Introduction to Study Design

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5.4 Common Types of Epidemiologic Studies

5.1 Introduction to Etiological Research

Hypothesis Statement

Hypotheses are nets: only he who casts will catch.—Novalis

The advancement of knowledge about the causes of ill-health is an ongoing process that progresses in overlapping stages. An issue may be brought to light by an intriguing case report. This may be followed by the analysis of readily available vital statistics, surveillance information, and routinely collected health survey data. Various types of refined studies may follow, perhaps culminating in case-control studies, cohort studies, and epidemiologic experiments. In all instances, the investigator pursues techniques that are most advantageous to revealing causal relations.

Not to be overlooked in this process is the need to have sharply focused research questions, clearly defined hypotheses, and study designs that connect research questions to data that will be collected. Foreseeable facets of study hypotheses are specified within the confines of pragmatism before the study is begun. As new questions arise, additional hypotheses are defined and articulated to guide further study.

Study hypotheses should identify those factors that influence disease occurrence and should, in general, address these aspects of the study’s design:

1. The characteristics of the population to which the hypothesis applies
2. The explanatory factors, attributes and exposures being considered as potential health determinants
3. The specific health-related outcome being studied, and how these are defined for the
purpose of study (the disease and its case definition)
4. The expected change in incidence associated with given levels of exposure (dose-response relation)
5. The time period that is thought to elapse between the exposure and its putative effect (time-response relation)
6. Cofactors that contribute to the health-related outcome being studied, and how these will be addressed by the study’s design
7. Plausible causal mechanism by which the exposure induces its effects
8. The sample size required to demonstrate the expected change in incidence

**Illustrative Example 5.1 (Example of a Hypothesis Statement).** (1) Let us consider the relationship between specific oral contraceptive formulations and the risk of venous thromboembolic disease in a population of women of childbearing age in the United States between 2002 and 2006. (2) The explanatory factor of this study will be different types of combination oral contraceptives, varying in their estrogen dose and progesterone type. (3) The case definition will be based on diagnostically confirmed and treated cases using specific clinical criteria for deep venous thrombosis and pulmonary embolism. (4) We expect that the effects of different oral contraceptives would increase according to the estrogen dose and progesterone type of the formulation and that (5) effects would manifest only during current use of the contraceptive product. (6) Information about cofactors associated with venous thromboembolism such as age, surgery, trauma, the post-partum period, obesity, life-threatening illness (and so on) will be collected and evaluated during the data analysis phase of the study. (7) The causal mechanism relates to laboratory findings suggesting increases in thrombogenesis and decreases in fibrinolysis with different formulations. (8) A sample size of approximately 60,000 women in each of the groups studied for a year is needed to detect a risk differential of 8 per 10,000 in some formulations compared to 4 per 10,000 in others with 80% power at an alpha level of .05.

**Variables**

The typical generic epidemiologic research question is: “Is there a causal relation between the explanatory factor X and health outcome Y?”

Explanatory Factor X → Health-Related Outcome Y

The **explanatory factor** may represent any personal attribute, environmental factor, social factor, personal attribute or behavior thought to influence health. This is the **independent variable** of the analysis. In the epidemiologic literature, this has traditionally been referred to as the “exposure.”

The **health-related outcome** may represent any disease, illness, or injury, or any surrogate or predictor of ill- or good-health. This is the **dependent variable** of the analysis, and has traditionally been referred to as merely the “disease” in epidemiologic research.

