Chapter 9 - Learning Objectives

After completing this chapter you should be able to:

1. Define the terms:

   prospective cohort study
   retrospective cohort study
   exposed group
   unexposed group
   selection bias
   information bias

2. Describe how study subjects will be identified with respect to exposure status.

3. Define the study outcome in measurable terms.

4. Specify the data collection methods to be used in the study.

5. Develop a data table for analysis of the association between the exposure and outcome.

6. Calculate relative risk and confidence limits for cumulative incidence relative risk and incidence density relative risk.

7. Interpret relative risk.

8. Recognize advantages and disadvantages of cohort studies.

9. Design a hypothetical cohort study in outline form.

9 Cohort Studies

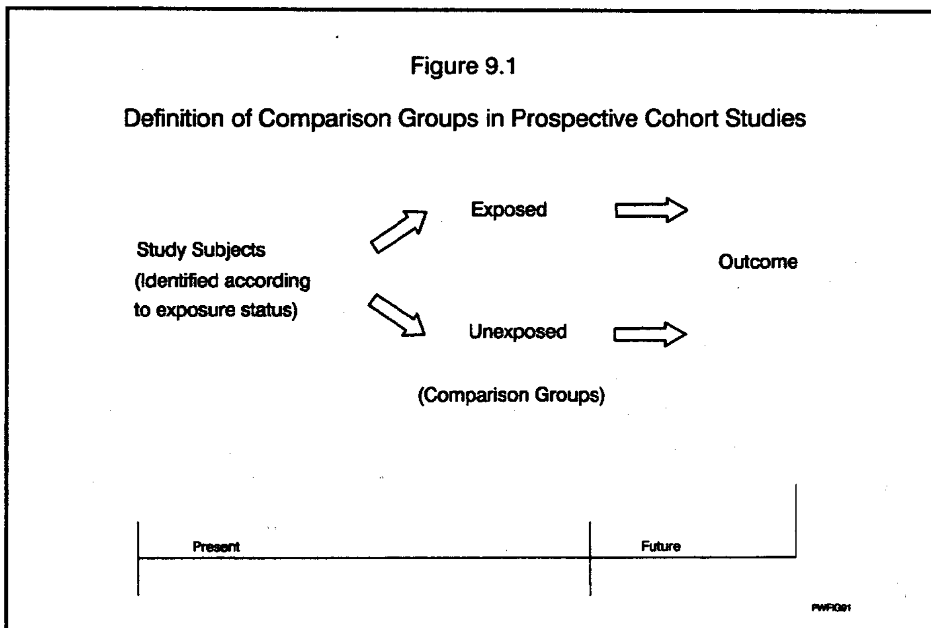
Introduction

Cohort study defined

The cohort study is an analytic epidemiologic research design in which the study population is composed of individuals who are classified as exposed or not exposed to a particular risk factor (comparison groups). These groups are followed forward for a specific period of time to estimate the incidence rates of an outcome or the development of a health problem (Figure 9.1). The exposed group is composed of individuals who have been exposed to a postulated causal or protective factor for a health problem. The unexposed group is composed of individuals who are similar to the exposed group but who are known not to have been exposed to the causal or protective factor. Depending on whether the study is designed to examine a postulated causal or protective factor, the individuals in the exposed group are hypothesized to be at greater or lesser risk of developing the

Figure 9.1

Definition of Comparison Groups in Prospective Cohort Studies



health problem than the individuals in the unexposed group. In designing a cohort study, investigators should clearly state the research hypothesis and specify the expected relationship between the exposure groups and the health problem of interest.

Cohort studies are similar to randomized clinical trials in that they proceed from exposure to outcome. Unlike the randomized clinical trial, however, the investigator observes rather than assigns exposure status. The study groups are identified by exposure status before outcome status. Each person in both the exposed and unexposed groups (study subjects) is followed in an identical manner until one of the following outcomes occurs:

- The study subjects develop the health problem under study.
- The study subjects die.
- The study ends.
- The study subjects are lost to follow-up.

In the randomized clinical trial, the investigator determines the exposure status. In the cohort study, the exposure status is determined by:

- genetics or biology (i.e., male or female, presence or absence of sickle cell anemia)
- a conscious choice made by the subject (smoker or nonsmoker; contraceptive user or nonuser)
- circumstances (living in a poorly served rural area or in a large city).

Prospective cohort study

Historical cohort study

Cohort studies may be either prospective or historical. In a prospective cohort study, exposure status is determined when the study begins, and the exposed and unexposed groups are followed forward in time to observe whether they develop the study outcome. In a historical cohort study, the study subjects have developed the health problem or outcome and have been exposed before the study begins. The exposure and the health problem are determined from existing records. A historical cohort study is essentially the reconstruction of a cohort study that has already taken place. In Example 9.2, we use a hypothetical study of maternal thalassemia and fetal death *in utero* to illustrate a prospective and a historical cohort study design.

Example 9.2

Maternal Thalassemia and Fetal Death in Utero

A hypothetical cohort study is to be conducted to assess the association between maternal thalassemia and fetal death in utero.

Design 1: A Prospective Cohort Study

In a hypothetical prospective cohort study, women with thalassemia who come to a clinic for their first prenatal visit would compose the exposed group. The unexposed group would be women without thalassemia who also come to the clinic for their first prenatal visit. In both groups, each woman would be followed throughout her pregnancy to observe the occurrence of fetal death in utero (outcome).

Design 2: A Historical Cohort Study

The association between maternal thalassemia and fetal death in utero could also be evaluated using a historical cohort study design, if the quality of the records and the follow-up procedures at the study site were good. Using this design, investigators would identify all women with thalassemia who came to the clinic for their first prenatal visit at some specified time in the past (exposed), and all women without thalassemia who had their first prenatal visit during the same time period (unexposed). The medical records of these women would be reviewed to determine whether fetal death in utero (outcome) had occurred. In a historical study, the exposure (thalassemia) would be identified first; then the outcome (fetal death) would be ascertained. Both the exposure and outcome may have occurred months or even years in the past. This design is a cohort study because exposed and unexposed groups are the comparison groups; it is retrospective because both exposure and outcome occurred before the study was initiated.

In cohort studies, investigators can examine more than one health problem that may be the result of the exposure under study. For example, in a study of the effects of oral contraceptives, investigators may be primarily interested in cardiovascular disease, but the study could provide the opportunity to examine a variety of other outcomes hypothesized to be related to oral contraceptive exposure, including deep venous thrombosis, myocardial infarction, and cerebrovascular accidents.

Design and Data Collection Methods

Population Sources and Follow-up

An important step in designing a cohort study is selecting exposed and unexposed populations that can be adequately followed over time. A high rate of follow-up for both exposed and unexposed study subjects is needed if the conclusions of the study are to be considered valid. Both exposed and unexposed groups will need to be followed in an identical manner to determine if they develop the study outcome. For example, if the exposed subjects are followed up with in-person interviews and physical examinations, the unexposed subjects should be followed up by identical data collection methods to minimize bias in the detection of the health problem.

