occurrence of symptoms, disease, and death in the exposed and unexposed groups. If it is not possible to find a completely unexposed group to serve as the comparison, then the least exposed group is used. The occurrence of the outcome is usually measured using cumulative incidence or incidence rates, and the relationship between the exposure and outcome is quantified using absolute or relative difference between the risks or rates, as described in Chapter 3.

Overview of Case-Control Studies

The case-control study has traditionally been viewed as an inferior alternative to the cohort study. In the traditional view, subjects are selected on the basis of whether they have or do not have the disease. Those who have the disease are termed *cases*, and those who do not have the disease are termed *controls*. The exposure histories of cases and controls are then obtained and compared. Thus, the central feature of the traditional view is the comparison of the cases' and controls' exposure histories. This differs from the logic of experimental and cohort study designs, in which the key comparison is disease incidence between the exposed and unexposed (or least exposed) groups.

Over the last two decades, the traditional view that a case-control study is a backwards cohort study has been supplanted by a modern view that asserts that it is merely an efficient way to learn about the relationship between an exposure and disease.¹⁰ More specifically, a case-control study is a method of sampling a population in which researchers identify and enroll cases of disease and a sample of the source population that gave rise to the cases. The sample of the source population is known as the control group. Its purpose is to provide information on the exposure distribution in the population that produced the cases, so that the rates of disease in exposed and nonexposed groups can be compared. Thus, the key comparison in the modern view is the same as that of a cohort study.

Selection of Cases

The first step in the selection of cases for a case-control study is the formulation of a disease or case definition. A case definition is usually based on a combination of signs and symptoms, physical and pathological examinations, and results of diagnostic tests. It is best to use all available evidence to define with as much accuracy as possible the true cases of disease.

Once investigators have created a case definition, they can begin case identification and enrollment. Typical sources for identifying cases are hospital or clinic patient rosters, death certificates, special surveys, and reporting systems such as cancer or birth defects registries. Investigators consider both accuracy and efficiency in selecting a particular source for case identification. The goal is to identify as many true cases of disease as quickly and cheaply as possible.

Another important issue in selecting cases is whether they should be incident or prevalent. Researchers who study the causes of disease prefer incident cases because they are usually interested in the factors that lead to developing a disease rather than factors that affect its duration. However, sometimes epidemiologists have no choice but to rely on prevalent cases (for example, when studying the causes of insidious diseases whose exact onset is difficult to pinpoint). Studies using prevalent cases must be interpreted cautiously, because it is impossible to determine if the exposure is related to the inception of the disease, its duration, or a combination of the two.

Selection of Controls

Controls are a sample of the population that produced the cases. The guiding principle for the valid selection of controls is that they come from the same base population as the cases. If this condition is met, then a member of the control group who gets the disease under study *would* end up as a case in the study. This concept is known as the *would criterion*, and its fulfillment is crucial to the validity of a case-control study. Another important principle is that controls must be sampled independently of exposure status. In other words, exposed and unexposed controls should have the same probability of selection.

Epidemiologists use several sources for identifying controls in case-control studies. They may sample: (1) individuals from the general population, (2) individuals attending a hospital or clinic, (3) friends or relatives identified by the cases, or (4) individuals who have died. Population controls are typically selected when cases are identified from a well-defined population such as residents of a geographic area. These controls are usually identified using voter registration lists, driver's license rosters, telephone directories, and random digit dialing (a method for identifying telephone subscribers living in a defined geographic area).

Population controls have one principal advantage that makes them preferable to other types of controls. Because of the manner in which population controls are identified, investigators are usually assured that the controls come from the same population as the cases. Thus, investigators are usually confident that population controls are comparable to the cases with respect to demographic and other important variables. However, population controls have several disadvantages. First, they are time-consuming and expensive to identify. Second, these individuals do not have the same level of interest in participating as do cases and controls identified from other sources. Third, because they are generally healthy, their recall may be less accurate than that of cases who are likely reviewing their history in search of a “reason” for their illness.

Epidemiologists usually select hospital and clinic controls when they identify cases from these health care facilities. Thus, these controls have diseases or have experienced events (such as a car accident) for which they have sought medical care. The most difficult aspect of using these types of controls is determining which diseases or events are suitable for inclusion. In this regard, investigators should follow two general principles. First, the illnesses in the control group should, on the basis of current knowledge, be unrelated to the exposure under study. For example, a case-control study of cigarette smoking and emphysema should not use lung cancer patients as controls, because lung cancer is known to be caused by smoking cigarettes. Second, the control’s illness should have the same referral pattern to the health care facility as the case’s illness. For example, a case-control study of acute appendicitis should use patients with other acute conditions as controls. Following this principle will help ensure that the cases and controls come from the same source population.

There are several advantages to the use of hospital and clinic controls. Because they are easy to identify and have good participation rates, hospital and clinic controls are less expensive to identify than population controls. In addition, because they come from the same source population they will have comparable characteristics to the cases. Finally, their recall of prior exposures will be similar to the cases’ recall, because they are also ill. The main disadvantage of this type of control is the difficulty in determining appropriate illnesses for inclusion.