In addition to the explanatory factor X and health-outcome Y, the research question must also address other factors associated with factors X and Y. These additional factors are...
referred to as potential confounders, control variables, extraneous variables, or simply as cofactors. The objective of etiologic research is to determine the effect of explanatory factor X on health-outcome Y while accounting for the contributions of cofactors C₁, C₂, … Cₖ.

\[ X \rightarrow Y \]
\[ C_1 \]
\[ \vdots \]
\[ C_k \]

For the hypothesis suggested by Illustrative Example 5.1, the variables corresponds to:

\[ \text{OC type} \rightarrow \text{Venous thrombembolism} \]
\[ \text{Age} \]
\[ \text{Surgery} \]
\[ \vdots \]
\[ \text{etc.} \]

**Data**

The data that constitute variables X, Y, C₁, C₂, … Cₖ may be derived from a variety of sources including personal interviews, interviews of surrogates (e.g., relatives, roommates), self-administered questionnaires, employment records, environmental records, medical and pharmacy records, administrative databases, government data systems, and direct examination. The type of data used, of course, will depend on the research question being addressed, the cost of obtaining data, the need for confidentiality, the type population studied, and available technology.

Collection of information from medical and health service records requires cooperation from study subjects, hospitals, medical practitioners, and the health care systems that “own” the data. Obtaining cooperation from these parties can be difficult and requires special care be paid to principals of confidentiality and ethical guidelines for research involving human subjects, as discussed in the following section.

The information in medical records must be abstracted for analysis. Training medical record abstractors is essential to obtain accurate and uniform information. It is often advisable to blind the medical abstractor to the study hypothesis and selected information in the medical records to prevent conscious and unconscious biases from entering into the abstraction process. When more than one medical record abstractor is involved in a study, it is wise to produce separate analyses for their data to check for consistency of results. Lack of consistent results, such as a positive association derived by data from one reviewer but not the other, is clearly cause for concern.

Questionnaires and abstraction forms should be brief and simple to complete. The art of creating clearly worded, non-ambiguous, non-presumptuous, and non-leading questions
takes extra thought and planning (Payne, 1951). Data collection forms must be piloted and tested repeatedly to remove ambiguities and redundancies before being used in the study proper. Completed interviews are reviewed by the study coordinator before being entered and validated. After data from the various sources (i.e., questionnaire, interview, examination, medical record abstraction) are collected, information are entered into a database, documented, and audited for validity before being merged to form the study database.

5.2 Ethical Conduct of Studies Involving Human Subjects

Table 5.1 lists three fundamental ethical principals for conducting research using human subjects. These include respect for persons, beneficence, and justice.

**TABLE 5.1. Principles of Ethical Research Involving Human Subjects**

<table>
<thead>
<tr>
<th>Ethical Principle</th>
<th>Research Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respect for persons</td>
<td>Informed consent given freely. Implies ability to comprehend consequences; confidentiality is maintained for private information.</td>
</tr>
<tr>
<td>Beneficence</td>
<td>Risk and benefits are assessed. Benefits can be direct, indirect, collateral, or aspirational. Harms may involve physiological, psychological, or socioeconomic consequences.</td>
</tr>
<tr>
<td>Justice</td>
<td>Selection of study groups should be inclusive, equitable, and avoid exploitation.</td>
</tr>
</tbody>
</table>

Source: *The Belmont Report (1979)*

In addition, for studies involving participation, subjects must freely give their informed consent before being allowed to participate in a study. Informed consent implies the subject is given a chance to ask questions, is not coerced, is under no obligation to participate in the study, and may withdraw from the study at any time. A signed statement of consent is required.

Ethical safeguards of studies are overseen by human subjects committees known as institutional review boards (IRBs). IRBs are committees composed of researchers, clinicians, administrators, and laypeople who review the study protocol before the study is begun. Their primary objective is to ensure the ethical treatment of human subjects and to oversee informed consent procedures.

Separate from the IRB, studies involving interventions require a Data and Safety Monitoring Board (DSMB). The DSMB is an independent group of outside experts that periodically reviews and evaluates accumulated evidence from the study to monitor its safety and progress. The job of the DSMB is to make recommendations concerning the continuation, modification, or termination of the study.

Studies that require treatments and interventions present additional special concerns in their design. To ethically assign treatments, none of the treatments can be known to be superior to any other. Treatments that present special hazards cannot be ethically
assigned and, just as importantly, treatments that are held to be beneficial cannot be ethically withheld. Therefore, a true state of uncertainty about the pros and cons of the treatment must exist before it can be submitted to a trial. This balanced void of knowledge is sometimes referred to as **equipoise**.

