7

INTRODUCTION TO OBSERVATIONAL STUDIES

OBJECTIVES

After reading this chapter, you should be able to:

1. Differentiate between descriptive and explanatory studies.
2. Differentiate between experimental and observational studies.
3. Describe the general strength and weaknesses of experimental versus observational study designs for the identification and evaluation of causal factors.
4. Describe the three main elements of the 'unified approach' to observational study design.
5. Describe the advantages and limitations of case reports, case-series reports, and surveys as they relate to future epidemiologic studies.
6. Design a cross-sectional study which takes into account the strengths and weaknesses of this study type.
7. Identify circumstances in which a cross-sectional study is the appropriate observational study.
8. List and explain three approaches for obtaining incidence estimates from cross-sectional prevalence data.
9. Differentiate the advantages and disadvantages of using repeated cross-sectional studies versus following a cohort in a longitudinal study.
10. Apply the items listed in STROBE to reporting a cross-sectional study.

7.1 Introduction

A central occupation of epidemiologists is to identify causal factors that can be manipulated to maintain health (for our purposes health will be measured on a continuous or ordinal scale and include such features as weight, blood pressure, level of cholesterol *etc*), or to prevent disease (or minimise its harmful effects). Here we ask the question 'how do we best go about the task?' As epidemiologists, we have two general approaches: experimental and observational studies. The latter constitute the major approach taken and they set our discipline apart from many branches of health sciences that are largely experimental. The specific objectives of the research and the context in which the study is conducted have a major impact on the choice of approach and study type. In order to select the optimal study design, we must bear in mind these objectives as well as the advantages and limitations of each design. Hence, in Sections 7.1.1 and 7.1.2, we provide an overview of the range of study types used by epidemiologists. Overview articles include those by Grimes & Schulz (2002a; 2002b); Hajat (2011); Hoffman and Lim (2007); Levin (2005); Stephenson and Babiker (2000); Whittemore and Neilson (1999); and Williams *et al* (2011).

7.1.1 Descriptive versus explanatory studies

Epidemiologic studies can be classified into 2 major categories: descriptive and explanatory (see Table 7.1 and Fig. 7.1). **Descriptive studies** include case-reports, case-series reports and surveys. Although our classification of study types is by no means universally accepted, descriptive studies are designed solely to describe the nature and distribution of outcome events such as health-related phenomena (Grimes and Schulz, 2002b). Although a descriptive survey is not designed to assess hypotheses about manipulatable causes of the outcome event (disease), the frequency of the outcome usually is described in the different categories of age, race, sex, season, and space (the who, what, when, and where of the outcome). Descriptive studies are described in more detail in Section 7.3.

Table 7.1 Characteristics of various study types

Type of study	Level of difficulty	Level of investigator control	Strength of 'proof' of causal association	Relevance to 'real-world' situations
Descriptive				
Case report	very easy	very low	not applicable	low to high
Case series	easy	very low	not applicable	low to high
Survey	moderate	moderate	not applicable	high
Explanatory - experimental				
Laboratory trial	moderate	very high	very high	low
Controlled field trial	moderate	high	very high	high
Explanatory - observational				
Cross-sectional	moderate	low	low	moderate
Cohort	difficult	high	high	high
Case control	moderate	moderate	moderate	high

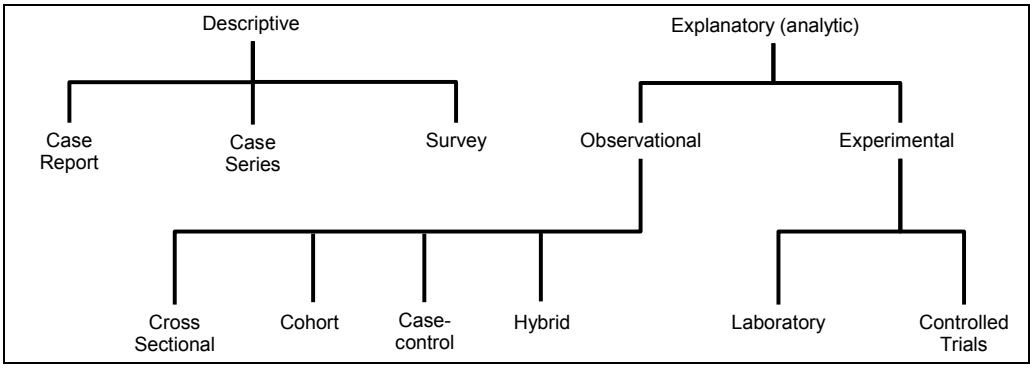

Fig. 7.1 Schematic representation of study types

Explanatory studies (aka **analytic studies)** are designed to make comparisons and contrasts between subgroups of study subjects based on exposure or outcome status. This allows the investigator to identify statistical associations between exposures of interest (*eg* risk factors, treatments *etc*) and outcomes of interest, such as health status (*eg* blood pressure), or disease occurrence. This is a first step to making inferences about causal relationships (see Chapters 1 and 13 for more details).

7.1.2 Experimental versus observational studies

Explanatory studies can be subdivided into experimental and observational studies. Experimental studies are those in which the investigator controls (usually through an intervention following randomisation of study subjects) the allocation of the study subjects to the study groups (*eg* treated versus non-treated, exposed to a risk factor versus non-exposed) (see Chapter 11 for details). In contrast, in observational studies, the investigators try not to influence, let alone control, the natural course of events for the study subjects. We confine our activities to making careful observations (which might include collection of data and a variety of biological samples) about the study subjects with particular attention paid to the exposures and outcomes of interest. In experimental studies we try to reduce variation from all sources through selection of study subjects and control of the experimental setting; whereas, in observational studies we embrace the presence of natural variation in order to identify important interactions among key variables and the exposure-disease association. The price paid through the use of observational studies is that considerable efforts are required to prevent confounding (aka bias) of the exposure-disease association (see Chapter 13 for a discussion of confounding).