The population used in a given study will depend on the exposure and outcome of interest and on the ease of gathering sufficient information on exposure and outcome in the population. The choice of the study population may be affected by the delay between exposure and outcome (latency). If latency is long, extensive follow-up will be necessary. Potential sources for the study population may include the general population, a sample of the general population, special groups (such as nurses or government employees who can be readily followed over time), attendees to clinics with good record-keeping and follow-up procedures, or occupational groups with different levels of exposure. Populations or samples of populations are most appropriate for a cohort study design when the exposure is relatively common. If the study exposure is uncommon, investigators should select special groups who have experienced a higher level of exposure than the general population. For example, investigators who study a possible association between injectable contraceptives and cancer might use a population of family planning clinic attendees instead of women in the general population, especially if the prevalence of contraceptive use is low in the population.

Latency

Selection of the Exposed Group

The exposed group

The exposed group in a cohort study are the individuals who have the exposure of interest. Before the exposed individuals can be identified, the investigators must develop an unambiguous and objective description of what constitutes exposure. Where applicable,

the definitions should include the minimal acceptable levels of the exposure (e.g., more than ten cigarettes per day) and the minimal duration of exposure (e.g., use of oral contraceptives continuously for at least a year). Other eligibility criteria for entry in the study, such as age, sex, and absence of preexisting medical problems, should also be determined. In particular, the individuals should not have a history of the outcome.

A cohort study may have more than one exposed group; the merits of using more than one exposed group should be considered in the initial study design. For example, in a study of smoking and intrauterine growth retardation (IUGR), the investigators may wish to compare the effects of heavy smoking (≥ 20 cigarettes per day) with the effects of lighter smoking (< 20 cigarettes per day) on IUGR. The study could include two exposure groups: the group that smokes < 20 cigarettes per day, and the group that smokes ≥ 20 cigarettes per day. In the analysis, both exposure groups would be compared with the women who do not smoke during pregnancy (unexposed group). However, the number of heavy smokers may be too small to make valid conclusions about the association. In general, if detailed information about the effects of different levels of exposure is needed, the investigators should consider using more than one exposure group. Example 9.3 presents a cohort study of the association between oral contraceptive use and breast cancer among nurses (Romieu et al., 1989). In this study, women who were current users of oral contraceptives (OC) and women who were past users were followed up and compared to women who had never used OCs.

Preferably, only the study subjects who are potentially at risk for the outcome of interest should be enrolled in the study. For example, investigators studying smoking and adverse pregnancy outcomes should exclude women who have had a tubal ligation because these women are not at risk of pregnancy. The decision to include or exclude individuals from the study population will depend on the exposure and outcome of interest and on whether heterogeneity is managed by restricting admission to certain groups or by performing stratified analyses after the data are collected. In general, the more restrictive the admission criteria, the more difficult it is to assemble an appropriate cohort.

Example 9.3
Oral Contraceptives and Breast Cancer

Problem: Are oral contraceptives associated with an increased risk of breast cancer?

Research Hypothesis: Women who use oral contraceptives have a higher risk of breast cancer than women who have never used oral contraceptives.

Study Design: Prospective cohort study of 121,700 female registered nurses 30 to 55 years old who are living in 11 states of the United States.

Exposed: Women who had used oral contraceptives for at least one month in the past and who had never experienced angina pectoris, myocardial infarction, or stroke before the beginning of the study in 1976. Women who had used oral contraceptives were further categorized as women who were currently using oral contraceptives and women who had used oral contraceptives in the past but were no longer currently using them.

Unexposed: Women who had never used oral contraceptives and who had never experienced angina pectoris, myocardial infarction, or stroke before the beginning of the study in 1976.

Outcome: All breast cancer cases reported by the woman (or next of kin for decedents) for whom relevant hospital records confirmed the diagnosis.

Follow-up: The follow-up was conducted every two years using a mailed questionnaire. A repeat mailing was done for those who did not respond. Approximately 5% of the women were lost to follow-up.

Data Collection Methods: Self-administered questionnaires included information on medical conditions and life-style practices. Follow-up data were collected with self-administered questionnaires every two years. Outcomes reported by women were verified by review of medical records; deaths were reported by next of kin or postal authorities (when the questionnaires could not be delivered) or identified from vital records.

Results:

	Oral Contraceptive Use		
	Current	Past	Never
Breast cancer	32	685	1,041
Person-years	22,622	472,828	592,364
Rate/1,000 person-years	1.41	1.45	1.76
Crude IDR	0.8	0.8	
95% CI	(0.6, 1.1)	(0.7, 0.9)	

(Romieu et al., 1989)

Selection of the Unexposed Group

The unexposed group

The unexposed subjects should be similar to the exposed in all ways except they should not have the exposure under study. The unexposed group is used to determine the incidence of the health problem among those without the exposure. Then, the investigators compare the incidence of the outcome among the individuals in the exposed and unexposed groups. Thus, the exposed and unexposed populations should be as similar as possible.

In a cohort study, the unexposed subjects should have the same general criteria for entry into the study as the exposed (e.g., age, sex, absence of preexisting medical problems, no history of the outcome of interest). They should also be at potential risk of developing the outcome under study. Finally, the unexposed study subjects should have the same opportunity as the exposed to be diagnosed with the outcome.

Selection processes

Ideally, the unexposed study subjects should be chosen using the following criteria:

- Take the total population or a sample of the population (e.g., all the attendees at a specific clinic or a random sample of the population in a rural village).

- Determine the exposure status of each individual.

- Classify each individual into the appropriate exposure category.

By using these built-in or internal comparison groups, investigators are afforded considerable advantages that include decreasing the potential for bias attributable to differences in the study populations and to differences in ascertaining the outcome between the exposed and unexposed study subjects. In the study outlined in Example 9.3, participants were asked on the initial questionnaire whether they currently used or whether they had ever used oral contraceptives (Romieu et al., 1989). Based on this information, the investigators divided the cohort into women who had ever (currently or in the past) used oral contraceptives (exposed) and women who had never used oral contraceptives (unexposed).

Consider the following hypothetical cohort study that also uses an internal comparison group to examine the effect of low birthweight on infant survival. The investigator designed a study in which all live-born infants in five villages were weighed at birth by midwives using simple scales and followed for one year. The total population of babies could be divided into an exposed group (birthweight < 2,500 g) and an unexposed group (birthweight ≥ 2,500 g) and followed at monthly intervals to determine the outcome of survival at the end of the study period (the child's first birthday). Alternatively, all the low-birthweight babies could be used as the exposed group and only a sample of the ≥ 2,500 g babies would be used as the unexposed group, since these larger babies will considerably outnumber the low-birthweight babies.

In another hypothetical cohort study, investigators used an internal comparison group to investigate the effects of anemia on premature births among a population of women who attend a prenatal clinic. The investigators could screen all women for anemia who come to the clinic for the initial prenatal exam in their first trimester during a specified year. Those women with low hemoglobin could comprise the exposed group, and those with normal hemoglobin could comprise the unexposed group. The women in both groups could be followed to determine who delivered premature infants.

When an appropriate unexposed group cannot be selected within the same population, two less-than-ideal methods are sometimes used. The first method compares the exposed group with another group that is similar in composition but does not have the exposure. In Example 9.4, investigators used this method to select a sample of unexposed women.