### 5.3 Selected Elements of Study Design

**Necessity of a Referent or “Control” Group**

The effect of a factor can be judged only in relation to what would have occurred in its absence. This is why etiologic research requires at least two groups: one that is exposed to the study factor (the **index group**), and another that not exposed (a **referent** or **control group**).

The effects of treatments, for example, are not always obvious. If a patient recovers following a treatment, how do we know whether recovery was due to the treatment or might not have occurred spontaneously? In fact, how do we know that the treatment did not delay recovery? Now consider administering the treatment to one group of patients while leaving an identical group of patients untreated. If the treated patients experienced a higher incidence of recovery than the control group, we may safely conclude that either: (a) the treatment had a positive effect, (b) the difference was due to chance, or (c) the groups differed in some important way other than the treatment. It is our job to weight the evidence concerning these three possible explanations.

The same situation applies to non-experimental studies. If a child that lives near a high tension electric power lines develops leukemia, the public will be tempted to attribute the leukemia to the electromagnetic fields that emanated from that power line. In a similar vein, when a brain tumor develops in an individual who uses their cell phone heavily, they will be tempted to attribute their condition to cell phone use. These outcomes, however unfortunate, cannot arbitrarily attributed to these particular environmental exposures. The question of course is not whether there is an association within these particular individuals. The question is whether these specific environmental exposures caused these outcomes. On a population basis, this translates to these exposures increase risks of occurrence. Thus, nonexposed referent group are needed to compare leukemia rates in children who are and who are not exposed to electromagnetic fields; brain tumor rates must be compared in heavy- and light-users of cell phones. *If* differences are then observed, the same three explanations listed above must be entertained. Either: (a) the exposure had an effect, (b) the observed difference are due to chance, or (c) the exposed and nonexposed groups differ is some other important way.

In both experimental and non-experimental studies, the purpose of the referent group is to provide a baseline rate that reflects its incidence in the absence of exposure. Without this referent rate, it is nearly impossible to determine whether an exposure has a positive or negative effect, or makes no difference at all. There are many ways to incorporate a nonexposed referent group into a study. Experimentation provides one archetype.
Experimental vs. Nonexperimental (Observational) Designs

**Experimentation** allows the investigator to assign an experimental treatment to some study subjects while leaving other study subjects unexposed to the experimental treatment. The allocation of experimental treatments can be based on chance mechanisms (randomized controlled trials; RCTs) or on deliberate mechanisms (nonrandomized controlled trials). Either way, the method of allocating the treatment is built into the study’s protocol. Randomized designs are superior because randomization encourages extraneous factors that might otherwise confound the results of the study to balance among the treatment groups.

In a randomized controlled experiment, individuals are randomly assigned to either a treatment group or control group. Study outcomes are then followed and monitored during the follow-up period.

**Randomized Experiment**

\[
\begin{align*}
&\text{Recruit} \rightarrow \text{randomize} \\
&\text{group 1} \rightarrow \text{treatment 1} \rightarrow \text{follow-up & assess} \rightarrow \text{incidence}_1 \\
&\text{group 2} \rightarrow \text{treatment 2} \rightarrow \text{follow-up & assess} \rightarrow \text{incidence}_0
\end{align*}
\]

In contrast, nonexperimental designs (also called observational designs) delineate relationships between study exposures and outcomes without experimental allocation of the study exposure. That is, the exposures are attributes of study subjects or their environment, or are self-selected by the study subjects themselves. In the observations design known as an **observational cohort study**, the epidemiologist assembles individuals and classifies them according to an attributes or exposure. Participants are then followed over time and periodically assessed for the occurrence of the study outcome.