The optimal choice between using an experimental or an observational approach to answering the research question might be evident early on in the planning process. However, it is often valuable to consider the full range of study designs rather than fixing on a particular study design too early and then trying to fit the investigation of the problem to the chosen design. Experiments often are the preferred choice if the treatment (or exposure) is straightforward and easily manipulated, such as a vaccine, or a specific therapeutic agent—a hormone or antibiotic, for example. The major advantage of the experimental approach is the ability to control potential confounders, both measured and unmeasured, through the process of randomisation. This feature has led to the general conclusion that experimental studies provide more valid

answers than observational studies, although recent evidence casts doubt on the general assertion (Concato, 2004; Hernan, 2011b). Observational studies usually are the preferred study design if the exposure is more complex (*eg* if multiple exposures are of interest), or if the exposure is not easily manipulated by the researcher for practical, ethical, or economic reasons. The studies have the advantage that a much wider array of hypotheses can be tested. In many instances, the study subjects will be exposed to the potential risk factor(s) whether the study is done or not, and thus, observational studies can capitalise on these 'natural events' to investigate possible causal associations. Nonetheless, if a controlled trial (experimental) of a specified intervention can be done then, this would be the approach of choice. Freudenheim (1999) discusses the use of epidemiologic methods in the field of human nutrition. Merkow and Ko (2011) stress the need for both types of research in the field of surgery. Nitta *et al* (2010) describe epidemiologic methods in the context of environmental studies. Harris (2000) and Carney *et al* (2004) suggest using epidemiologic approaches to study medical education. Hamburg (2011) outlines the potential roles for epidemiologic research methods in supporting regulations to improve drug safety. When comparing the real-world effects of treatments or procedures, on clinical outcomes, the general research approach has become known as comparative effectiveness research (Leonard, 2010).

Experimental studies can be classified as laboratory-based or field-based trials. Laboratory trials are carried out under strictly controlled 'in-house' conditions. These have the advantage that the investigator has almost complete control over the experimental conditions (*eg* type of experimental animals (or characteristic of persons) used, environmental conditions, timing, level and route of exposure, method of outcome assessment *etc*). Notwithstanding the observations of Concato (2004) and Hernan (2011a), it is generally accepted that evidence of an association between an exposure and a factor obtained from this type of study provides better evidence of causation than do observational studies. However, given the very artificial environment in which laboratory trials are conducted, the relevance of the results to 'real-world' conditions is often somewhat in doubt. Because epidemiologists are interested in health events in populations, laboratory-based trials are not major components of our work and will not be discussed further in this text. However, epidemiologists frequently use field trials to investigate health problems. In a field trial, the investigator 'controls' the allocation of people to the study groups (*ie* through randomisation), and the study is performed under natural 'real-world' conditions (hence, these studies are often referred to as **controlled field trials, randomised controlled trials**, or **controlled trials**). The design and implementation of controlled trials is discussed in Chapter 11.

As noted, observational studies make up a substantial portion of the research carried out by epidemiologists; these can be broadly classified as **cross-sectional** (Section 7.5), **cohort** (Chapter 8), **case-control** (Chapter 9) and **hybrid** (Chapter 10) studies. Observational studies can often take advantage of the fact that exposed subjects already exist and therefore, with an appropriate design, the impact of the exposure can be investigated without having to manipulate the exposure status of the selected study subjects. It would be a stretch to imply that all of these are 'natural' experiments, but the fact that subjects are being exposed, and the outcomes are happening regardless of the presence or absence of the study begs the question 'why not seize the opportunity to capture data that can help assess possible associations between the exposure and the outcome'? Kalsbeek and Heiss (2000), in their discussion of the role of sampling populations, noted that most empirical knowledge has been based on observations of samples (*ie* selected subgroups) of human (subject) experience. Often it is impractical to study the entire population and thus sampling strategies must be considered; indeed, the sampling strategy is the basis for the

classification of the observational approaches introduced here and in Chapters 8–10.

7.2 A UNIFIED APPROACH TO STUDY DESIGN

Since observational studies are so important to the work of epidemiologists, there is considerable literature on how best to design and implement specific study types. Here we introduce some key global concepts and approaches that apply to the design of all observational studies.

Hernan (2005) has stressed that, when we are considering using an observational study design in an attempt to find a possible causal association between an exposure and an outcome, we should think about the design of a field experiment to accomplish that same objective. This approach is reinforced by Rubin (2007) who emphasises that 'design trumps analysis' in that all elements of the study design should be completed before seeing any outcome data. We concur with these views. There are a number of reasons to think about the details of a field experiment even if it is clear that such an experiment cannot be implemented. In any event, as a first step in considering an epidemiological study, a 'thought experiment' can be accomplished and should specify the key elements of study group, its selection, assignment to exposure, procedures for follow-up, and detecting the outcome. The important part of the 'thought experiment' is the fact that formal randomisation would ensure 'exchangeability' which, for our purposes here, can be taken to mean that the groups being compared are so similar that it does not matter which group was assigned to exposure and which group to non-exposure. Confounding would not be an issue. However, if the causal association is to be pursued through an observational study, the exposed and non-exposed groups (or the cases and controls) might differ in ways that could bias the findings (*ie* confounding would be present—see Chapter 13). The 'thought experiment' can help identify ways in which the groups being compared can be made as similar as possible with respect to variables that could influence the exposure-outcome association.

This leads to the second major component of observational study design, where the challenge is to prevent bias through subject exclusion, selection criteria, and control of confounding. Rubin (2007) provides examples of how a group of experts met and discussed these issues until all parties were in agreement that the process would achieve balance in the covariates between the exposed and non-exposed groups. The key to this second component is that all design features are completed before anyone has seen the outcome data (this is what we would hope to accomplish in an actual experiment). Rubin formalises the process through propensity scores (these scores are the probability of exposure given the covariates) in the exposed and non-exposed groups. Unless these are virtually equal in the 2 groups, then some degree of confounding is possible. See also the follow-up exchange between Shrier (2008) and Rubin for further discussion of the issues.