In rare circumstances, deceased and “special” controls are enrolled. Deceased controls are occasionally used when some or all of the cases are deceased by the time data collection begins. Researchers usually identify these controls by reviewing death records of individuals who lived in the same geographic area and died during the same time period as the cases. The main rationale for selecting dead controls is to ensure comparable data collection procedures between the two groups. For example, if researchers collect data by interview, they would conduct proxy interviews with subjects’ spouses, children, relatives, or friends for both the dead cases and dead controls.

However, many epidemiologists discourage the use of dead controls because these controls may not be a representative sample of the source population that produced the cases, which—by definition—consists of living people. Furthermore, the investigator must consider the study hypothesis before deciding to use dead controls, because they are more likely than living controls to have used tobacco, alcohol, or drugs.¹¹ Consequently, dead controls may not be appropriate if the study hypothesis involves one of these exposures.

In unusual circumstances, a friend, spouse, or relative (usually a sibling) is nominated by a case to serve as his or her control. These “special” controls are used because they are likely to share the cases’ socioeconomic status, race, age, educational level, and genetic characteristics, if they are related to the cases. However, cases may be unwilling or unable to nominate people to serve as their controls. In addition, biased results are possible if the study hypothesis involves a shared activity among the cases and controls.

Methods for Sampling Controls

Epidemiologists use three main strategies for sampling controls in a case-control study. Investigators can select controls from the “non-cases” or “survivors” at the end of the case diagnosis and accrual period. This method of selection, which is known as *survivor sampling*, is the predominant method for selecting controls in traditional case-control studies. In *case-based* or *case-cohort* sampling, investigators select controls from the population at risk at the beginning of the case diagnosis and accrual period. In *risk set sampling*, controls are selected from the population at risk as the cases are diagnosed.

When case-based and risk set sampling methods are used, the control group may include future cases of disease. Although this may seem incorrect, modern epidemiologic theory supports it. Recall that both diseased and nondiseased individuals contribute to the denominators of the risks and rates in cohort studies. Thus, it is reasonable for the control group to include future cases of disease because it is merely an efficient way to obtain the denominator data for the risks and rates.

Sources of Exposure Information

Case-control studies are used to investigate the risk of disease in relation to a wide variety of exposures, including those related to lifestyle, occupation, environment, genes, diet, reproduction, and the use of medications.¹² Most exposures that are studied are complex, and so investigators must attempt to obtain sufficiently detailed information on the nature, sources, frequency, and duration of these exposures. Sources available for obtaining exposure data include in-person and telephone

interviews; self-administered questionnaires; preexisting medical, pharmacy, registry, employment, insurance, birth, death, and environmental records; and biological specimens.¹² When selecting a particular source, investigators consider its availability, its accuracy, and the logistics and cost of data collection. Accuracy is a particular concern in case-control studies because exposure data are retrospective. In fact, the relevant exposures may have occurred many years before data collection, making it difficult to gather correct information.

Analysis

As described above, controls are a sample of the population that produced the cases. However, in most instances the sampling fraction is not known, so the investigator cannot fill in the total population in the margin of a two-by-two table or obtain the rates and risks of disease. Instead, the researcher obtains a number called an *odds*, which functions as a rate or risk. An odds is defined as the probability that an event will occur divided by the probability that it will not occur. In a case-control study, epidemiologists typically calculate the odds of being a case among the exposed (a/b) compared to the odds of being a case among the nonexposed (c/d). The ratio of these two odds is expressed as follows:

$$\frac{a/b}{c/d} \text{ or } \frac{ad}{bc}$$

This ratio, known as the disease odds ratio, provides an estimate of the relative risk just as the incidence rate ratio and cumulative incidence ratio do. Risk or rate differences are not usually obtainable in a case-control study. However, it is possible to obtain the attributable proportion among the exposed. Analytic issues for case-control studies are described in more detail in Chapter 9.

Case-Crossover Study

The case-crossover study is a relatively new variant of the case-control study that was developed for settings in which the risk of the outcome is increased for only a brief time following the exposure.¹³ The period of increased risk following the exposure is termed the hazard period.¹⁴ In the case-crossover study, cases serve as their own controls, and the exposure frequency during the hazard period is compared to that from a control period. Because cases serve as their own controls, this design has several advantages including the elimination of confounding by characteristics such as gender and race and the elimination of a type of bias that results from selecting unrepresentative controls. In addition, because

variability is reduced, this design requires fewer subjects than the traditional case-control study.

When Is It Desirable to Use a Particular Study Design?

The goal of every epidemiologic study is to gather correct and sharply defined data on the relationship between an exposure and a health-related state or event in a population. The three main study designs represent different ways of gathering this information. Given the strengths and weaknesses of each design, there are circumstances for which a particular type of study is clearly indicated. These situations are described in the following paragraphs.