**Observational Cohort**

\[
\begin{align*}
&\text{Recruit} \rightarrow \text{classify} \\
&\text{group 1 ("exposed")} \rightarrow \text{follow-up & assess} \rightarrow \text{incidence}_1 \\
&\text{group 2 ("nonexp")} \rightarrow \text{follow-up & assess} \rightarrow \text{incidence}_0
\end{align*}
\]

One of the leading concerns in both experimental and observational research is the comparability of the study groups. For comparisons to be valid, the groups being compared should be similar in all relevant ways except for the study exposure. Experimentation is helpful in achieving “like-to-like” comparisons.

**Illustrative Example 5.2 (Experimental and Observational Designs, Women’s Health Initiative).** The Women's Health Initiative (WHI) is a major 15-year research program sponsored by the National Heart, Lung, and Blood Institute. The objective of this program is to address the common causes of death, disability, and poor quality of life in postmenopausal women (WHI, 2010).

The WHI program included both experimental studies and observational studies. The experimental part of the WHI was designed to test the effects of postmenopausal
hormone therapy, diet modification, and calcium and vitamin D supplements on heart
disease, fractures, and breast and colorectal cancer. In the hormone trial, participants
were randomly assigned to groups that received a pill containing estrogen, estrogen plus
progesterone, or an identical-looking pill that contained no active ingredients. Incidents
of various health outcomes (e.g., coronary disease, stroke, pulmonary embolism, breast
cancer) were tracked in the study subjects.

The observational part of the WHI study complemented the experimental study by
providing estimates of the extent to which various risk factors predicted heart disease,
cancers, fractures, and other adverse health outcomes in women. The observational study
tracked the experience of 93,676 postmenopausal women between the ages of 50 to 79.
Women who joined this part of the study filled out health forms and visited study clinics
periodically. The observation study participants were not required to take any medication
or change their health habits while being followed.

Unit of Observation

The unit of observation in an epidemiologic study refers to the level of aggregation of
the entity upon which measurements are recorded. Observations may be made at any
level of aggregation, from the individual person to an entire group living in a region, and
everything in-between.

persons ↔ social groups ↔ neighborhoods ↔ regions ↔ nations

This topic was introduced in §4.3 (Ecological Studies) and will not be covered here
except to note that person-level studies are generally preferable when making specific
judgments about pathogenesis. However, multi-level studies that combine various units
of observation, with some units of observation at the individual-level and some at the
environmental-level well-adapted for delineating how aggregate-level and person-level
variables interact as health determinants. The remainder of this chapter restricts itself to
studies that rely on individual-units of observation.

Cross-Sectional and Longitudinal Measurements

Person-level measurements can be either longitudinal or cross-sectional. Longitudinal
measurements record events over time within individuals. In contrast, cross-sectional
measurements do not permit the time-sequencing of events within individuals. For
example, a single serological measurement is cross-sectional because it cannot determine
when an individual became seropositive. In contrast, a series of serological measurements
obtained over time starting with a seronegative individual is longitudinal because it
derives an approximate date for the seroconversion event if it were to occur.

Longitudinal data are preferable when conducting etiologic research because, for a factor
to be causal, it must precede the event it caused by a reasonable amount of time.
However, for characteristics that do not change over time (e.g., blood type, eye color,
etnicity), it matters little whether the measurement is longitudinal or cross-sectional: if
we know the status of an individual now, we also know their status in the past. In addition, many human habits are potentially changeable, such as dietary choices, but display some degree of long-term permanence—dietary habits for instance. For stable characteristics such as these, the current status of the attributed might serve as a suitable proxy for its longitudinal measurement.

Although **cross-sectional field surveys** have been relegated a secondary role in etiological research, they still serve the need is to estimate the prevalence of health-related conditions in populations. The development of cross-sectional survey methods was particularly active in the period following World War II. Two such areas of development were in the areas of national morbidity surveys and community surveys of mental disorders.