We believe a third component of good study design is to use 'forward projection' (*ie* critical appraisal techniques) (Elwood, 2002). In this process, after completing the initial design, we project ourselves forward to the presentation of our study results under 3 different scenarios—1) the exposure appears to increase the risk of the disease; 2) the exposure appears to decrease the risk of the disease; or 3) the exposure does not appear to be associated with the disease. For each possible scenario we must defend the proposed design and through this process help identify potential weaknesses in the proposed design. The main features of this process are shown in Table 7.2. The formal implementation of these 3 strategies, in conjunction with the key elements of study design that should be reported (Section 7.9, Table 7.3), should help

ensure an efficient and appropriate study design for uncovering causal associations. Martin (2008), discusses these three components and other features of observational study design, analysis, interpretation, and causal inferences.

Table 7.2 A scheme for critical assessment of study design

Critical appraisal of causation	Application to study design
A. Description of the evidence	
1. What was the exposure or intervention?	1. Clear definitions required in study design.
2. What was the outcome?	2. Define key outcome and document it.
3. What was the study design?	3. Consider alternatives; justify choice.
4. What was the study population?	4. Define carefully; consider alternatives; justify choice.
5. What was the main result?	5. Consider the interpretation of positive, negative, and neutral results.
B. Internal validity—consideration of non-causal explanations	
6. Are the results likely to be affected by observation bias?	6. Consider methods to avoid bias.
7. Are the results likely to be affected by confounding?	7. Identify potential confounders, and decide on ways of controlling.
8. Are the results likely to be affected by chance variation?	8. Assess power and sample size.
C. Internal validity—consideration of positive features of causation	
9. Is there a correct time relationship?	9. When is start of exposure and of outcome? Consider latent effects.
10. Is the relationship strong?	10. What strength is likely or important?
11. Is there a dose-response relationship?	11. How will dose-response be shown?
12. Are the results consistent within the study?	12. What consistencies or specificity would be useful to test or amplify the hypothesis?
13. Can the study results be applied to the source population?	13. Consider response rates and how to assess representativeness, as well as eligibility and exclusion criteria.
D. External validity	
14. Can the study results be applied to the target population?	14. What evidence is there that the source population is representative of the target population?

From the perspective of drawing causal inferences, experimental studies usually are referred to as the gold standard with observational studies being of somewhat lower validity (you might refer again to the section on causality in Chapter 1). Also, non-randomised intervention studies (*ie* where the researcher controls, without randomisation, which study subjects become 'exposed' or 'treated'—these are sometimes called quasi-experiments) usually are ranked above observational study designs for causal inference purposes (Grimes and Schulz, 2002a). The issue of random allocation of subjects to interventions is discussed in Section 7 of Chapter 11. Within observational studies, cross-sectional studies are of lower 'causal inference' rank than other study designs because they measure prevalence not incidence, and because of the inability

to refute reverse-causation (*ie* determine which came first, the exposure or the outcome—see Section 7.7) for non-permanent exposures. Hence, when possible, other observational study designs should be used. Case-control and cohort studies are better for making valid causal inferences than cross-sectional studies because of the longitudinal nature of their designs and their use of incidence data, both of which should allow refutation of reverse-causation. Cohort studies are generally considered superior to case-control studies in this regard.

7.3 Descriptive studies

As the name implies, descriptive studies are used to describe the main features of a disease or health-related outcome. Although descriptive studies are not designed to evaluate any associations between exposures and outcomes of interest, the observations made in a descriptive study can form the basis of hypotheses which then are further investigated in analytic studies (Grimes and Schulz, 2002b). Three forms of descriptive studies are case reports, case-series reports, and surveys.

Case reports generally describe a rare condition or an unusual manifestation of a more common disease. Often, case reports are based on only one or a very few cases, and the fact that they are based on unusual cases might limit their relevance to typical 'real-world' conditions. However, these unusual observations also can help researchers generate useful hypotheses to be investigated in future studies. For example, Chaudhary *et al* (2007) describe a case of melanosis coli, in which there is a black or brown discolouration of the mucosa of the colon, in a 63-year-old woman presenting with abdominal pain and distension. Melanosis coli is normally a benign condition, which arises from chronic use of anthraquinone laxatives. In this case (only 5 others reported in the literature), the dark colouration was very extensive and had spread to the local lymph nodes. These features make it difficult to differentiate melanosis coli from the more serious ischemic colitis which often has to be treated by colectomy.

In some case reports, the author(s) attempts to draw conclusions about the cause, the outcome, or the relative merit of a therapy. However, these hypotheses are often purely conjecture as no data to support such a conclusion are available directly from a case report.

A case series report generally presents a description of the occurrence of, or usual clinical course of, the condition of interest in a group of subjects. Typically, the case series (*ie* the what) should document the who (*ie* the affected subjects), the when (*ie* the temporal aspects of the disease occurrence), and the where (*ie* the geographic aspects of disease occurrence). Case-series reports also might provide valuable information about the prognosis of the condition, provided the cases described are representative of most cases in the population. For example, Ferrer *et al* (2011) reviewed and summarised the features noted in a series of 1997 cases of tuberculosis of the spine reported between 1980 and 2011. They described the diagnostic workups and findings as well as the therapy and follow-up results of these cases. "The most common symptom reported was back pain, and the thoracic spine was the most frequent segment involved." The authors concluded that spinal tuberculosis is still an important public health issue, and it should be suspected in the presence of back pain with characteristic radiographic images. The diagnosis must be confirmed microbiologically. Although the features of many case series might help a researcher posit hypotheses about causal or prognostic factors for the outcome in question, the case series usually has limited data on these factors since only the characteristics of the cases are included and no explicit comparison group (*ie* a group of suitable non-cases) is present.

Descriptive surveys are proactive activities to estimate, with some specified precision, the frequency and distribution of selected outcomes in a defined population, rather than to obtain information about suspected risk factors. For example, Koseki *et al* (2011) surveyed iceberg lettuce for the presence of food-borne pathogens. The samples were obtained from one retailer who obtained lettuce from across Japan, between July 2008 and March 2009. They used both multiplex PCR and microbiological analysis of the samples. "No pathogenic bacteria, including *Salmonella, L. monocytogenes,* and *E. coli* O157:H7 were detected from any of the 419 samples." In other instances, the principal objective is to provide data about the frequency and distribution of a disease, or other outcome, in a specific population (see Example 7.1). As another example, Taylor *et al* (2010) conducted a survey with the primary objective of estimating the prevalence of trachoma, an infection of the conjunctiva caused by the bacteria *Chlamydia trachomatis,* in indigenous people in Australia.