Experimental Studies

Investigators conduct an experimental study when they wish to learn about a prevention or treatment for a disease. In addition, they conduct this type of study when they need data with a high degree of validity that is simply not possible in an observational study. The high degree of validity in an experimental study stems mainly from investigators' ability to randomize subjects to either the treatment group or the comparison group and thereby control for distortions produced by confounding variables. A high level of validity may be needed for studying a prevention or treatment that is expected to have a small effect—usually defined as a difference of 20% or less between groups. A difference of this size is difficult to detect using an observational study because of uncontrolled bias and confounding. When the difference between groups is small, even a small degree of bias or confounding can create or mask an effect.

Although most scientists agree that well-conducted experimental studies produce more scientifically rigorous data than do observational studies, several thorny issues make it difficult to conduct experimental studies. These issues include noncompliance, the need to maintain high follow-up rates, high costs, physicians' and patients' reluctance to participate, and numerous ethical issues. Investigators must address all of these issues when considering this design. In particular, it is ethical to conduct experimental studies only when there is a state of equipoise within the expert medical community regarding the treatment. Equipoise is a "state of mind characterized by legitimate uncertainty or indecision as to choice or course of action."^{6(p88)} In other words, there must be genuine confidence that a treatment may be worthwhile in order to administer it to some individuals and genuine reservations about the treatment in order to withhold it from others.

Observational Studies

Observational studies can be used to study the effects of a wider range of exposures than experimental studies, including preventions, treatments, and possible causes of disease. For example, observational studies provide information to explain the causes of disease incidence and the determinants of disease progression, to predict the future health care needs of a population, and to control disease by studying ways to prevent disease and prolong life with disease. The main limitation of observational studies is investigators' inability to have complete control over disturbing influences or extraneous factors. As Susser states: "Observational studies have a place in the epidemiological armament no less necessary and valid than controlled trials; they take second place in the hierarchy of rigor but not in practicability and generalizability. . . . Even when trials are possible, observational studies may yield more of the truth than randomized trials."¹⁵

Once an investigator has decided to conduct an observational study, the next decision is usually whether to select a cohort or case-control design. Because a cohort study can provide information on a large number of possible health effects, this type of study is preferable when little is known about the health consequences of an exposure. A cohort study is also efficient for investigating a rare exposure, which is usually defined as a frequency of less than 20%.

Case-control studies are preferable when little is known about the etiology of a disease because they can provide information on a large number of possible risk factors. Case-control studies take less time and cost less money than cohort studies, primarily because the control group is a sample of the source population. Case-control studies are also more efficient than cohort studies for studying rare diseases because fewer subjects are needed, and for studying diseases with long induction and latent periods because long-term prospective follow-up is avoided. (A long induction and latent period means that there is a long time between the causal action of an exposure and the eventual diagnosis of disease.¹⁶) Because of their relatively smaller sample size, case-control studies are preferred when the exposure data are difficult or expensive to obtain. Finally, they are desirable when the population under study is dynamic because it is difficult to keep track of a population that is constantly changing. Tracing is required for a typical cohort study but not a typical case-control study.

Case-control studies have a few important disadvantages. First, because of the retrospective nature of the data collection, there is a greater chance of bias. Some epidemiologists have argued that case-control studies are not well suited for detecting weak associations—those with odds ratios less than 1.5—because of the likelihood of bias.¹⁷ Second, because data collection is retrospective, it may be difficult to establish the correct temporal relationship between the exposure and disease.

If an investigator has decided to conduct a cohort study, he or she must make one more choice: should it be a retrospective or prospective cohort study? This decision depends on the particular research question, the practical constraints of time and money, and the availability of suitable study populations and records. For example, a retrospective design must be used to study historical exposures. In making this decision, the investigator must also take into account the complementary advantages and disadvantages of retrospective and prospective cohort studies. For example, retrospective cohort studies are more efficient than prospective ones for studying diseases with long induction and latent periods. However, minimal information is usually available on the exposure, outcome, confounders, and contacts for follow-up because retrospective cohort studies typically rely on existing records that were not designed for research purposes. In addition, the use of retrospective data makes it more difficult to establish the correct temporal relationship between the exposure and disease.

In prospective cohort studies, investigators can usually obtain more detailed information on exposures and confounders because they have more control of the data collection process and can gather information directly from the participants. Follow-up may be easier because the investigator can obtain tracing information from participants and can maintain periodic contact with subjects. Prospective cohort studies are considered less vulnerable to bias than retrospective studies, because the outcomes have not occurred when the cohort is assembled and the exposures are assessed. In addition, it is easier for investigators to establish a clear temporal relationship between exposure and outcome. A decision tree depicting the choices between the three main study designs is shown in Figure 6-1.

Other Types of Studies

In addition to the three main study designs described above, two other types of studies are commonly conducted in epidemiologic research: cross-sectional and ecologic studies (see Table 6-2). Although both are popular, these designs have important limitations that are not present in the other observational designs.