**Illustrative Example 5.3 (Cross-Sectional Study, Mental Health).** Table 5.2 contains data from a historically important mental health survey from the 1950s. Data were compiled by a team of psychiatrists and sociologists using a census of psychiatric patients and a five percent sample of the general population from the New Haven urban community. Social economic status (the explanatory factor or “independent variable”) was based on a combination of information about neighborhood of residence, occupation, and education. Psychosis and neurosis (the health related outcomes or “dependent variables”) were based on the diagnosis and treatment of these conditions in the community (Hollingshead & Redlich, 1953). Table 5.2 shows the results.

**TABLE 5.2. Prevalence per 100,000 of Psychosis and Neurosis by Social Economic Status (SES), Connecticut, 1950**

<table>
<thead>
<tr>
<th>SES</th>
<th>Psychosis</th>
<th>Neurosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2 (high)</td>
<td>188</td>
<td>349</td>
</tr>
<tr>
<td>3</td>
<td>291</td>
<td>250</td>
</tr>
<tr>
<td>4</td>
<td>518</td>
<td>114</td>
</tr>
<tr>
<td>5 (low)</td>
<td>1505</td>
<td>97</td>
</tr>
</tbody>
</table>


These data suggest a positive association between low socioeconomic status and psychosis. Just the opposite is seen with low socioeconomic status and neurosis.

The meaning of these correlations, however, is not self-evident. Problems in interpretation arise from these potential sources of bias:

- **Detection bias.** Some persons with mental disorders may not come to the attention of the health care system used to identify cases. This creates a problem of detection bias. Psychosis, for example, may come to the attention of psychiatrists through legal intervention. Since social class is strongly correlated with legal interventions, the selective forces that bring patients to care are also strongly correlated with the study exposure and study outcome. This could create or at least exaggerate the positive association between low SES and psychosis.

- **Diagnostic bias.** There may be a diagnostic bias associated with both of the study...
outcomes. For example, state hospitals, where the lower SES patients are more likely to be seen, may have been more likely to diagnosis psychosis than neurosis, whereas private providers may have been more likely to diagnose neurosis. Thus, the diagnosed rates may be a spurious function of the provider type, as opposed to SES. This is referred to as a diagnostic bias.

◊ Reverse-causality bias. Another source of bias that we must consider is called reverse-causality bias or cart-before-the-horse bias. Because data are cross-sectional, it is difficult to establish the correct temporal sequence of events. That is, the order of the exposure–disease may be turned around. An essential property of a causal factor is for the exposure to precede the onset of disease. With reverse causality bias, the temporal sequencing of events is reversed or inadequately documented. Although one may be tempted to say that low social status causes psychosis, another plausible explanation is that psychosis causes downward social mobility; psychotics cannot often maintain the normal social relations required to maintain a reasonable socioeconomic status. With cross-sectional data, the proper temporal sequence can only be assumed.

◊ Incidence-prevalence bias. Varying duration of illness may confuse the interpretation of results in a type of bias called prevalence-incidence bias (Neyman, 1955). Prevalence is related to both incidence and average duration of illness (see Chapter 3.4). In studying the prevalence of a condition, therefore, cases of long duration are more heavily weighted than those of short duration. If the socioeconomic groups had similar incidences of neurosis, for example, but SES groups had more persistent diagnoses, an apparent gradient in prevalence would exist with no difference in incidence. Indeed, this is what the researchers found in a subsequent analysis (Table 5.3). The incidence of neurosis was not linked to socio-economic status. However, rates of reentry to treatment and the continuous status were. In contrast, the positive association between low socioeconomic status and psychosis persisted when the analysis was restricted to incident cases.