Kalsbeek and Heiss (2000), and Speybroeck *et al* (2003) have described the appropriate analysis of surveys bearing in mind the study design (see Example 7.2). If the survey is designed to collect information about both an outcome of interest and potential exposures (risk factors) beyond the categories of people, place, and time, it then becomes a cross-sectional analytic study (Section 7.4) and as such, can be used to evaluate associations between exposures and outcomes.

7.4 Observational studies

Observational studies (a subgroup of analytic or explanatory studies) have an explicit formal contrast as part of their design: the prevalence of the outcome by exposure category. They differ from descriptive studies in that the comparison of 2 (or more) groups is the central foundation of their design. As noted, observational studies differ from experiments (*eg* controlled trials) in that the researcher has no control over the allocation of the study subjects to the exposure groups.

7.4.1 Prospective versus retrospective designs

Observational studies can also be classified as prospective or retrospective. Although the usage of these terms in the epidemiological literature is not consistent, in prospective studies, the disease or other outcome of interest has not occurred at the time the study starts. The design of prospective studies needs to include information-gathering techniques so that all the necessary data are recorded as part of the study itself, or the study could use existing data sources (called secondary data sources), supplementing these data as necessary. In retrospective studies, both the exposure and the outcome have occurred when the study begins; hence cross-sectional

Example 7.1 A survey of natural health product use

Levine *et al* (2009) conducted a telephone survey of older people living near Hamilton, Ontario. The outcome of interest was the use of a natural health product, defined as medicinal products derived from botanical or other natural sources (herbal products and vitamin and mineral supplements). The authors had estimated the required sample size as 1,200 people over 59 years of age. Randomly selected telephone numbers were called and over 10,000 households were contacted. Of 2,528 persons ≥60 years, 1,206 participants (48%) completed the telephone interview and had data included in the analysis.

studies are inherently retrospective in nature (see Section 7.4.2). Typically, retrospective studies rely on pre-recorded data from one or more secondary sources. Although the availability of pre-recorded data is a major advantage, the quality and scope of these data may be limitations of this approach. Alemayehu and Cappelleri (2011) provide a detailed discussion of how to minimise bias when using secondary data sources; however, their discussion applies to prospective data collection methods also. When using secondary data sources, selecting an optimal study design can maximise the information gained from the data available.

7.4.2 Sampling drives the study design

The choices of observational analytic study design have traditionally been among 3 main approaches which we will now introduce. In a cross-sectional study (Section 7.5), a sample of study subjects is obtained from the source population and the prevalence of both disease and exposure are determined at the time of study subject selection. Cross-sectional studies have been described as non-directional; however, we prefer to denote them as retrospective. In a cohort study (Chapter 8), a single sample of study subjects from a source population with heterogeneous exposure levels in its subjects, or a sample of 2 or more groups of study subjects defined by known exposure status, is obtained, and the incidence of the outcome in the follow-up period is determined. While these are often prospective in nature, with sufficient information recorded in routine data banks, they can be carried out retrospectively. In a case-control study (Chapter 9), subjects with the outcome of interest (usually a disease) are identified and the exposure history of these case subjects is contrasted with the exposure history of a sample (often randomly selected from a defined source) of non-case subjects (also called the control subjects). These studies are usually carried out retrospectively using a data bank of cases that have already occurred. A case-control study can be performed prospectively, by enrolling cases as they occur after the study begins. Because subjects are selected based on their outcome status, they differ from cohort studies, in which subjects are selected based on exposure status. Variations on these themes are described in Chapter 10.

Example 7.2 A survey of the prevalence of hypertension in the province of Ontario

The sampling frame consisted of the municipalities (cities) and dissemination areas (small areas composed of one or more neighbouring blocks, with a population of 400–700) (Fodor *et al*, 2008; Leenen *et al*, 2008). This source population included 94% of the target population. Three municipalities were selected (*ie* sampled) with certainty; 13 others were selected with probability proportional to their population size. In each selected municipality, a sample of dissemination areas was selected, and within each area, a systematic random sample of dwellings was selected. The eligible adult with the most recent birthday was selected as the respondent. Respondents who agreed to participate had their blood pressure measured with an automated device and became study subjects. Responses were weighted to the total adult population in Ontario and because of the complex sampling design, standard errors were estimated by bootstrapping.

From 6,436 eligible dwellings, contact was made with 4,559 potential participants, of whom 2,992 agreed to participate. Blood pressure measurements were obtained for 2,551 of these respondents (age 20–79 years). Hypertension, defined as systolic blood pressure of 140 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or treatment with an antihypertensive medication, was identified in 21.3% of the population overall (23.8% of men and 19.0% of women). Prevalence of hypertension increased with age, from 3.4% among subjects 20–39 years of age to 51.6% among those 60–79 years of age. Hypertension was more common among black people and people of South Asian background than among white people; hypertension was also associated with a higher body mass index.

7.4.3 Pre-study pilot studies

As you will note (Section 7.9) from the listing of items to consider and report on in an observational study (Table 7.3), some study designs can become very complex. Unless, proven methodologies are used and the researchers are comfortable that the design will work well in the study (source) population, it is worthwhile to do a pilot study (see Fodor *et al* (2008) for an example). Fodor and colleagues selected 4 cities as pilot sites and evaluated the following aspects of their study design: mailing of an information letter to selected households before the telephone contact or home visit, using nursing agency interviewers to recruit respondents; conducting survey clinics on weekdays, and administering the survey questionnaire during the clinic visit. As a result of their pilot study, the authors decided to deliver the information letters in person, to use professionally trained interviewers, to conduct the interviews in the home, to extend the clinic hours, to use professional nurses to measure blood pressure and obtain other physical measurements, and to use an automated blood pressure recorder to avoid bias because of interviewer/nurse presence. The sampling strategy and summary findings are shown in Example 7.2 and Leenen *et al* (2008).