Cross-Sectional Studies

A cross-sectional study “examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time.”^{2(p40)} Unlike populations studied in cohort and case-control studies, cross-sectional study

Goal: To Harvest Valid and Precise Information on Association
Between Exposure and Disease Using a Minimum of Resources

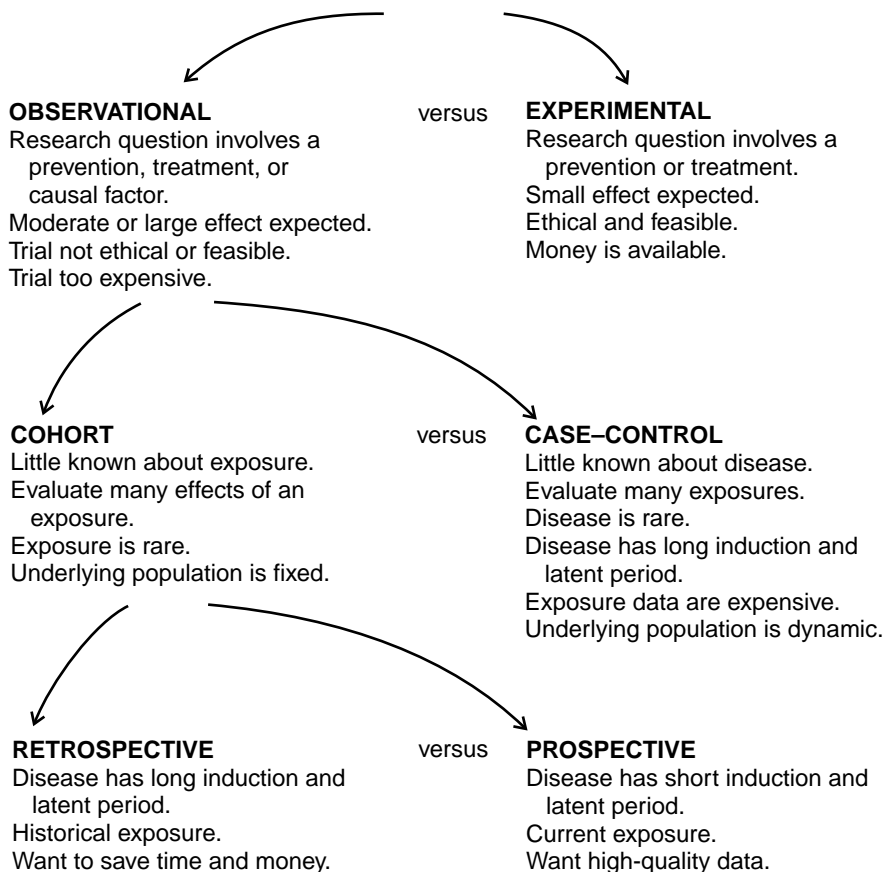


FIGURE 6-1. Decision Tree for Choosing Among Study Designs

populations are commonly selected without regard to exposure or disease status. Cross-sectional studies take a snapshot of a population at a single point in time and so measure the exposure prevalence in relation to the disease prevalence. In other words, current disease status is examined in relation to current exposure level.

Cross-sectional studies are carried out for public health planning and for etiologic research. Most governmental surveys conducted by the National Center for Health Statistics are cross-sectional in nature (see Chapter 4 for more details). For example, the National Survey of Family Growth is a periodic population-based survey focusing on factors that

TABLE 6-2 Key Features of Cross-Sectional and Ecologic Studies**Cross-sectional studies**

- Examine association at a single point in time, and so measure exposure prevalence in relation to disease prevalence.
- Cannot infer temporal sequence between exposure and disease if exposure is a changeable characteristic.
- Other limitations may include preponderance of prevalent cases of long duration and healthy worker survivor effect.
- Advantages include generalizability and low cost.

Ecologic studies

- Examine rates of disease in relation to a population-level factor.
- Population-level factors include summaries of individual population members, environmental measures, and global measures.
- Study groups are usually identified by place, time, or a combination of the two.
- Limitations include the ecological fallacy and lack of information on important variables.
- Advantages include low cost, wide range of exposure levels, and the ability to examine contextual effects on health.

affect maternal and child health. Its most recent cycle was based on a national probability sample of almost 11,000 civilian, noninstitutionalized women aged 15 to 44 years. In-person interviews gathered information on a woman's ability to become pregnant; pregnancy history; use of contraceptives, family planning, and infertility services; and breastfeeding practices.