| TABLE 5.3. Incidence, Reentry, Continuous, and Prevalence per 100,000 of Neurosis and Psychosis by Socioeconomic Status a |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| SES                            | Incidence       | Reentry         | Continuous      | Prevalence      |
| Neurosis                       |                 |                 |                 |                 |
| 1 and 2 (high)                 | 69              | 44              | 251             | 349             |
| 3                              | 78              | 30              | 137             | 250             |
| 4                              | 52              | 17              | 82              | 114             |
| 5 (low)                        | 66              | 35              | 65              | 97              |
| Psychosis                      |                 |                 |                 |                 |
| 1 and 2 (high)                 | 28              | 44              | 117             | 188             |
| 3                              | 36              | 38              | 217             | 291             |
| 4                              | 37              | 42              | 436             | 518             |
| 5 (low)                        | 73              | 88              | 1344            | 1505            |


aData have been adjusted for sex and age.
Historical efforts to correct some of the weaknesses of cross-sectional field survey when used for causal inferences have lead to greater rigor in epidemiologic methods and the development of longitudinal methods in the form of modern cohort and case-control studies.

**Cohort vs. Case-Control Studies**

Not losing sight of individual experiences from the beginning to the end underlies the basis of longitudinal analyses. The two primary types of observational studies that are longitudinal are cohort studies and case-control studies.

**Cohort studies** start by identifying disease-free individuals in a source population. Study subjects are recruited and classified according to risk factors thought to be associated with future disease occurrence. A follow-up period ensued during with relevant health events are monitored. Incidences of the health events are then compared among the groups, often in the form of a rate ratio, rate difference, or equivalent statistical form.

```
Cohort
Source population
\[\text{exposed individuals} \rightarrow \text{disease incidence}\]
\[\text{nonexposed individuals} \rightarrow \text{disease incidence}\]
```

**Case-control studies** can be viewed as a sampling variant of cohort studies. The case-control approach starts by identifying disease events in the source population: these study subjects form the *case* series. It then selects a sample of non-cases from the source population: this is the referent or *control* series. Prior exposures to possible risk factors are then ascertained from historical records or recall. We will see in Chapter 8 that the exposure odds ratio from a case-control study is stochastically equivalent to the rate ratio in the source population.

```
Case-Control
Source population
\[\text{cases} \rightarrow \text{prior exposure}\]
\[\text{non-cases} \rightarrow \text{prior exposure}\]
```

Because of the importance of cohort studies and case-control studies in modern epidemiology, each will be given its own chapter. Cohort studies will be covered in Chapter 7. Case-control studies will be covered in Chapter 8. At present, let us merely introduce simple examples of each study type.

**Illustrative Example 5.4 (Cohort Study, Oral Contraceptive Estrogen Dose).** A cohort study examined the incidence of venous thromboembolism (deep venous thrombosis and pulmonary embolism) in users of oral contraceptives with varying levels of estrogen. During the study period from 1980 through the third quarter of 1986, a total of 2,739,400 oral contraceptive prescriptions received by 234,218 women were analyzed (Gerstman et al., 1991).
- The rate of venous thromboembolism in women using low-dose formulations containing less than 50 µg of estrogen per pill was \( \frac{53 \text{ cases}}{127 \times 10^4 \text{ person-years}} = 0.42 \) per 1000 person-years.
- The rate in women using intermediate-dose formulations containing 50 µg of estrogen per pill was \( \frac{69 \text{ cases}}{98 \times 10^4 \text{ person-years}} = 0.70 \) per 1000 person-years.
- The rate in women using high-dose formulations containing more than 50 µg of estrogen per pill was \( \frac{20 \text{ cases}}{2 \times 10^4 \text{ person-years}} = 1.00 \) per 1000 person-years based on 20 cases.

The progressively higher incidences of venous thromboembolism associated with higher levels of estrogen indicates a positive association between oral contraceptive estrogen dose and venous thromboembolic disease risk.

Notice the large numbers of study subjects in the above cohort study. This was necessary because the outcome was relatively rare (less than one in thousand per year), and sizable cohorts were needed to derive a suitable number of cases to derive statistically reliable estimates of risk. Case-control studies overcome the need to study large numbers of individuals through an efficient sampling of “the study base.”