7.5 Cross-sectional studies

The defining feature of a cross-sectional study is that it is an observational study whose outcome frequency measure is prevalence (*ie* it is based on the number of cases that exist in the source population when the study begins) (Levin, 2006). The basis of the cross-sectional design is that a sample, or census, of subjects is obtained from the source population and the presence or absence of the outcome is ascertained at that point. Usually, the current or pre-existing exposure status, and the demographic characteristics of the study subjects are noted at the first contact with the study subjects after their selection. This allows the researchers to test possible associations between the risk factors and the prevalence of disease and control for confounding by demographic factors. Despite their disadvantages for supporting causal inferences, cross-sectional studies are one of the most frequently chosen study designs in epidemiology. Perhaps because the basic structure is straightforward, there is very little written concerning details of their design relative to what is written regarding other designs such as cohort and case-control studies.

7.5.1 Obtaining the study group

If the researcher wants to make inferences about the frequency of the outcome or the prevalence of exposure in a **target population**, then the study subjects should be obtained by a formal random sampling procedure (see Examples 7.1). The target population in the study of hypertension by Fodor *et al* (2008) was all those aged 20–79 years in Ontario (Example 7.2). The **source population** is that listing (real or implied) of potential study subjects from which the members of the study group are obtained. Often, not all members of the target population are contained within the source population as the latter may have constraints such as ‘a fixed residence’ or an ‘email address’. In most instances, some judgement is required to assess if such constraints will seriously limit causal inferences (see Example 7.2). As another example, Febriani *et al* (2010) randomly selected people from rural areas in Quebec using their telephone numbers. When the home was contacted, the number of individuals in the family was obtained and the person to be interviewed was selected randomly. As these examples illustrate, the exact random process used to select study subjects can vary but could include stratified, cluster, or

multistage sampling approaches as discussed in Chapter 2. Ultimately, the **study group** is that set of subjects who agree to take part in the study.

If the primary objective does not entail estimating population parameters, but is limited to the evaluation of associations between the exposure(s) and outcome(s) of interest, a purposive non-random sample of study subjects is often obtained. Thus, the target population may not be clearly defined even though the source population is; for example, Fabry *et al* (2011) based their study of postpartum depression on pregnant or early-postpartum women at one hospital in a city (Example 7.5, page 169). One can easily imagine the target population in this example, but it is not clear how representative the source population is of that population. Some researchers decry this non-random approach because the design is open to considerable selection bias. However, although the potential selection bias limits the external validity of the study (ability to extrapolate results beyond the source population), the design of the study should ensure that the internal validity (ability to extrapolate results from the study group to the source population) remains good. In another study one could imagine the target population as 'community dwelling elderly' but the source population was less clearly defined; for example, Sai *et al* (2010) obtained their study subjects using volunteer responders to a newspaper advertisement, or a flier placed in assisted-living communities, in a city. The less definable the target population and/or source population, the more constraints there are when extending inferences beyond the study group; this need not however, have an impact on the internal validity of the study.

As noted, studies using a one-time sampling of study subjects for the presence of a disease, microorganism, or level of toxin are using 'prevalence' as an outcome measure. It is possible, with repeated samplings of the same subjects over time, to estimate the incidence of new infections. Often, the prevalence of the outcome might change with the passage of time (*eg* with age or season). Thus, studies evaluating outcomes which change, model the prevalence at each sampling as the outcome (Febriani *et al*, 2010).

7.5.2 Assessing exposure

Usually, the exposure and other covariate status, such as demographic data, are obtained at the time of study subject selection or first contact/examination; however, not infrequently, an additional and more detailed history of prior exposure may be sought after the subjects are selected. Because the outcome measure is prevalence, it is sometimes difficult to know the appropriate time frame in which the exposure, if time-varying, might cause the outcome. For example, Sai *et al* (2010) investigated risk factors for elderly people with a history of falling at the time they were recruited for the study, and then followed these same people and obtained data on 'new falls' over the period of one year. Thus, this study combined elements of a cross-sectional study and a cohort study. Danaei *et al* (2012) point out that studying currently (prevalent) exposed subjects can also lead to bias when interpreting the impact of these exposures (the currently exposed are a biased subset of all those who have been exposed). In other studies the major putative risk factor might not be an individual level factor; for example in the study by Febriani *et al* (2010), the primary risk factor was living in an area with intensive farming activities. This exposure was measured at a municipality-level and the authors adjusted for correlations between study subjects within a rural municipality in their analysis. When researchers try to reconstruct the exposure history of the selected study subjects, for time-varying exposures, the approach has been denoted as a cross-sectional cohort study and the strengths and weaknesses of this approach have been discussed by Hudson *et al* (2005).

Although the cross-sectional study design can support the investigation of a variety of potential causal factors and a number of outcomes, usually one primary outcome of interest is chosen and a set of potential causal factors is selected for investigation of each factor's association with the prevalence of the outcome. A potential drawback to this study design is that the search for potential causes may not be very focused and thus a lot of data-mining for statistically significant associations may result.

7.5.3 Assessing the outcome of interest

Although it should go without saying, it is important to clearly define the outcome/disease of interest. Grimes and Schulz (2005) stress that research should focus on outcomes that matter and that, in general, great care should be used if the outcome is a surrogate for a clinically important event. For example, Shafir *et al* (2011) found that the prevalence of antibodies to H1N1 was much higher than the prevalence of clinical signs/symptoms of influenza.

It is also important that widely accepted diagnostic criteria be used to identify the disease or outcome of interest (see Example 7.3 for a clinical score outcome and Example 7.4 for a measured, quantitative outcome). For example, in the absence of a full psychological workup, Lanes *et al* (2011) used an established method, the Edinburgh Postnatal Depression Scale, to infer postpartum depression in their study, and Leenen *et al* (2008) used an established cutpoint (140 mgm mercury) to infer hypertension in their study subjects. Kang *et al* (2005) discuss cross-sectional design issues when using biomarkers as the endpoint.