Cross-sectional studies are fairly common in occupational settings using data from preemployment physical examinations and company health insurance plans.^{18(p144)} For example, investigators conducted a cross-sectional study to determine the relationship between low back pain and sedentary work among crane operators, straddle-carrier drivers, and office workers.¹⁹ All three groups had sedentary jobs that required prolonged sitting. Company records were used to identify approximately 300 currently employed male workers aged 25 through 60 years who had been employed for at least 1 year in their current job. Investigators assessed the "postural load" by observing workers' postures (such as straight upright position, forward or lateral flexion) and movements (such as sitting, standing, and walking). The investigators found that the prevalence of current and recent low back pain was more common among crane operators and straddle-carrier drivers than office workers. The crane operators and straddle-carrier drivers had two to three times the risk of low back pain

than did the office workers. The authors postulated that these differences resulted from crane operators' and straddle-carrier drivers' more frequent adoption of "non-neutral" trunk positions involving back flexion and rotation while on the job.¹⁹

Unfortunately, when epidemiologists measure the exposure prevalence in relation to disease prevalence in cross-sectional studies, they are not able to infer the temporal sequence between the exposure and disease. They cannot tell which came first—the exposure or the disease. This occurs when the exposure under study is a changeable characteristic such as a place of residence or a habit such as cigarette smoking. Consider, for example, a hypothetical cross-sectional study of cigarette smoking and the risk of tubal infertility conducted among patients seeking treatment at an infertility clinic. The current smoking status of women who have a diagnosis of tubal infertility is compared with that of fertile women whose husbands are the source of the infertility. If the frequency of cigarette smoking is three times greater among the infertile women, one could conclude that there is a moderately strong association between smoking and tubal infertility. However, it is difficult to know if smoking caused the infertility, because the women may have begun smoking after they began having difficulties achieving a pregnancy. This is quite possible, given that precise onset of infertility is difficult to determine and that medical treatment for infertility usually does not begin until a couple has been trying to conceive for at least 1 year. This is an important limitation of cross-sectional studies, because epidemiologists must establish the correct temporal sequence between an exposure and a disease in order to support the hypothesis that an exposure causes a disease (see Chapter 15 for more details).

Another disadvantage of cross-sectional studies is that such studies identify a high proportion of prevalent cases of long duration. People who die soon after diagnosis or who recover quickly are less likely to be identified as diseased. This can bias the results if the duration of disease is associated with the exposure under study.

Still another bias may occur when cross-sectional studies are conducted in occupational settings. Because these studies include only current and not former workers, the results may be influenced by the selective departure of sick individuals from the workforce. Those who remain employed tend to be healthier than those who leave employment. This phenomenon, known as the "healthy worker survivor effect," generally attenuates an adverse effect of an exposure. For example, the strength of the association observed in the study of low back pain among sedentary workers may have been biased by the self-selection out of employment of workers with low back pain.

Cross-sectional studies also have several advantages. First, when they are based on a sample of the general population, their results are highly

generalizable. This is particularly true of the cross-sectional surveys conducted by the National Center for Health Statistics. Second, they can be carried out in a relatively short period of time, thereby reducing their cost. Furthermore, the temporal inference problem can be avoided if an inalterable characteristic, such as a genetic trait, is the focus of the investigation. It can also be avoided if the exposure measure reflects not only present but also past exposure. For example, an x-ray fluorescence (XRF) measurement of an individual's bone lead level reflects that person's cumulative exposure over many years.²⁰ Thus, a cross-sectional study of infertility and bone lead levels using XRF measurements would not suffer from the same temporal inference problem as the study of infertility and cigarette smoking described above.

Ecologic Studies

A classical ecologic study examines the rates of disease in relation to a factor described on a population level. Thus, "the units of analysis are populations or groups of people rather than individuals."^{2(p52)} The population-level factor may be an aggregate measure that summarizes the individual members of the population (for example, the proportion of individuals above the age of 65 years), an environmental measure that describes the geographic location where the population resides or works (for example, the air pollution level), or a global measure that has no analog on the individual level (such as the population density or existence of a specific law or health care system).^{21(p460)} Thus, the two key features that distinguish a traditional ecologic study from other types of epidemiologic studies are: (1) the population unit of analysis and (2) an exposure status that is the property of the population.

Ecologic studies usually identify groups by place, time, or a combination of the two.^{21(p463)} For example, researchers conducted an ecologic study with groups identified by place to determine the association between air pollution and mortality rates.²² The study authors obtained 1978–1981 air pollution levels from monitoring stations throughout the United States and 1980 mortality rates for 305 Standard Metropolitan Statistical Areas (SMSAs). SMSAs are geographic areas that typically include a city and its surrounding areas.^{2(pp160–161)} The investigators examined correlations between the air pollution variables (such as total suspended particulates and sulfates) and mortality. They observed a positive association between annual mean sulfate concentration and total mortality. That is, SMSAs with high sulfate concentrations tended to have high mortality rates (for example, Scranton, Pennsylvania), while those with low sulfate concentrations tended to have low mortality rates (for example, Salt Lake City, Utah) (see Figure 6–2).