The second method compares the outcomes among exposed study subjects and a population rate. Using this method, investigators compare the outcomes in a study cohort and the experience of the general population while the cohort is being followed. For example, investigators could compare the mortality rates of women who have used oral contraceptives and died of thromboembolism and the mortality rates of women of comparable age in the general population. This method is only possible when population rates are available (e.g., death rates).

Example 9.4

Selection of an Unexposed Group from a Different Population

Investigators designed a study to examine the effects of malaria on placental weight among women in certain villages; almost all of the women are infected with malaria. To obtain the unexposed group, the investigators select women from villages located in nonmalarious areas. Although the selected villages are demographically similar, and the villagers have access to comparable health services, the investigators' decision to use women from different villages is not ideal. The exposed and unexposed populations may differ in tangible and intangible ways, and they may not be strictly comparable. There may not be other options in this situation, and the investigators may have difficulty determining whether differences in the relative risk for the health problem under study are related to the exposure or to differences in the two populations.

Matching

Individual and frequency matching

Matching refers to procedures for selecting a study group and a comparison group so that they are comparable with respect to extraneous factors (Last, 1988). *Individual matching* involves identifying individuals for the comparison group such that each resembles a certain study subject on the matched variable(s). *Frequency matching* involves matching on selected variables so that the frequency distributions of the matched variables are similar in the study and comparison groups (Last, 1988) (Example 9.5). In frequency matching, the investigator estimates the number of exposed subjects in a given subgroup before the study begins. The estimate is based on a preliminary analysis of the distribution of individuals with the exposure of interest; then the requisite number of unexposed subjects in the subgroup is enrolled in the study (Last, 1988).

In most circumstances, the preferred approach to matching is simply to take a population or population sample, separate the selected individuals into exposed and unexposed groups, and then in the analysis stratify by other variables that are likely to affect the relationship between exposure and outcome. Investigators should be cautious about matching for several reasons:

Example 9.5

Individual and Frequency Matching

A Hypothetical Study

Investigators design a study to examine the effects of anemia on pregnancy outcome among women at a certain prenatal clinic. They decide that parity is likely to affect the relationship between the two variables and that matching may be necessary. Two methods of matching are considered.

Frequency matching. The investigators determined in a preliminary study that 20% of the women with anemia who come to the clinic for their first prenatal visit have had no previous pregnancies. They decide to enroll 100 women with anemia and 100 women without anemia. For the unexposed group, they would identify women without anemia who have had no previous pregnancies as they come into the clinic, until 20 women (with no children) are enrolled.

Individual matching. If this method is used, the investigators could match the first woman diagnosed with anemia who has had no previous pregnancy (exposed) with the next woman seen at the clinic who is not anemic and who has had no previous pregnancy (unexposed). If the next woman to be seen at the clinic has anemia and has had three children, she would be matched with the next woman who has had three children but who is not anemic. This enrollment process would continue until the required number of women is obtained for the study.

Cautions about matching

- Matching on a particular variable prohibits studying its association with the outcome.
- Matching may greatly increase the amount of work required to find appropriate unexposed individuals with the same characteristics as the exposed.
- A matched variable that is in the causal pathway between exposure and disease, or a variable that is related to the outcome but not the exposure may cause problems in interpreting the results of a study.
- Individual matching requires a matched analysis to ensure that the individuals in the matched sets are compared to one another.

Since matched analyses can be difficult, matched designs should be used only when the advantages outweigh the disadvantages.

Measuring Exposure

In a prospective cohort study, investigators measure exposure at the time of enrollment. In some studies, persons may be enrolled at the time they first experience the exposure (e.g., at the time they begin using a certain contraceptive or have a sterilization procedure). More commonly, the exposure has been occurring for some time (e.g., smoking), and both current and historical exposure data are generally collected. Exposure status may be determined from interviews, self-administered questionnaires, or existing records, such as clinic or hospital charts and laboratory or employment records. To adequately describe the relationship between an exposure and an outcome, investigators should include measures related to frequency, duration, dose, and timing (e.g., dates of first and last exposure).

Sources of exposure data

Some exposures are one-time events (e.g., a surgical procedure such as a tubal ligation or vasectomy) or are biologically determined and unchangeable (e.g., hemoglobinopathies or maternal height). Others, however, may change after an individual is enrolled in the study. For example, a woman who is using an intrauterine device (IUD) might decide to change methods or might choose not to use a contraceptive; a person classified as a smoker at the beginning of the study may quit during the study. Alternatively, an initially unexposed person may begin to use an IUD or may begin smoking after being enrolled in the unexposed group. In these instances, maintaining the original designation of exposed or unexposed is a conservative approach that tends to bias the results toward the null effect.

From a conservative perspective, the exposure status of the study subjects should not be changed, for purposes of analysis, after initial classification, but investigators should note changes in exposure status over time. If such information is available, investigators can look at the effect of differing durations or intensities of exposure on the health problem under study. For example, it might be interesting to determine if the development of a myocardial infarction is dependent on the length of time a

woman uses OCs or how long the risk of an infarction persists after a woman stops using them.

Determination of Outcome

When the study begins, the outcome must be defined precisely and as unambiguously and objectively as possible. The definition must be applied uniformly for both the exposed and unexposed. If many medical providers will be diagnosing the health problem or identifying the outcome under study in a number of different study sites, the investigators should consider the skills of the providers and the likelihood that certain diagnostic tests will be performed when they define the outcome. If possible, the processes by which an outcome is defined and diagnosed should be standardized and outlined in a. training program. However, such a program must be designed carefully. If the medical providers are made aware of the hypothesis under study, they may be more likely to diagnose the outcome among the individuals in the exposed group than among the individuals in the unexposed group.

In a historical cohort study the medical providers who diagnose the outcome should be unaware of the exposure status of the study subjects since such knowledge may potentially bias the investigators' determination of the outcome. Restricting knowledge of any aspect of the study from anyone involved in the study is referred to as blinding.

Determining outcome may be logistically more complicated in a prospective cohort study. For example, if the disease (e.g., cancer) has a long latency period, the follow-up will have to be conducted over a prolonged period of time. When the study is designed, the investigators must develop methods to ensure the highest possible follow-up rates for both exposed and unexposed study subjects.

Follow-up methods

The specific methods used to determine outcome will depend on the outcome under study. If the outcome involves changes in behavior or minor illnesses that are unlikely to require hospitalization, for example, follow-up would involve recontacting the subjects on a periodic basis. For individuals with more severe outcomes that typically require hospitalization, investigators may periodically review the admissions records at the hospitals where the study subjects are likely to go if they become ill. For outcomes such as death or cancer, the best method of follow-up may be to review death certificates or cancer registries on a regular schedule.

In the design of the study, the investigators must carefully consider the methods that will be used to adequately ascertain the outcome, since the resources required to perform the study and the validity of the study's results are highly dependent on the follow-up methods. If the follow-up is to be conducted through regular reviews of vital records (or cancer registry records), the detailed personal identifiers for each individual should be collected at the beginning of the study and attempts should be made periodically to update this information. If follow-up is conducted through contact with the study subjects or their health care providers, the investigators may want to gather not only personal identifiers on the individual but the names of relatives or friends who are likely to know where to locate the individual in the future. Well-documented specifications on what constitutes adequate follow-up is not available, but if more than 40% of the study subjects are lost to follow-up, results of the study are likely to be seriously questioned. Even a 20% loss to follow-up may introduce doubts about a study's validity. As in historical cohort studies, the outcome should be ascertained without knowledge of the exposure, and identical methods must be used to follow up and ascertain outcomes for individuals in both the exposed and unexposed groups. These measures are necessary to avoid biases that may lead to erroneous conclusions.