7.5.4 Sample-size aspects

If the sampling is to be purposive or if a simple random sample of individuals will be selected, the risk-based approach to sample-size estimation shown in Chapter 2 is often sufficient for planning purposes when one major outcome is of interest (Harvey and Lang, 2010). If the

Example 7.3 A cross-sectional study of postpartum depression and its risk factors in Canadian women

Lanes *et al* (2011) conducted a study to look at the prevalence and characteristics of postpartum depression symptomatology (PPDS) among Canadian women. The survey was conducted by Statistics Canada between October 23, 2006 and January 31, 2007. In the provinces, computer-assisted telephone interviews were used for data collection, whereas in the territories, a personal interview with a paper version of the questionnaire was offered, if a telephone interview was not possible. PPDS was measured based on the Edinburgh Post-natal Depression Scale (EPDS). In developed countries, a EPDS score of 0–9 inclusively indicates no risk of experiencing symptoms of PPDS; a score of 10–12 indicates a minor/major risk of experiencing symptoms of PPDS; and a score of 13 or greater indicates a major risk of experiencing symptoms of PPDS. The sensitivity and specificity of this score, at a cut-off value of 13, has been found to be 75% and 84%, respectively. Potential risk factors included socioeconomic status, demographic factors, and maternal characteristics and these were assessed in a 3-level multinomial regression model (non-stressed was the referent category). All the potential risk factors were self-reported by the mother. A total of 8,542 Canadian women were selected, out of which 6,421 responded to the survey. The national prevalence of minor/major and major PPDS was found to be 8.46% and 8.69%, respectively. Based on the magnitude of the odds ratio, the mother's stress level during pregnancy, the availability of support after pregnancy, and a prior diagnosis of depression were the characteristics that had the strongest significant association with the development of PPDS.

Example 7.4 The association between intima-media thickness, central obesity, and diastolic blood pressure in obese and overweight children: a cross-sectional school-based study

Elkiran *et al* (2011) evaluated a total of 2,765 school children chosen from the 6th, 7th, and 8th grades of 18 primary schools randomly selected in Elâziğ, Turkey. Based on their data, 67 individuals were found to be obese, 24 overweight, and 32 'normal'-weight children were selected as controls. Thirteen students who either personally declined to participate in the study or whose parents did not give consent were excluded from the study. Carotid intima-media thickness (carotid IMT) was measured in all three groups using β-mode Doppler ultrasound. The measurements were performed by the same radiodiagnostic specialist who was blinded to the participants' cardiovascular risk factor status. In one of their analyses, using a multiple linear regression model, carotid IMT (in millimeters) was the outcome of interest, and systolic blood pressure (BP), diastolic BP, Body Mass Index, waist circumference, fat-mass percentage, were the predictor variables. Differences were considered statistically significant at a P-value of 0.05 or less. The authors reported a significant relationship between carotid IMT and waist circumference (P=0.045), and diastolic BP (P=0.031).

association between exposure and outcome in specific subsets of the source population is the principal goal, then the researcher should ensure that adequate numbers of study subjects are available within these subgroups to provide reasonable power for assessing the hypotheses. Unfortunately, in the brief literature search we conducted in preparing this text, many authors do not specifically comment on sample-size estimation.

Marschner (1994) provides sample-size formulae for estimating an overall sample size and also the sample size for estimating age-specific parameters. Delucchi (2004) discusses sample-size estimation when the risk factors are correlated and stresses the need to align sample-size estimation with the proposed method of analysis. Lancaster *et al* (2007) provide a recent thorough discussion of sample-size estimation for studies with only one major risk factor, for studies with multiple risk factors (using information from the variance inflation factor), and for studies where cluster sampling is used (the latter requires knowledge of the intra-class correlation coefficient and the cluster size).

7.5.5 Ensuring that the exposed and non-exposed study subjects are comparable

Alemayehu and Cappelleri (2011) provide a general review and discussion of this topic (prevention of bias) with emphasis on studies using secondary data.

Exclusion and restricted sampling

The two main approaches used to prevent bias, from factors associated with the outcome and whose distribution differs between the exposure groups (*ie* confounders), are exclusion (restricted sampling) and analytic (statistical) control. As an example of restricted sampling, if all study subjects are restricted to the same age and sex (*eg* women aged 25–30), then age and sex cannot bias the observed association between exposure and the outcome. Matching to prevent confounding cannot be applied in cross-sectional studies. Analytic control requires the use of a multivariable model. See Chapter 13 for an elaboration of these approaches.

Analysis

The main comparison in a cross-sectional study is between the prevalence of the outcome in the exposed subjects and the prevalence in the non-exposed subjects, and the natural measure of association is the prevalence risk ratio (see Chapter 4). However, since many researchers use

logistic regression for multivariable modelling of their cross-sectional data, odds ratios are the usual measure of association. As noted in the subsequent section on cohort studies (see Chapter 8), a Poisson model with robust variance, or a log binomial model could be used to obtain direct estimates of the prevalence risk ratio (Barros and Hirakata, 2003; Schiaffino *et al*, 2003).

If the natural outcome measure is in the form of a continuous variable (*eg* blood pressure), linear models (see Chapter 14) can be used for analysis (Choy *et al*, 2011). When the outcome can be measured on a continuous scale, there are advantages to analysing the data in the continuous scale. Bayer *et al* (2009) studied the potential association between sleep duration (the risk factor) and blood pressure, both continuous variables, using linear models. The authors reported that the initial negative association (β=-0.80; each hour more sleep was related to 0.8 mm Hg lower blood pressure) was not significant statistically when BMI and physical activity measures were included in the model. However, often we note that authors have dichotomised the outcome and used a logistic model to analyse the data (*eg* Fasting *et al* (2008)), although the process of dichotomisation results in the loss of considerable information. As an aside, later in this text (Chapter 13) we discuss how to decide on whether to include or exclude variables as confounders; the goal is to exclude variables which might intervene between the putative causal factor (*eg* sleep duration) and the outcome (*eg* blood pressure). Thus, in this example, one would need to consider whether sleep duration might affect BMI and/or physical activity, and if so, whether they should be included as confounders.