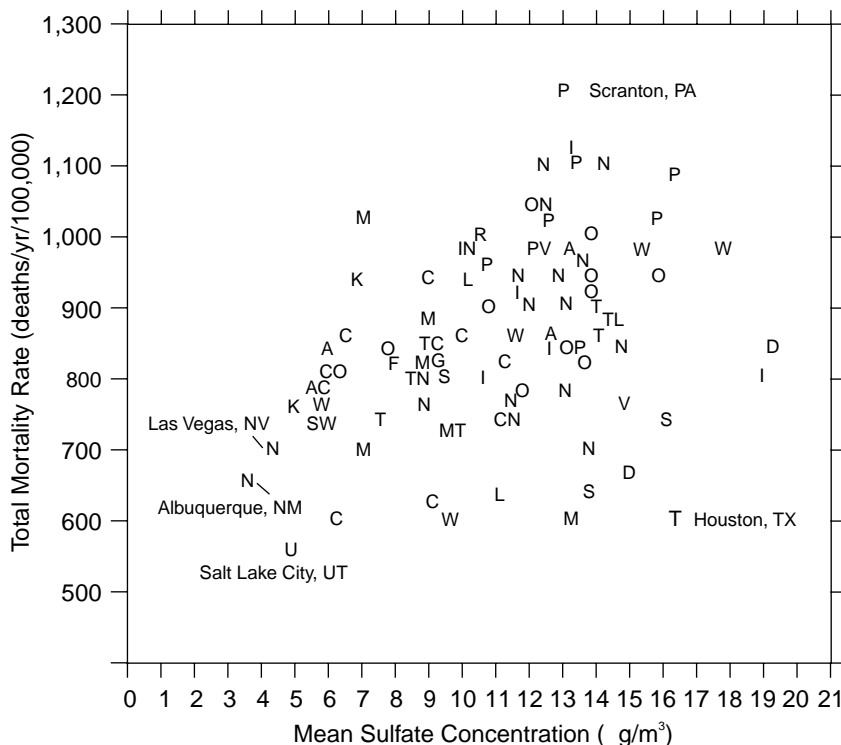


FIGURE 6-2. Plot of Total Mortality Rate versus Annual Mean Sulfate Concentration in an Ecological Study

Source: Reprinted from Ozkaynak H, Thurston GD. Association between 1980 US mortality rates and alternative measures of airborne particle concentration. *Risk Analysis*. 1987;7:454.

Ecologic studies that identify groups by time often compare disease rates over time in geographically defined populations.^{21(p464)} For example, investigators conducted an ecologic study to compare HIV seroprevalence changes over time among injecting drug users in cities with and without needle-exchange programs.²³ The investigators hypothesized that introduction of needle-exchange programs (programs that allow drug users to obtain clean needles and syringes free of charge) would decrease HIV transmission and lead to lower seroprevalence rates. The authors obtained information on HIV seroprevalence among injecting drug users during the 1980s and 1990s from published studies and from unpublished reports from the Centers for Disease Control and Prevention. They obtained information on the implementation of the needle-exchange programs from published reports and experts. They found that the average HIV seroprevalence *increased* by 5.9% per year in 52 cities without needle-exchange programs, and it *decreased* by 5.8% per year in 29 cities with needle-

exchange programs. Thus, the average annual change in seroprevalence was 11.7% lower in cities with needle-exchange programs.

A special type of time-trend ecologic study tries to separate the effects of three time-related variables: age, calendar time, and year of birth.^{21(p465)} For example, a recent ecologic study examined homicide mortality data from the United States during the period 1935 through 1994 in order to understand better these three time-related variables.²⁴ The authors found that death rates caused by homicide doubled over this period, and that most of the increase occurred from 1960 through 1974. Peak ages for homicide deaths ranged from 20 to 39 years. No associations with year of birth were seen among women; however, there was a large increase in the risk of homicide mortality among men born around 1965. Men in this "birth cohort" accounted for the increase in homicide mortality from 1985 through 1994. The authors postulated that the increased prevalence of alcohol and drug abuse and the availability of lethal weapons may account for the association with year of birth among males.

Some investigations cannot be classified as traditional ecologic studies because they have both ecologic and individual-level components. Consider, for example, a "partially" ecologic study that was recently conducted in Norway to determine if chlorinated drinking water was associated with the occurrence of birth defects.²⁵ Chlorinated water contains numerous chemicals called disinfection byproducts that may be harmful to developing embryos. Because the study used group-level data on the exposure and individual-level data on the birth defects and confounding variables, it is considered partially ecologic. The study population consisted of children born in Norway from 1993 through 1995 who lived in an area with information on water chlorination ($n = 141,077$ children). Investigators examined the prevalence of birth defects in relation to the proportion of the population served by chlorinated water. They examined four groups of municipalities: those with 0% chlorinated water, 0.1% to 49.9% chlorinated water, 50 to 99.9% chlorinated water, and 100% chlorinated water. Individual-level characteristics that were controlled included maternal age and parity and place of birth, as obtained from the children's birth records. The study suggested there was a 15% increased risk of birth defects overall and a 99% increased risk of urinary tract defects among women whose water was chlorinated. However, the authors acknowledged that the study did not directly measure the concentrations of the disinfection byproducts on the individual level.