**Illustrative Example 5.5 (Case-Control Study, Toxic Shock Syndrome).** Toxic shock syndrome is an illness characterized by high fever, vomiting, diarrhea, confusion, and an exfoliating skin rash. It is fatal in 3% to 15% of cases, and is caused by the exotoxin of a particular strain of *Staphylococcus* species. In late 1979 and early 1980, the Centers for Disease Control received an unusual number of report of this syndrome from state health departments in Wisconsin, Minnesota, Illinois, Utah, and Idaho (CDC, 1980). The cases occurred almost exclusively in women of childbearing age. Several case-control studies followed. One of the case-control studies evaluated prior exposures to risk factors in 52 cases and 52 age- and sex-matched controls (Shands et al., 1980). All 52 cases had used tampons during the menstrual periods coincident with the onset of illness. In contrast, 44 of the controls had used tampons during the period before the interview. Among the case-control pairs in which both women had used tampons, 42 of the 44 cases used tampons throughout menstruation, while 34 of 44 controls did similarly. Thus, cases were more likely than controls to use tampons and, when they did, were more likely to use them continuously. This was one of the clues that led eventually to the discovery of a highly absorbent brand of tampon as a risk factor for the proliferation of toxogenic *Staphylococci*.

Notice the relatively small number of individuals in the above case-control study (104 total, 52 cases and 52 controls). Despite the small number of study subjects, this study was able to provide evidence about the relationship between antecedent tampon use and subsequent disease. Also note that case-control sampling does not permit an estimate of the sizes of the populations at risk from which cases arose. They are therefore unable to
determine rates of events: the incidence of toxic shock syndrome in those exposed and not exposed to tampons cannot be determined from the above study. Nevertheless, case-control studies can derive a measure of association between the exposure and disease with a statistic called the exposure odds ratio. Exposure odds ratios will be studied in Chapter 8.

5.4 Common Types of Epidemiologic Studies

Figure 5.1 presents this book’s scheme for discussing the most common types of epidemiologic studies that are in use today. Studies are initially classified according to whether they are observational or experimental. As discussed earlier, experimental studies allows the investigator to assign an experimental treatment to some study subjects while leaving other study subjects unexposed. Observational studies study individuals as they are, without intervention.

Observational studies are divided according to whether observations are primarily made at the aggregate-level (ecological) or at the person-level. Person-level observational studies are divided according to whether the analysis is cross-sectional or longitudinal. Longitudinal studies, which permit the tracking of individual experience over time, are classified as cohort or case-control.

Experimental studies are divided into community trials, field trials, or clinical trials. Community trials address the efficacy of preventive interventions applied to groups (e.g., marketing campaigns), field trials address preventive interventions applied to individuals (e.g., a vaccine trials), and clinical trials address the efficacy of therapeutic interventions (e.g., a treatments for illnesses). Since experimental studies provide the archetype studies of epidemiologic research, we will commence with their consideration in the next chapter.

EXERCISES

5.1 For each of the brief descriptions below, decide whether the study is (a) an ecological study, (b) a cross-sectional study, (c) an observational cohort study, (d) a case-control study, or (d) an experimental study. In addition, explain each response by considering whether the unit of observation is at the aggregate- or individual level, whether observations are longitudinal or cross-sectional, and whether the design is experimental or observational.

(A) Epidemiologists suspect that avian adeno-associated virus is caused by exposure to poultry. Serum samples from poultry workers and the general population are tested to determine the proportion of individuals positive for avian A–V antibody in each group.

(B) The behavioral pattern identified as Type A behavior is characterized by a
hard-driving personality susceptible to anger and time urgency. This type of behavior is thought to be associated with increased risk for coronary heart disease. Type A behavior is ascertained in a group of men in a postcoronary disease rehabilitation program. Men not falling into the type A category are classified as Type B. Type A and Type B men are then followed for 5 years to assess for the recurrence of acute coronary symptoms.

(C) Investigators studying bus company employees want to test the hypothesis that occupational stress causes high blood pressure. Two groups of employees are compared: bus drivers and office workers for bus companies in the same salary range as bus drivers matched on age, sex, race, and length of employment. The investigators take blood pressure measurements of all study subjects and find that the mean blood pressure of bus drivers is higher than that of office workers.