7.6 Estimating incidence from one or more cross-sectional studies

As Roy and Stewart (2010) state "Strictly speaking, the cross-sectional design refers to a study of current exposure or health status or the association of the two." However, many times incidence data are more desirable. Some authors have used clinic data collected over time to estimate incidence (Hillemanns *et al*, 2008), although this method depends on the proportion of affected people that attend such clinics. Krantz *et al* (1989) used parental recall of whooping cough in the children (from 4 birth cohorts) to estimate incidence of the disease and changes in incidence over time (they also claimed this method avoided issues of underreporting).

A simple way to obtain population-level incidence data is to perform two cross-sectional studies, one after the other. For example Miller *et al* (2010) performed two cross-sectional studies, one before and one after the 2009 H1N1 epidemic in England. This gives a population-based estimate of incidence since the individuals in the two samples may not have been the same people. Other approaches include using two different tests, one that detects early immune response and one that detects long-lasting immunity response (see Gras *et al* (2004)). Others have refined this, especially for HIV studies where they use two tests—one very sensitive and one less so (Wang and Lagakos, 2010). People who test negatively to the less sensitive test are followed forward for a defined time period to ascertain how many become positive. Under certain assumptions, the incidence rate can be estimated as a function of the the number positive to the sensitive test divided by the product of the number negative to both tests multiplied by the recent infection state duration—this is the period during which an infected person that tests positive to the sensitive test would test negative to the less sensitive test. Clagget *et al* (2011) developed a method of estimating the appropriate time period for follow-up in order to identify the proportion of people who will remain negative after infection, including the impact of therapy (retroviral treatment) on this time period. Roy and Stewart (2010), discuss the situation where individuals are asked to estimate when they developed the disease of interest, and what impact the uncertainty of this estimated timing has on the results.

Example 7.5 Determinants of A (H1N1) vaccination: Cross-sectional study in a population of pregnant women in Quebec

This present study was aimed at identifying factors influencing the decision-making of pregnant women regarding H1N1 vaccination (Fabry *et al*, 2011). A cross-sectional survey was conducted at the Sherbrooke University hospital Centre in the province of Quebec. Pregnant women or early post-partum women present for hospitalisation or a consultation from February 15 to February 24, 2010 were requested to complete a self-administered and anonymous questionnaire. Potential risk factors and outcome variable (vaccinated or not) included: socio-demographic data, information sources consulted, knowledge on vaccination effectiveness and risks of vaccination, severity and vulnerability towards influenza. The associations between questionnaire variables and vaccination status were assessed by univariable and multivariable analysis.

Of the 250 women interviewed, 95% knew that vaccination was recommended, but only 76% received the vaccine. Variables positively associated with vaccination were late vaccination during pregnancy (*OR*=7.3), belief in the efficacy of the vaccine (*OR*=7), and consultation of the Pandémie-Québec website (*OR*=4.5). However, the belief that the vaccine had not been adequately tested (*OR*=0.08) and consultation of mainstream websites (*OR*=0.22) were associated with lower vaccination rates.

Rajan and Sokal (2011) describe how to estimate age-specific incidence from prevalence data when the disease (or response, *eg* titre) is long lasting and has little impact on mortality. In general their approach is shown in Eq 7.1 where the incidence rate at year '*a*' is:

$$I_a = 1 - [1 - (P_{a+n} - P_a)/(1 - P_a)]^{1/n} \qquad \textit{Eq 7.1}$$

when '*n*' is the time between the two-point prevalence estimates (P_a and P_{a+n}) in the cross-sectional survey. For example, n=1 when yearly age-specific prevalence data are available. If ages are grouped into categories of width '*n*' where n>1, then the slight modifications of this formula that are needed are described by Rajan and Sokal (2011). As an example of this approach, Leenen *et al* (2008) reported the prevalence of hypertension by 20-year age classes. These ranged from 4% in males aged 20–39, 24.7% in those aged 40–59, and 61.1% in those aged 60–79. Using the method proposed by Rajan and Sokal these percentages translate into an annual incidence of 1.2 per 100 person-years in the 20–39-year-olds, and 3.2 per 100 person-years in the 40–59-year-olds.

7.7 Inferential limitations of cross-sectional studies

By its nature, a cross-sectional study design measures prevalence which is a function of both incidence and duration of the disease. Consequently, it is often difficult to disentangle factors associated with persistence of the outcome (or survival of study subjects with the outcome) from factors associated with developing the outcome in the first instance (*ie* becoming a new incident case). Thus, people with a factor which contributes to their survival once they have the disease of interest (or to the persistence of the disease), will be included as 'diseased' in a cross-sectional study more frequently than people without the factor. Thus, if the factor is associated with the disease, the investigators might conclude that it is a cause of the disease, when in reality the factor affects the duration, but not the occurrence of the disease.

Cross-sectional studies are best suited for time-invariant exposures such as race or sex. In these instances, the investigator can be certain that the exposure preceded, or at least was not caused by the outcome (one of the fundamental criteria for establishing causation). However, it does

not circumvent the problem of the factor affecting only the duration of the outcome. When the exposure factors are time-varying, it is often very difficult to differentiate cause and effect because of the so-called reverse-causation problem (Fodor *et al*, 2009). For example, if one is studying the relationship between dog ownership and blood pressure, if the association is negative, one cannot differentiate between people that obtained a dog because they had low or 'normal' blood pressure from those whose lifestyle changed, consequently lowering their blood pressure after obtaining a dog (see Example 7.6; which is the cause and which the effect?). The more changeable the exposure, the worse this issue becomes. If the factor truly is preventive and often implemented when the disease has occurred, or after it has reached a threshold frequency, the positive and negative associations could cancel each other leaving the factor appearing to be independent of the outcome. Many researchers attempt to circumvent this problem by trying to ascertain when the exposure to the potential causal factors occurred; however, unless the timing of disease occurrence (*ie* its incidence) is known, with some certainty, the problem is not fully resolvable.