The lack of individual-level information leads to a limitation of ecologic studies known as the "ecological fallacy" or "ecological bias." The ecological fallacy means that "an association observed between variables on an aggregate level does not necessarily represent the association that

exists at the individual level.”^{2(p51)} In other words, one cannot necessarily infer the same relationship from the group level to the individual level. In the Norway study, we do not know if the women who drank chlorinated water were the same women who gave birth to babies with defects. This is particularly true for the two middle exposure groups (municipalities with 0.1 to 49.9% and 50 to 99.9% of the population with chlorinated water), because women with chlorinated and unchlorinated water were grouped together. On a practical level, the ecological bias means that the investigator cannot fill in the cells of a two-by-two table from the data available in a traditional ecologic study.

Additional limitations of ecologic studies include investigators’ inability to detect subtle or complicated relationships (such as a *J*-shaped or other curvilinear relationships) because of the crude nature of the data, and the lack of information on characteristics that might distort the association. For example, although the ecologic study of changes in HIV seroprevalence over time suggests that needle-exchange programs reduce HIV transmission, other factors may have accounted for this change, including the simultaneous implementation of other types of HIV prevention strategies.

In spite of these limitations, ecologic studies remain a popular study design among epidemiologists for several reasons.^{21(p462)} They can be done quickly and inexpensively because they often rely on preexisting data. Their analysis and presentation are relatively simple and easy to understand. They have the ability to achieve a wider range of exposure levels than could be expected from a typical individual-level study. And, last but not least, epidemiologists have a genuine interest in ecologic effects. For example, ecologic studies can be used “to understand how context affects the health of persons and groups through selection, distribution, interaction, adaption, and other responses.” As Susser states, “Measures of individual attributes cannot account for these processes; pairings, families, peer groups, schools, communities, cultures, and laws are all contexts that alter outcomes in ways not explicable by studies that focus solely on individuals.”²⁶ This observation is particularly true for studies of the transmission of infectious disease. For example, investigators conducted an ecological analysis to determine the risk factors for dengue fever (a viral infection transmitted by the *Aedes aegypti* mosquito) in 70 Mexican villages.²⁷ They measured exposure by the average proportion of *Aedes* larvae among households in each village in relation to the proportion of affected individuals in the village. The study found a strong relationship between dengue antibody levels and the village-level larval concentrations. This association was not seen when an individual-level study was carried out, because it did not take into account transmission dynamics at the population level.

Summary

Epidemiologists use both experimental and observational study designs to answer research questions. Each type of design represents a different way of harvesting the necessary information. The selection of one design over another depends on the research question and takes into account validity, efficiency, and ethical concerns.

For ethical reasons, experimental studies can only be used to investigate preventions and treatments for diseases. The hallmark of an experimental study is the investigator's active manipulation of the agent under study. Here, the investigator assigns subjects (usually at random) to two or more groups that either receive or do not receive the preventive or therapeutic agent. Investigators select this study design when they need data with a high degree of validity that is simply not possible in an observational study. However, experimental studies are expensive and often infeasible and unethical, and so most epidemiologic research consists of observational studies.

Observational studies can be used to investigate a broader range of exposures including causes, preventions, and treatments for diseases. The two most important types of observational studies are the cohort study and the case-control study. Epidemiologists use a cohort study when little is known about an exposure, because this type of study allows investigators to examine many health effects in relation to an exposure. In a cohort study, subjects are defined according to their exposure levels and are followed for disease occurrence. In contrast, investigators use a case-control study when little is known about a disease, because this type of study allows researchers to examine many exposures in relation to a disease. In a case-control study, cases with the disease and controls are defined and their exposure histories are collected and compared.

Cross-sectional and ecologic studies are two other popular types of observational studies. Cross-sectional studies examine exposure prevalence in relation to disease prevalence in a defined population at a single point in time. Ecologic studies examine disease rates in relation to a population-level factor. Both types of design have important limitations absent from the other observational studies. An unclear temporal relationship between exposure and disease arises in cross-sectional studies of changeable exposures. Problems making cross-level inferences from the group to the individual (known as the ecological fallacy) occur in ecologic studies.

References

1. MacMahon B, Trichopoulos D. *Epidemiology Principles and Methods*. 2nd ed. Boston, MA: Little, Brown and Company; 1996.
2. Last JM. *A Dictionary of Epidemiology*. 3rd ed. New York, NY: Oxford University Press; 1995.