Loss to follow-up

Examples 9.6 and 9.7 illustrate follow-up procedures and methods used to ensure the complete and accurate assessment of outcomes.

Example 9.6

Risk Factors for Maternal Mortality in Bangladesh

Problem: Is increased maternal age associated with a higher risk of maternal death in Bangladesh?

Research Hypothesis: In Bangladesh, women who are at least 30 years old at delivery have a higher risk of maternal death than younger women.

Study Design: Prospective cohort study

Exposed: Women in the study population who are at least 30 years old.

Unexposed: Women in the study population who are younger than 30 years old.

Example 9.6 (continued)

Outcome: Death from any cause during pregnancy, at delivery, or in the 42 days after termination of the pregnancy.

Follow-up: Follow-up was conducted through personal interviews every two weeks until 42 days after delivery to determine pregnancy outcomes.

Data Collection Methods: Interviewers identified pregnant women during visits to each of the study villages and tracked their outcomes.

(Alauddin, 1986)

Example 9.7

Instillation Methods for Second Trimester Abortion

Problem: Is urea-prostaglandin instillation a safer method than saline instillation for second trimester abortion.

Research Hypothesis: Women who undergo urea-prostaglandin abortions have less risk of complications than women who undergo saline instillations.

Study Design: Prospective cohort study

Exposed: Women at least 20 years old who had had urea-prostaglandin instillation abortions at one of 13 study institutions during 1975-1978.

Unexposed: Women at least 20 years old who had had saline instillation procedures at the same institutions.

Women in both groups who had concurrent sterilization procedures, ectopic pregnancies, and hydatidiform moles were excluded from the analysis.

Outcome: The study outcomes were defined as the following major complications: fever $\geq$ 38°C for 3 or more days, hemorrhage requiring transfusion, or unintended abdominal surgery.

Follow-up: Complications were recorded on routine follow-up visits 2 to 6 weeks after abortion.

Data Collection Methods: Data were collected through regular reviews of records from participating clinics.

(Binkin et al., 1983)

Validity and Bias

When conducting epidemiologic studies, investigators must be concerned about making false conclusions that are a result of the research methodology used. The purpose of the cohort study design is to allow the investigator to determine what effect the exposure has on the outcome. If the methodology used by the investigator alters the true effect of an exposure, this misrepresentation is called bias. If no bias is present in the study, the measure of effect calculated is said to be a valid estimate of the effect of the exposure on the health problem.

Potential sources of bias

Two important types of bias can occur in cohort studies—selection bias and information bias. Potential sources of bias should be carefully considered in the design of a study. Except for the exposure of interest, the study subjects should have comparable risks of developing the outcome of interest.

Selection bias. This type of bias may be present if the individuals who are enrolled in the study have different characteristics than the population they are supposed to represent. Selection bias occurs if the individuals selected for participation in the study differ somehow from the individuals who were not selected (Examples 9.8 and 9.9).

Example 9.8

Delivery During the Harvest Season and the Risk of Complications
Selection Bias

A Hypothetical Study

A physician observes that women who deliver their infants during the harvest season tend to have more labor and delivery complications than women who deliver their infants at other times of the year. He hypothesizes that the complications may be attributed to high levels of physical activity in the weeks before labor since most women are working in the fields up to 12 hours per day during the harvest season. He designs a hospital-based study to compare women who have their infants during the harvest (the exposed) and women who deliver 3 months after the harvest, when routine daily activities have returned to normal (unexposed); the women are matched on age and parity. He finds that complications are, in fact, greater for women who deliver during the harvest. He also notes that the number of hospital-based

Example 9.8 (continued)

deliveries declined considerably during the harvest months. In a discussion with local midwives and trained birth attendants, he discovers that during the harvest season, women tend to deliver in their villages to minimize the time away from work. Most of the women who do make the long trip to the hospital during this period are those with prolonged or difficult labor.

This study provides an example of selection bias. Although women who deliver in the hospital after the harvest may be fairly representative of the women in the hospital's catchment area, those women who deliver in the hospital during the harvest season are not representative of all women who have their babies during this time period. As a result, the study probably overestimates the risk of complications related to increased physical activity. To conduct this study properly, the physician should conduct a population-based study to examine complication rates among women who deliver at hospitals, at health centers, and at home.

Example 9.9

Intrauterine Devices and Pelvic Inflammatory Disease
Selection Bias

Another example of potential selection bias is a hypothetical cohort study in which an association between intrauterine device (IUD) use and pelvic inflammatory disease (PID) is investigated. If women using oral contraceptives and barrier methods composed the unexposed group, an erroneous conclusion might be made, since both methods of contraception are known to reduce the risk of PID. A better alternative for the unexposed group would be women who are sexually active but not using contraceptives. The study could be matched or stratified by number of sexual partners and any other variables that may be different between IUD users and women who do not use contraceptives, or by variables that may affect the incidence of PID independent of exposure to IUDs.

Information bias

Information bias. If information on exposure or outcome is obtained differently for the exposed and unexposed groups, information bias may result. In prospective cohort studies, information bias related to exposure is minimal because exposure status is determined before the disease occurs. However, in prospective cohort studies, the outcome may be subject to information bias because exposure status is known before the outcome is

determined. In historical cohort studies, both exposure and outcome information are potentially subject to this bias because information on both variables is collected after the outcome has occurred. For example, information bias might occur if ascertainment of outcome among the individuals in the exposed group was based on periodic attempts to recontact the individual and a review of death certificates, while outcome for the unexposed individuals was obtained by only reviewing death certificates. Information bias is best avoided by ensuring that the same attention is given to each study subject in the exposed and the unexposed groups. Preferably, the persons who collect outcome information should be blinded to the exposure status of the study subjects (Example 9.10). Information bias generally is best managed while the study is in the field and not during the analysis phase.

Example 9.10

Oral Contraceptives and Cervical Carcinoma in Situ
Information Bias

In a hypothetical study of oral contraceptive (OC) use and cervical carcinoma *in situ*, women who use OCs compose the exposed group and women who use the barrier method compose the unexposed group. The women are identified through visits to a family planning clinic. Women with cancer *in situ* are identified from hospital laboratory records. A potential concern is that OC users who return more frequently for prescription renewals are more likely to receive a Pap smear and to be diagnosed with cancer *in situ* than women who use barrier methods. To overcome this problem, the study protocol states that women in both the exposed and unexposed groups should receive Pap smears at the same intervals.

Another form of information bias could occur if, during the study, results showing a positive link between OC use and carcinoma *in situ* were published by other investigators. As a result, physicians might be more likely to perform Pap smears more often on women using OCs. Additionally, the pathologists who read the Pap smears may be more likely to read borderline smears in an OC user as positive if they are aware of the woman's contraceptive status. The former problem is best prevented by requiring that the Pap smears be done at comparable intervals for women in the exposed and unexposed study subjects. The problem of exposure status affecting the pathologist's reading is best managed by having the pathologist read the smears without knowledge of the exposure status.