(D) One hundred newly diagnosed breast cancer patients are interviewed to determine dietary histories. A similar number of healthy first-degree relatives (mothers or sisters) are interviewed in a similar manner. We compare the proportion of women reporting a history of high dietary fat consumption in the two groups.

(E) Fifteen hundred men working for an aircraft manufacturing company are recruited to participate in a study of coronary heart disease. Every 3 years, study subjects are examined for the onset of disease. Coronary disease rates are compared among groups defined by various personal characteristics (e.g., job category, blood pressure, diet type, exercise program) that were recorded at the beginning of the study.

(F) A sample of sedentary middle-aged men is selected from four census tracts. Each man is examined for coronary heart disease. Subjects having evidence of pre-existing coronary heart disease are excluded from further study. All others are assigned to either (a) a group that is coached to pursue regular moderate exercise or (b) a control group that gets a sham intervention. Subjects are examined semiannually to determine their cardiac health.

(G) One hundred incident cases of infectious hepatitis and 100 healthy neighbor controls are asked about their history of eating raw clams and oysters over the preceding year.

(H) Questionnaires are mailed to every tenth person listed in a city directory. Each person is asked to list his or her age, sex, occupation, socioeconomic status, smoking habits, and musculoskeletal symptoms during the preceding 7 days. About three-quarters of the questionnaires are completed and returned. The frequency of various types of musculoskeletal symptoms is compared in smokers and nonsmokers, controlling for age, sex, and socioeconomic status.

(I) An investigator collects information on the size of manufacturing plants
and their rates of accidents. She finds that the five largest plants have accident rates that are 50% higher than the five smallest plants.

5.2 What is the primary distinction between an experimental and non-experimental epidemiologic study design. Why are randomized designs generally superior to non-randomized designs, and how does randomization work?

5.3 What makes an epidemiologic study ecological?

5.4 Both cohort studies and case-control studies are longitudinal observational study designs. What distinguishes the two?

5.5 What is the primary distinction between cross-sectional and longitudinal analyses?

5.6 You have developed the hypothesis that automobile drivers that talk on their cell phones have a higher rate of fatal automobile accidents than those who do not. How would you design a cohort study to test this hypothesis?

(A) How would you define the exposure groups in this study?

(B) How would you identify the cases in this study?

(C) What additional characteristics must you strive to measure similarly in the cohort members?

(D) What difficulties would be encountered in measuring these characteristics?

(E) Since fatal automobile accidents are, fortunately, a relatively rare occurrence, you have reconsidered pursuing this hypothesis with a cohort study and are now considering a case-control approach. How would you design a case-control study to test the hypothesis?

5.7 A cohort study evaluated risk factors for agriculture-related injuries among African-American and Caucasian farmers and African-American farm workers (McGwin et al., 2000). A total of 1,246 subjects (685 Caucasian owners, 321 African-American owners, and 240 African-American workers) were enrolled between January 1994 and June 1996. Demographic, farming, and behavioral information was collected at baseline. Subjects were contacted biannually to monitor the occurrence of an agriculture-related injury (McGwin et al., 2000). Some of the data from this study are presented in this Table:

<table>
<thead>
<tr>
<th>Group</th>
<th>Agricultural-related Injuries</th>
<th>Person-years of Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian Farm Owners</td>
<td>67</td>
<td>2047</td>
</tr>
<tr>
<td>Af-American Farm Owners</td>
<td>27</td>
<td>821</td>
</tr>
<tr>
<td>Af-American Workers</td>
<td>37</td>
<td>359</td>
</tr>
</tbody>
</table>
(A) List the two exposure variables addressed by the data in this table.

(B) Identify the study outcome (“disease”) variable.

(C) Explain why experimentation was not possible when addressing this issue.

5.8 Explain why rates in open populations are not longitudinal.

REFERENCES