3. Benenson AS. *Control of Communicable Diseases in Man*. 15th ed. Washington, DC: American Public Health Association; 1990.
4. Pickett JP, exec. ed. *The American Heritage Dictionary of the English language*. 4th ed. Boston, MA: Houghton Mifflin; 2000.
5. Colton T. *Statistics in Medicine*. Boston, MA: Little, Brown and Company; 1974.
6. Meinert CL. *Clinical Trials Dictionary, Terminology and Usage Recommendations*. Baltimore, MD: The Johns Hopkins Center for Clinical Trials; 1996.
7. Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. 2nd ed. Littleton, MA: PSG Publishing Co; 1985.
8. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol*. 1992;21:837–841.
9. Hunt JR, White E. Retaining and tracking cohort study members. *Epidemiol Rev*. 1998;20:57–70.
10. Miettinen OS. The “case-control” study: valid selection of study subjects. *J Chron Dis*. 1985;38:543–548.
11. McLaughlin JK, Blot WJ, Mehl ES, Mandel JS. Problems in the use of dead controls in case-control studies. I. General results. *Am J Epidemiol*. 1985;121:131–139.
12. Correa A, Stewart WF, Yeh H-C, Santos-Burgoa C. Exposure measurement in case-control studies: reported methods and recommendations. *Epidemiol Rev*. 1994;16:18–32.
13. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
14. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol*. 1995;142:91–98.
15. Susser M. Editorial: The tribulations of trials—interventions in communities. *Am J Public Health*. 1995;85:156–158.
16. Rothman KJ. Induction and latent periods. *Am J Epidemiol*. 1981;114:253–259.
17. Austin H, Hill HA, Flanders WD, Greenberg RS. Limitations in the application of case-control methodology. *Epidemiol Rev*. 1994;16:65–76.
18. Monson RR. *Occupational Epidemiology*. 2nd ed. Boca Raton, FL: CRC Press; 1990.
19. Burdorf A, Naaktgeboren B, de Groot H. Occupational risk factors for low back pain among sedentary workers. *J Occup Med*. 1993;35:1213–1220.
20. Hu H. Bone lead as a new biologic marker of lead dose: recent findings and implications for public health. *Environ Health Perspect*. 1998;106:961–967.
21. Morgenstern H. Ecologic studies. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology*. Philadelphia, PA: Lippincott-Raven Publishers; 1998.
22. Ozkaynak H, Thurston GD. Association between 1980 US mortality rates and alternative measures of airborne particle concentration. *Risk Anal*. 1987;7:459–480.
23. Hurley SF, Jolley DJ, Kaldor JM. Effectiveness of needle-exchange programmes for prevention of HIV infection. *Lancet*. 1997;349:1797–1800.
24. Shahpar C, Li G. Homicide mortality in the United States, 1935–1994: age, period and cohort effects. *Am J Epidemiol*. 1999;150:1213–1222.

25. Magnus P, Jaakkola JJK, Skrondal A, Alexander J, Becher G, Krogh T, Dybing E. Water chlorination and birth defects. *Epidemiology*. 1999;10:513–517.
26. Susser M. The logic in ecological: I. The logic of analysis. *Am J Public Health*. 1994;84:825–829.
27. Koopman JS, Longini IM. The ecological effects of individual exposures and nonlinear disease dynamics in populations. *Am J Public Health*. 1994;84:836–842.

EXERCISES

1. State the main difference between the following study designs:
 - A. Observational and experimental studies
 - B. Retrospective cohort and prospective cohort studies
 - C. Cohort and case-control studies
2. Briefly describe a cross-sectional study and indicate its main limitation.
3. Briefly describe an ecologic study and indicate its main limitation.
4. State which observational study design is best (that is, most efficient and logical) in each of the following scenarios:
 - A. Identifying the causes of a rare disease
 - B. Identifying the long-term effects of a rare exposure
 - C. Studying the health effects of an exposure for which information is difficult and expensive to obtain
 - D. Identifying the causes of a new disease about which little is known
 - E. Identifying the short-term health effects of a new exposure about which little is known
 - F. Identifying the causes of a disease with a long latent period
5. Which type of study is being described in each of the following scenarios?
 - A. A study that examines the death rates from cervical cancer in each of the 50 U.S. states in relation to the average percentage of women in each state undergoing annual PAP smear screening.
 - B. A study that compares the prevalence of back pain among current members of the plumbers and pipefitters union with that of current members of the bakers and confectionary union.
 - C. A study that evaluates the relationship between breast cancer and a woman's history of breastfeeding. The investigator selects women with breast cancer and an age-matched sample of women who live in the same neighborhoods as the women with breast

cancer. Study subjects are interviewed to determine if they breast-fed any of their children.

- D. A study that evaluates two treatments for breast cancer. Women with stage 1 breast cancer are randomized to receive either lumpectomy alone or lumpectomy with breast radiation. Women are followed for 5 years to determine if there are any differences in breast cancer recurrence and survival.
- E. A study of the relationship between exposure to chest irradiation and subsequent risk of breast cancer that was begun in 2001. In this study, women who received radiation therapy for postpartum mastitis (an inflammation of the breast that occurs after giving birth) in the 1940s were compared to women who received a nonradiation therapy for postpartum mastitis in the 1940s. The women were followed for 40 years to determine the incidence rates of breast cancer in each group.