Data Analysis Methods

Ideally, the analytic methods are determined concurrently with the design of the study protocol and the data collection forms to ensure that information is collected for all required variables and that the sample size is adequate. After data collection is complete, the first steps of the analysis are to organize the data into the tables developed when the analysis was planned. Several types of tables are used to organize cohort study data and to make comparisons between exposed and unexposed study subjects. The first tables presented for

Table 9.11

Characteristics of Women Undergoing Abortion by Intra-Amniotic Instillation

Characteristic	Urea-prostaglandin (n= 2,805) %	Saline Solution (n = 4,778) %
Age (year)		
≤ 19	55.3	49.0
20-24	27.3	31.3
≥ 25	17.4	19.7
Race		
White	54.7	59.6
Black and other	45.3	40.4
Marital status		
Currently married	10.6	10.5
Unmarried	89.4	89.5
Prior pregnancies		
None	56.3	53.7
1 or more	43.7	46.3
Prior abortions		
None	82.4	83.4
1 or more	17.6	16.6

(Binkin et al., 1983)

the analysis of cohort studies are usually demographic characteristics and risk factors for the study subjects in the exposed and unexposed groups (Table 9.11). Additional tables present information about the magnitude of the association between the exposure and the health problem under study and information about the risk of the health problem among subgroups of the exposed and unexposed study subjects.

Analysis Table of Characteristics of Exposed and Unexposed Study Subjects

The analysis should begin with a description of the demographic and medical characteristics of the exposed and unexposed study subjects. These data permit a comparison of the individuals in the exposed and unexposed groups. For example, in Table 9.11 women who underwent abortion by intra-amniotic instillation differed slightly by age, race, and type of instillation (Table 9.11). Otherwise, the two groups of women were similar with respect to marital status and pregnancy history.

Cohort Study Analysis Table for Relative Risk and Confidence Interval

Analysis of data from cohort studies involves the comparison of rates of the health problem among the exposed and unexposed study subjects. Relative risk is the most commonly used measure of association between exposure to a particular factor and risk of specified outcome. Relative risk is the incidence of the outcome among the exposed study subjects divided by the incidence of the outcome among the unexposed study subjects. The relative risk shown in Table 9.12 is known as *cumulative incidence* relative risk (CIR); it measures the risk of the study subject developing the health problem during the entire study period.

Cumulative incidence relative risk (CIR)

For example, pregnant women in Bangladesh who were at least 30 years old had almost two times the risk (CIR = 1.8) of maternal death as pregnant women who were younger than 30 years old (Example 9.13). In the study of the relationship between complications after abortion and the type of instillation procedure, the overall risk of serious complications was more than two times (CIR = 2.3) greater for saline abortions than for urea-prosta-

Table 9.12

Cohort Study Analysis Table for Cumulative Incidence Relative Risk

	Exposed	Unexposed	Total Subjects
Subjects developing outcome	a	b	m_1
Subjects not developing outcome	c	d	m_0
Total subjects	n_1	n_0	t

Cumulative Incidence Relative Risk (CIR) = $\frac{\text{The proportion of the outcome among the exposed study subjects}}{\text{The proportion of outcome among the unexposed study subjects}}$

$$= \frac{a/n_1}{b/n_0} \qquad (9.12.1)$$

where *a* is the number of persons with the exposure who have the outcome, *b* is the number of persons without the exposure who have the outcome, *c* is the number of persons with the exposure who do not have the outcome, and *d* is the number with neither the exposure nor the outcome. n_1 represents the total number of persons exposed, and n_0 the total number of persons unexposed. m_1 represents the total number of persons who have the outcome, m_0 represents the total number of persons who do not have the outcome, and *t* is the total number of persons under study.

(Rothman and Boice, 1979)

Example 9.13

Risk Factors for Maternal Mortality in Bangladesh

Results:

Outcome	Maternal Age (years) ≥ 30	< 30
Number of pregnant women who died within 42 days of delivery	18	11
Number of pregnant women still living 42 days after delivery	4,318	4,774
Total	4,336	4,785

$$\text{CIR} = \frac{\text{Incidence of maternal deaths in women} \geq 30 \text{ years}}{\text{Incidence of maternal deaths in women} < 30 \text{ years}}$$

$$= \frac{18/4{,}336}{11/4{,}785}$$

= 1.8 (95% CI: 0.9 - 3.8)

(Adapted from Alauddin, 1986)

Table 9.14

Complication Rates and Additional Treatments Associated with Urea-Prostaglandin and Saline Solution Instillations

Complication or Treatment	Rate* Urea-Prostaglandin	Saline Solution	Adjusted Relative Risk†	95% Confidence Interval
Serious complications:	1.03	2.18	2.3	(1.4 - 3.6)
Hemorrhage necessitating transfusion	0.32	1.72	5.9	(2.7 - 13.0)
Fever ≥ 38° C for ≥ 3 days	0.71	0.50	0.84	(0.43 - 1.6)

Table 9.14 (continued)

Complication or Treatment	Rate* Urea-Prostaglandin	Rate* Saline Solution	Adjusted Relative Risk†	95% Confidence Interval
Other complications:				
Hemorrhage	6.20	2.20	0.23	(0.17 - 0.30)
Fever ≥ 38° C for ≥ 1 day	6.27	4.96	0.77	(0.61 - 0.96)
Endometritis	5.31	3.26	0.53	(0.41 - 0.69)
Cervical injury	1.32	0.42	0.12	(0.06 - 0.25)
Treatments:				
Uterine evacuation	10.34	14.82	1.4	(1.2 - 1.6)

* Per 100 abortions

† Adjusted for follow-up, previous pregnancies, use of laminaria, prophylactic antibiotics, and use of oxytocin at or before instillation

‡ Numbers too small for logistic regression analysis; using an exact procedure, relative risk = 2.3 with a 95% confidence interval of 0.23 to 120

(Binkin et al., 1983)

glandin instillations (Table 9.14). The risk of hemorrhage requiring transfusion was approximately six times greater (CIR = 5.9).

Person-time

Incidence density relative risk (IDR)

Some studies use person-time as the denominator in the relative risk calculation instead of the number of persons enrolled in the study. This type of relative risk is known as incidence density relative risk (IDR). The person-time denominator simultaneously considers the number of persons under observation and the duration of observation for each person. For example, if 10 persons participate in a study for 15 years, they are said to have contributed 150 (10 persons * 15 years) person-years of observation. The same figure may be derived if 150 persons were under observation for one year or 300 persons for six months. This method allows the investigator to more satisfactorily manage situations when the dates the study subjects enter the cohort study vary, or when, during the course of the study, some study subjects are no longer under observation because of death, loss of contact, or other reasons. The basic analytic table for computing the IDR is presented in Table 9.15 (Rothman and Boice, 1979).