7.8 Repeated cross-sectional versus cohort studies

Sometimes it is desirable to follow a population over time and here one must consider whether to use repeated cross-sectional samplings of the population, or a longitudinal study of the initial study subjects (this is called a cohort approach but note that in this instance, we are following a study group some of which will have had the outcome event at the start of the follow-up) (Diehr *et al*, 1995). The time period between samplings can be short (*eg* monthly) or longer, such as annual surveys. Briefly, if the objective is to follow specific individuals over time, then following the same cohort of study subjects (see Chapter 8) is preferable. Because of the repeated observations on the same individuals, the analysis may need to adjust for the within-subject correlation (see Chapters 20–24). With the cohort approach, as the length of the study period increases, the individuals remaining in the study will become increasingly different from the existing population at that time (*eg* they will be much older, and in many instances, represent a highly selected surviving subgroup of those originally studied). Thus, when the research objective relates more to the events and associations within the full population at different periods of time, then a series of repeated cross-sectional studies might be the preferred

Example 7.6 Two cross-sectional studies of pet ownership and blood pressure

Both studies used a continuous measure of outcome (blood pressure) rather than a dichotomous (diseased/non-diseased response). Wright *et al* (2007) followed 1137 people who had answered a questionnaire on pet ownership in 1991–92 and determined their blood pressure (elevated blood pressure was the outcome) at some point between 1992 and 1996. Unconditional analyses indicated an association of 'current' (based on the 1991–92 survey) pet ownership with subsequent blood pressure, but after adjustment for co-variates (chiefly age, and a number of other factors some of which could be intervening variables) no association was observed.

Parslow and Jorm (2003) conducted a cross-sectional study of over 5000 randomly selected people from 2 areas in New South Wales, Australia. The history of pet ownership was obtained by interview and 2 readings of blood pressure were taken shortly thereafter, their average being the outcome measure of interest. Age, sex, and education were controlled when assessing the association of pet ownership and blood pressure; interactions between these covariates and pet ownership were also evaluated. Those with pets had significantly higher diastolic blood pressure than those without.

Both studies are limited by the potential reverse causation and other biases.

approach. In this design, depending on the sampling fraction, most of the study subjects selected at different points will not have been included in prior samples. However, with larger sampling fractions, sufficient subjects might be selected in 2 or more samplings to allow within study-subject comparisons (*eg* occurrence of new disease) over time.

7.9 Reporting of observational studies

Lang (2010), in tracing the history of research reporting and the development of modern standards for reporting research, states that reporting is perhaps the most important stage of the research process. He notes that the standard structure for reporting research (Introduction, Materials and Methods, Results, and Discussion) was introduced by Pasteur in 1858. Vandenbroucke *et al* (2007) and von Elm *et al* (2008), note that research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn. They indicated that the credibility of research depends on a critical assessment of the strengths and weaknesses in study design, conduct, and analysis. Despite the importance of 'good reporting', they observed that important information is often missing or unclear in published observational research. Thus, in 2004, a network of methodologists, researchers, and journal editors was established to develop what we now know as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. We have reproduced the checklist of 22 items they consider to be essential for good reporting of observational studies in Table 7.3. We refer to these items throughout this and the following chapters on study design. The reader also is referred to epidem.com for details and ongoing discussion on this topic. Lang (2010) reviewed the modern standards for reporting epidemiologic studies, in STROBE and other standards, and stressed the need to invoke these standards when reviewing research papers. Dreyer (2011) stresses the need to have these standards/guidelines available to decision-makers so that they can more validly interpret observational research. Dreyer *et al* (2010) also comment on a new set of guidelines called GRACE (Good Research or Comparative Effectiveness). Comparative effectiveness research is now enshrined in United States' law which mandates the creation of a Patient-Centered Outcomes Research Institute to establish national research priorities and methodological standards as well as carrying out research (Hernan, 2011a).

Despite all the efforts that have gone into reporting standards, inadequate reporting and/or interpretation of research remains a problem (Bhopal, 2009). With respect to reporting, these 'errors' relate to inadequate description of the study population, inadequate attention to measurement error, failure to ensure there is minimal confounding, not providing both absolute and relative summary measures, and overstatement or understatement of the case for causality. Bhopal suggests how to correct these 'errors' and makes a plea for a universally accepted set of guidelines for making causal inferences. More recently, Hernan (2011a), has echoed the concern over data quality and strongly supports thinking about all observational study design, implementation, analyses, and reporting as a 'controlled trial' done observationally.

Comment on examples
The examples used in this text cannot be reported as fully as suggested by STROBE for reasons of space. We have tried to include sufficient detail in each example to stimulate interest and make focused points about the study design. In addition, sometimes the data reporting by the original authors does not meet established standards and we periodically point that out in specific examples.

Table 7.3 The STROBE—Checklist of items that should be addressed in reports of observational studies

TITLE and ABSTRACT
1 (a) Indicate the study's design with a commonly used term in the title or the abstract
(b) Provide in the abstract an informative and balanced summary of what was done and what was found
INTRODUCTION
2 Explain the scientific background and rationale for the investigation being reported
3 State specific objectives, including any pre-specified hypotheses
METHODS
4 Present key elements of study design early in the paper
5 Describe the setting, locations, and dates, including periods of recruitment, exposure, follow-up, and data collection
6 (a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
(b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed
Case-control study—For matched studies, give matching criteria and the number of controls per case
7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
8 For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
9 Describe any efforts to address potential sources of bias
10 Explain how the study size was arrived at
11 Explain how quantitative variables were handled in the analyses. Describe which groupings were chosen, and why
12 (a) Describe all statistical methods, including those used to control for confounding
(b) Describe any methods used to examine subgroups and interactions
(c) Explain how missing data were addressed
(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed
Case-control study—If applicable, explain how matching of cases and controls was addressed
Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
(e) Describe any sensitivity analyses

Table 7.3 (continued)

RESULTS
13 (a) Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
(b) Give reasons for non-participation at each stage
(c) Consider use of a flow diagram
14 (a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders
(b) Indicate the number of participants with missing data for each variable of interest
(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
15 *Cohort study*—Report numbers of outcome events or summary measures over time
Case-control study—Report numbers in each exposure category, or summary measures of exposure
Cross-sectional study—Report numbers of outcome events or summary measures
16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included
(b) Report category boundaries when continuous variables were categorised
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
17 Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses
DISCUSSION
18 Summarise key results with reference to study objectives
19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
21 Discuss the generalisability (external validity) of the study results
22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

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