Table 9.15

Cohort Study Analysis Table for Incidence Density Relative Risk

	Exposed	Unexposed	Total
Cases	a	b	m_1
Person-time	n_1	n_0	t

$$IDR = \frac{a / n_1}{b / n_0} \quad (9.15.1)$$

where a is the number of cases among the exposed, b is the number of cases among the unexposed, n_1 is the person-time in the exposed group, and n_0 is the person-time in the unexposed group. m_1 represents the person-time among the cases and t is the person-time for all study subjects.

(Rothman and Boice, 1979)

The confidence interval for the CIR and the IDR is given in formula 9.15.2.

(9.15.2)

$$\text{Confidence Interval} = RR^{(1 \pm z/\chi)}$$

where RR = CIR or IDR, z is a normal variate, $\chi = \sqrt{\chi^2_{RR}}$, and

(9.15.3)

$$\chi^2_{CIR} = \frac{(t - 1) * [(a * d) - (b * c)]^2}{n_1 * n_0 * m_1 * m_0} \qquad \chi^2_{IDR} = \frac{(a - n_1 * m_1 / t)^2}{n_1 * n_0 * m_1 / t^2}$$

(Rothman and Boice, 1979). In Example 9.13, the CIR of 1.8 was not statistically significant since the 95% confidence interval (0.9 - 3.8) includes 1.0. Using the data in Example 9.13, the confidence interval for the CIR is computed by performing the following steps:

Step 1: $$\chi^2 = \frac{9{,}120 * (18 * 4{,}774 - 11 * 4{,}318)^2}{4{,}336 * 4{,}785 * 29 * 9{,}092}$$

$$= 2.46$$

$$\chi = \sqrt{\chi^2}$$

$$= 1.57$$

Step 2: For 95% confidence interval, $z = 1.96$

Step 3: Lower limit $= CIR^{(1 - z/\chi)}$

$$= e^{[\ln CIR * (1 - z/\chi)]}$$

$$= e^{[\ln 1.8 * (1 - 1.96/1.57)]}$$

$$= 0.9$$

Upper limit $= CIR^{(1 + z/\chi)}$

$$= e^{[\ln 1.8 * (1 + 1.96/1.57)]}$$

$$= 3.8$$

For Example 9.3, the unadjusted IDR for past users compared to never users was 0.8 with 95% confidence interval (0.7 - 0.9). This estimate suggests that women who have used OCs in the past have a statistically significant reduced risk of breast cancer than women who have never used OCs. The estimate is statistically significant since the confidence interval does not include 1.0.

Controlling for Confounding in the Analysis

Confounding is a form of bias that occurs when an extraneous factor related to both the exposure and outcome obscures the true relationship between exposure and outcome. To be a confounder, a variable must be associated with, but not a consequence of, the exposure and independent of its association with the exposure, be associated with the outcome. Stratified analysis is often used to correct for confounding. The relative risk estimate, which has been adjusted by the confounding variable, is computed and compared with the crude estimate. If the difference between the crude and adjusted estimates is more than some percentage specified before analysis,

Table 9.16

Neonatal Outcome by Maternity Clinic or District Hospital

Outcomes of Neonates at Seven days	Maternity Clinic	District Hospital
Died	94	50
Living	11,906	4,950
Total	12,000	5,000
Early neonatal mortality rate	7.8 / 1,000	10.0 / 1,000

CIR = 0.8

then the variable may be considered a confounder and should be controlled for in the analyses. Details of calculating the adjusted relative risk and confidence intervals are introduced in Chapter 4.

In a hypothetical historical cohort study, investigators designed a study to examine whether delivery at the maternity clinic in a certain district is associated with a higher risk of early neonatal mortality than at the district hospital. Records from the maternity clinic and the district hospital are abstracted; the results are shown in Table 9.16. Instead of finding a higher risk of early neonatal mortality associated with delivering in the maternity clinic, the investigator finds the risk is actually lower in the maternity clinic than in the district hospital.

The district has a referral system in which a score system has been developed to identify high-risk pregnancies. Women seen at the maternity clinic for prenatal care are referred to the district hospital for further care and delivery if they have a high maternal risk score. Thus, the investigator decides to examine whether maternal risk score may be confounding the comparison of early neonatal mortality rates at the clinic and the hospital (Table 9.17).

For both strata, the risk of early neonatal mortality is higher for the maternity clinic. The relative risk adjusted for maternal risk score also reflects the higher risk for the maternity clinic. In this example, maternal risk score is a confounder: it is associated with, but not a consequence of, the delivery sites, independent of its

Table 9.17

Neonatal Outcome by Risk Score for Maternity Clinic and District Hospital

Early neonatal outcome	Maternity Clinic	District Hospital
High maternal risk score:		
Died	30	38
Living	820	1,262
Total	850	1,300
Early neonatal mortality rate	35/1,000	29.2/1,000
CIR = 1.2		
Low maternal risk score:		
Died	64	12
Living	11,086	3,688
Total	11,150	3,700
Early neonatal mortality rate	5.7/1,000	3.2/1,000
CIR = 1.8		
Crude CIR = 0.8		
CIR adjusted for maternal risk score = 1.4		

association with delivery site, it is associated with poor early neonatal outcome.

There are essentially three ways to manage potentially confounding variables in a cohort study:

- Restrict admission to the study (e.g., admit only exposed and unexposed women with a maternal risk score lower than some specified level).

- Match on the potentially confounding variable.

- Control for the confounding variable in the analysis by calculating an adjusted measure of effect.

The risk estimate in Table 9.17 after adjusting for the confounding effect of maternal risk score is 1.4; the unadjusted risk is 0.8. Adjusted measures of relative risk can be computed using formula 4.12.1 or 4.12.4.

Effect Modification Analysis Table

Effect modification is a phenomenon that is frequently discussed in conjunction with confounding, although it is not a form of bias. Effect modification is present when the relationship between exposure and outcome is different for various subgroups in the population. Effect modification is detected by stratifying by the variable of interest, calculating a measure of association for each stratum, and looking for differences in the relative risks among strata. Differences may reflect biologic or other factors that can modify the relationship between exposure and outcome. For example, measles vaccine may result in a much lower risk of contracting measles when administered to children older than one year than to younger children. These differences are related to the interference of maternally transmitted antibodies with development of immunity in the infant and have important implications for vaccine policy.

Both confounding and effect modification can occur at the same time. When both are present, the effect modification should be noted, the confounding should be controlled for in the analysis, and the findings should be stratified by the variable that confounds and modifies the association under study.

Consider the analysis of the relationship between anemia and birthweight (Table 9.18). The overall crude CIR is 1.7 and the adjusted CIR is 1.6. These results indicate that maternal age is not a confounder. However, maternal age appears to modify the effect of anemia on low birthweight; young anemic women are twice as likely to have a low-birthweight baby than those without anemia (CIR = 2.2). Among older women, however, anemia is not associated with an increased risk of low birthweight (CIR = 1.0).

Table 9.18

Anemia and Low Birthweight According to Maternal Age

Maternal Age < 25 Years	Anemia	No Anemia
Low Birthweight	13	4
Normal Birthweight	18	17
Total	31	21

CIR = 2.2 (95% CI: 0.8 - 5.8)

Maternal Age ≥ 25 Years	Anemia	No Anemia
Low Birthweight	5	4
Normal Birthweight	37	31
Total	42	35

CIR = 1.0 (95% CI: 0.3 - 3.6)

Advantages and Disadvantages of Cohort Studies

Cohort studies have several advantages:

- They allow a complete description of the individuals' experiences subsequent to exposure, including the natural history of disease.
- They provide a clear temporal sequence of exposure and disease.
- They provide an excellent opportunity to study rare exposures.
- They permit the assessment of multiple outcomes (risks and benefits) that may be related to a specific exposure.
- They permit the direct estimation of the rate of the health problem and the relative risk associated with the exposure of interest.

- They present generally more understandable information to nonepidemiologists.

- They do not require withholding treatment as in a randomized clinical trial.

Disadvantages include the following:

- Large numbers of subjects are required to study rare diseases in cohort study designs.

- Long-term follow-up may be necessary when the latency period for the outcome of interest is long.

- Follow-up may be difficult and loss-to-follow-up may affect the study's results.

- The studies may be relatively expensive to conduct.

- The exposure status, which is present at enrollment into the study, may change during the conduct of the study.

Practice Exercises

1. Consider the following study of the risk of dehiscence among obstetric patients who were not seen at the hospital before delivery.

Example 9.19

The Risk of Dehiscence Among Women Who Were Not Seen at the Hospital Before Delivery

Problem: Is the risk of dehiscence (wound disruption) after cesarean section different for obstetric patients who were *booked* (seen at the hospital one or more times before delivery) or *unbooked* (seen for the first time when in labor)?

Research Hypothesis: Obstetric patients who were unbooked have a greater risk of dehiscence than patients who were booked.

Study Design: Cohort study

Exposed: Women who were not seen at the hospital before having a cesarean section.

Unexposed: Women who were seen at the hospital before having a cesarean section.

Outcome: Dehiscence (i.e., an abdominal wound breakdown involving all layers, including the peritoneum) at any time after cesarean section.

Follow-up: Information on dehiscence was collected at the 6-week follow-up visit.

Data Collection Methods: Data were abstracted from medical records for all cesarean deliveries at a single hospital in Nigeria for a 5-year period ending May 1977.

Results:

	Exposure (Prior Booking)	
	Unbooked	**Booked**
Number of women with dehiscence	39	12
Number of women without dehiscence	1,259	678
Total number of cesarean deliveries	1,298	690

CIR = 1.7 (95% CI: 0.9 - 3.3)

(Chukudebelu and Okafor, 1978)

(a) Considering the 95% confidence interval, is it possible that women who were unbooked have less risk of dehiscence than women who were booked?

(b) What differences between the booked and unbooked patients might account for the results?

2. Consider a hypothetical study of maternal education and the risk of neonatal death.

Example 9.20

Maternal Education and Neonatal Death

Problem: Is maternal education related to neonatal death?

Research Hypothesis: Women with less than six years of schooling have an increased risk of delivering an infant who will die during the neonatal period than do women with at least six years of schooling.

Study Design: Cohort study

Exposed: Women who had had less than six years of formal education.

Unexposed: Women who had had six or more years of formal education.

Outcome: Neonatal death (defined as death occurring between birth and 28 days following birth).

Follow-up: Information on neonatal deaths was collected at the 6-week follow-up visit.

Data Collection Methods: Personal interview data were collected from all women coming to the Maternity Clinic between January 1 and December 31, 1985.

(a) What characteristics might differ between the women in the exposed group and those in the unexposed group?

(b) Which of these characteristics might also be related to neonatal death?

(c) Eighty percent of the women who had had at least six years of schooling returned for follow-up, whereas only 65% of the less educated women returned for follow-up. How might this affect the results? What might be done about this problem?

(d) Construct a data analysis table for computing the cumulative incidence relative risk.

3. Consider an analysis from the Collaboration Review of Sterilization Study.

Example 9.21

Interval Sterilization Procedures by Electrocoagulation and Silastic Bands

Problem: Are interval tubal sterilization procedures (TSP) by electrocoagulation less safe than sterilization using silastic bands?

Research Hypothesis: TSP by electrocoagulation has a greater risk of surgical complications than TSP using silastic bands.

Study Design: Prospective cohort study

Exposed: Women having interval TSP by electrocoagulation.

Unexposed: Women having interval TSP by silastic bands.

Outcome: Unintended major surgery, hemorrhage requiring blood transfusion, febrile morbidity, cardiopulmonary crisis, hospitalization, and death occurring in relation to the tubal sterilization procedure.

Follow-up: Subjects were followed up with a standard questionnaire two to 12 weeks postoperatively.

Data Collection Methods: Data were collected at nine hospitals in the United States from 1978-1980. Information was obtained from standard questionnaires administered to all study subjects and from medical charts.

Data Analysis:

	Exposure	
Outcome	Electrocoagulation	Silastic Band
Surgical Complications	53	12
No Surgical Complications	2,344	1,097
Total Subjects:	2,397	1,109

(Adapted from DeStefano et al., 1983)

(a) Compute the CIR and the 95% confidence interval and interpret the results.

(b) Reverse exposed and unexposed groups in Table 9.21 to obtain Table 9.22; that is, let the exposed be the silastic band group and let the unexposed be the electrocoagulation group. Compute the CIR and the 95% confidence interval and interpret the results.

Table 9.22

Interval Sterilization and Silastic Bands Versus Electrocoagulation

	Exposure	
Outcome	Silastic Band	Electrocoagulation
Surgical complications	12	53
No complications	1,097	2,397
Total subjects	1,109	2,397

(Adapted from DeStefano et al., 1983)

4. Design a prospective cohort study in outline form based on the following problem situation. Briefly state the problem, define the exposed and unexposed groups, and describe how study subjects for each group will be identified. Specify the measurable outcome and the data collection methods. Develop an analysis table. Describe potential strengths and limitations of your study design.

   Background: Voluntary female sterilization is the most prevalent method of contraception in the world. Approximately 100 million couples use this method, and the demand is expected to increase during this century. One concern is that female sterilization may cause changes in menstrual patterns. For this exercise we will focus on an increase in the severity of dysmenorrhea as our outcome. The level of dysmenorrhea could be subjectively reported or measured in any way you choose. While designing this study, consider previous contraceptive use, the age of study subjects, the reasons for sterilization, potential losses to follow-up, and the appropriate length of follow-up for assessing a change in dysmenorrhea.

   Problem:

   Study design:

   Exposed:

   Unexposed:

   Outcome:

   Follow-up:

Data Collection Methods:

Potential Strengths and Weaknesses:

5. Circle true (T) or false (F).

   (a) T/F In a cohort design, the study groups are identified by exposure status before ascertaining disease status.

   (b) T/F In a historical cohort study, the researcher selects individuals based upon outcome and then determines exposure.

   (c) T/F In a prospective cohort study, the exposure has not happened before the study begins.

   (d) T/F Instead of using an unexposed group, investigators may compare the frequency of an outcome in the exposed study population with that of the general population.

   (e) T/F If a person's exposure status changes after initial assignment to an exposed or unexposed group, the person should remain in the group to which he or she was originally assigned.

   (f) T/F The process by which an outcome is defined needs to be standardized without making staff aware of the hypothesis under study.

   (g) T/F Cohort studies are well adapted for studying rare diseases.

   (h) T/F A 20% loss to follow-up may make study results questionable.

   (i) T/F Relative risk is the incidence rate for those who were exposed to some risk factor divided by the incidence rate for those who were not exposed.

(j) T/F A relative risk greater than 1 occurs when the risk in the unexposed group is greater than in the exposed group.

(k) T/F Information bias is greater in prospective cohort studies than in historical cohort studies.

(l) T/F Frequency matching involves enrolling an exposed individual and then selecting the next unexposed person with characteristics similar to the exposed individual.

6. Consider the hypothetical data presented below:

Table 9.23

Outcome Z and Exposure Q

	Exposure	
Outcome	Exposed to Q	Not exposed to Q
Health problem Z	225	75
Person-years	22,750	24,250

(a) Compute the IDR and the 95% confidence interval.

(b) Interpret the IDR and confidence interval.

Suggested Answers to Practice Exercises

1. The risk of dehiscence among obstetric patients.

   (a) Yes, it is possible that patients who were *unbooked* have less risk than patients who were *booked*, since the lower confidence limit for CIR is 0.9. However, it seems reasonable that patients who were *unbooked* would be at greater risk.

   (b) Possible problems with interpretation include the fact that, besides not receiving antenatal care, the unbooked patients are more likely to represent emergency cases with prolonged labor and have greater potential for preadmission complications. They are also more likely to be from a lower socioeconomic class. Additionally, because they may be more likely to be from rural areas, they may have begun physical labor sooner than women from urban areas and thus may have increased their risk of dehiscence. The same women who are not booked may be less likely to seek medical attention for problems such as wound infections and thus may have increased their risk of dehiscence. These differences could explain the study results.

2. Maternal education and the risk of neonatal death.

   (a) Income, nutritional status, access to health services (including prenatal care, maternity services, and care for the infant) differences in cultural practices affecting infant outcome (e.g., management of the umbilical stump in a way that may increase the risk of neonatal tetanus), intrapartum interval, infant feeding practices, etc.

   (b) Virtually all of the above are also associated with poor infant outcome.

   (c) It may underestimate the risk in the less educated women, if failure to return for follow-up is associated with adverse infant outcome. To correct the problem, arrange active follow-up on both the exposed and unexposed to ensure the highest possible response rate in both groups. Alternatively, select a random sample of those who do not return from each exposure group to ensure that they do not

differ substantially in their outcomes from those who did return for follow-up.

(d)

Data
Analysis:

	Lower Education	Higher Education
Neonatal death	a	b
Survival to 28 days	c	d
Total	n_1	n_0

3. Interval sterilization procedures by electrocoagulation and silastic bands.

(a) CIR = 2.2/1.1 = 2 (95% CI: 1.1 - 3.8). In this study, TSP by electrocoagulation appears to be associated with an increased risk (two times) of surgical complications than silastic bands. Since the confidence interval does not include 1.0, the CIR is a statistically significant increased risk; that is, TSP by electrocoagulation appears to be associated with a statistically significant 2-fold increased risk of surgical complications compared with TSP by silastic bands. The data analysis confirmed the research hypothesis.

(b) If you reverse the "exposed" and "unexposed", the relative risk becomes less than one; the cumulative incidences would be 1.1% and 2.2%, and the CIR = 1.1/2.2 = 0.5 (95% CI: 0.3 - 0.9). Since the confidence interval does not include 1.0, this finding is statistically significant. TSP by silastic bands appears to be half as likely as TSP by electrocoagulation to be associated with surgical complications.

4. These are only suggested answers. The exposure groups and outcome you choose will vary, and many responses will be acceptable. The answer provided is based on the report of the actual study referenced.

Example 9.24

Female Sterilization and Dysmenorrhea

Problem: Does dysmenorrhea increase after female sterilization?

Research Hypothesis: More women who have had sterilization surgery report dysmenorrhea after surgery than women who did not undergo sterilization surgery.

Study Design: Cohort study

Exposed: Healthy women aged 25 to 34 years who are at least six months postpartum, are menstruating, and have not used hormonal or intrauterine contraception in the three months before seeking voluntary sterilization.

Unexposed: Healthy women aged 25 to 34 years who are at least six months postpartum, are menstruating, and have not used hormonal or intrauterine contraception in the three months before admission to the study and who are presently using barrier contraceptives.

Outcome: Dysmenorrhea is classified as none, mild, moderate, or severe as subjectively reported by the study subject in response to a standard set of questions.

Follow-up: Two years after the procedure, follow-up data were collected by telephone interviews with each woman.

Data Collection Methods: At admission to the study, subjects reporting dysmenorrhea will be given gynecologic examinations to determine the cause of the condition. If the cause is not idiopathic, the women will be dropped from the study. Each subject will be asked about the characteristics of her most recent menstrual period at admission; one and two years later, each women will be reinterviewed about the characteristics of her menstrual periods over the last 6 months. The interviewer will not know whether the subject is in the exposed or unexposed group.

Data Analysis: The data will be summarized in the following data table.

Example 9.24 (continued)

Outcome	Exposure: Voluntary Sterilization	Exposure: Barrier Methods
Dysmemorrhea		
None		
Mild		
Moderate		

Incidence Density:

Since we are able to establish accurately the time since sterilization for exposed groups and the time from entry into the study for barrier users, we will use incidence density as our incidence measure. The incidence density and confidence limits will be calculated from the data in the table. Finally, we will need to determine if the age and parity distribution differ in the two comparison groups.

Potential Strengths and Weaknesses:

Strengths—Voluntary sterilizations have been separated from medically indicated ones. The effects of prior contraceptive use have been controlled. The evaluator of dysmenorrhea will not know the exposure status of the subjects.

Weaknesses—Level of dysmenorrhea is a subjective outcome. Many subjects may be lost from the unexposed group because they change contraceptives or become pregnant.

(DeStefano et al., 1983)

5. True or false.

   (a) T Introduction

   (b) F In a historical cohort study, exposure and outcome have occurred before the study begins; as in prospective cohort studies, the subjects are selected according to exposure status rather than outcome.

   (c) F In a prospective study, exposure status is determined when the study begins, and the exposed and unexposed groups are followed forward in time to observe whether they develop the study outcome. Often, the exposure has been going on for some time when the study begins.

(d) T Population Sources and Follow-up

(e) T Measuring Exposure

(f) T Determination of Outcome

(g) F Advantages and Disadvantages. Cohort studies are well adapted for studying rare exposures.

(h) T Population Sources and Follow-up

(i) T Relative Risk

(j) F Relative Risk. A relative risk greater than 1 occurs when the risk in the exposed group is greater than the risk in the unexposed group.

(k) F Validity and Bias. Information bias is likely to be larger in historical cohort studies than in prospective cohort studies.

(l) F Matching. Frequency matching involves enrolling exposed individuals and categorizing them into subgroups and then enrolling a specified number of unexposed individuals with the appropriate characteristics for the subgroup.

6. Outcome Z and exposure Q.

6.1 IDR = 3.2 (95% CI: 2.5 - 4.1)

6.2 Women exposed to Q have an approximately threefold increased risk of developing health problem Z as women who have never been exposed to Q. This finding is statistically significant because the 95% confidence interval does not include 1.0.

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