### **14.1 Introduction**

### **Every year, thousands of epidemiological studies are published in various journals in the United States alone. These studies address a wide range of biomedical and clinical subjects and belong largely to two categories: observational studies and experimental studies. The purpose of these studies is to test hypotheses, find answers to puzzling questions, provide guidance for policy formulation, and help in clinical decision making. Epidemiological studies help in clinical decision making by not only enhancing our understanding of the frequency and distribution of diseases, but also by providing clues about how and why diseases happen and who gets afflicted with what disease and why. Some studies use existing information available through medical records and patient registries, whereas others involve recruitment of subjects from whom information is directly obtained over a short or long period.**

### **Healthcare managers do not make clinical decisions and may not need to know the etiology or treatment for various diseases. However, they need to have some understanding of how epidemiological investigations are conducted; how one kind of study methodologically differs from another; and the objectives, advantages, and disadvantages of one study design over another. Given the frequency of clinical trials and research studies being conducted in academic and nonacademic healthcare settings and many administrative challenges posed by such undertakings, including potential conflict of interest, patient safety concerns, and logistical challenges, it is imperative for healthcare managers to be familiar with the theoretical and operational framework of such investigations. This chapter is designed to provide necessary information and tools related to one of the two most common categories of epidemiological investigations: the observational studies.**

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### **14.2 Observational Studies**

As shown in [**FIGURE 14.1**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_02.xhtml#ch14-fig1), under the rubric of *analytic* studies, the category of epidemiological investigations known as the [**observational studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss164) is entirely distinct from the category known as the [**experimental studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss82). Observational studies differ from experimental studies in that the researcher does not manipulate the subjects or attempt to change the health status of participants; alter the natural course of events; or test the effectiveness or safety of a new medication, procedure, or technology. In other words, the role of the researcher in observational studies is merely to be a passive observer of events. However, the researcher makes critical decisions about where, when, and how the observation takes place and who the subject of observation is. Depending on the answers to these questions, observational studies are classified into the following three forms of studies: ecological studies, cohort studies, and case-control studies. In the following sections, we will discuss the theoretical and operational framework of these three forms of observational studies and provide relevant examples from the current literature.

Classification of epidemiologic studies.

Epidemiologic studies is broadly classified into Descriptive Studies and Analytic Studies. Descriptive Studies includes case reports and cross-sectional studies while Analytic studies is further classified into observational studies and experimental studies. Observational studies could be of three types: Ecological, Cohort, and Case control studies. Experimental studies includes randomized control trials that is further divided into parallel trials, crossover trials, and factorial trials. Also, cohort studies is of three types: prospective studies, historical prospective studies, and retrospective studies.

**FIGURE 14.1** A schematic diagram of different types of epidemiologic studies.

Data from Friis, 2010; Swallen KC, University of Wisconsin-Madison.

### **14.3 Ecological Studies**

[**Ecological studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss70) investigate the effects of some phenomenon, risk factor, or intervention—whether natural or manmade—in the same population over different periods or in a population in one geographic area as compared with one or more other populations in other areas. For example, an ecological study might investigate the health effects of air pollution in Delhi or Shanghai by examining the [**incidence**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss108) and prevalence of acute and chronic respiratory diseases in these cities in comparison with London, Paris, or Berlin. Likewise, one might study in children the short- and long-term health effects of exposure to a lead-contaminated municipal water supply system in Flint, Michigan, in 2014 and 2015. One can then compare the occurrence of health outcomes, such as developmental delays, neurologic deficit, and learning disabilities, in this population with the population of children in other towns of similar size and demographic characteristics. Subjects in ecological studies can be grouped by geographic areas such as cities, counties, or ZIP codes ([**multi-group study design**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss151)) or by time if changes in the same group are investigated longitudinally over time (*time trend studies*). Subjects can also be grouped by both place and time if groups assigned to different geographic areas are studied longitudinally over a period of time (*mixed study design*).[**1**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib1)

Typically, ecological studies examine the relationship between mean outcomes such as mortality or morbidity rates (e.g., asthma or liver cirrhosis per 100,000 population) and mean levels of exposure (e.g., air pollution or alcohol consumption) across different population groups. Because comparisons have to be made at the population level, ecological studies require aggregated population-level information on risk factors and health outcomes.[**2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib2) Because the unit of analysis in these studies is the entire population rather than individuals, usually no individual-level data are sought. For the same reason, no individual-level conclusions are made, nor are inferences drawn regarding the impact of the variable of interest on individuals in the population. Commonly, ecological studies investigate the effect of time and spatial factors on group-level health outcomes or the impact of a health policy on different populations.[**1**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib1),[**3**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib3),[**4**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib4) These studies can also be used to investigate the impact of population-level interventions such as municipal fluoridation of water, fortification of milk with vitamin D, or levying a heavy tax on cigarettes. Ecological studies are frequently used in occupational epidemiology to understand the relationship of certain occupations with the frequency of one or the other disease.

The advantages of ecological studies, whether cross-sectional or longitudinal, include their simplicity of design and use of existing population-level data from sources such as the Bureau of the Census, disease registries, and local or state health departments. Sources of data for ecological studies in the United States also include the U.S. Centers for Medicare and Medicaid Services, the U.S. Centers for Disease Control and Prevention, and many other private or public sector national and international agencies.

Despite the advantages of simplicity, convenience, time saving, and low cost, ecological studies are prone to a variety of methodological problems, including the potential for bias, inadequate control of confounders, the use of inappropriate statistical techniques for data analysis, and unwarranted interpretation of results.[**1**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib1) One limitation of ecological studies, commonly known as the [**ecological fallacy**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss69) (or [**ecological bias**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss68)), results from the fact that the unit of analysis is an entire population rather than an individual. Ecological fallacy means that an association observed between a variable of interest and a population does not directly translate into the same association between the risk factor and an individual.[**5**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib5) The issue of ecological fallacy in ecological studies stems from the underlying reality that individual-level health outcomes or events such as mortality or morbidity are not linked directly with individual-level [**exposure**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss83) to the risk factor, as they are in individual-level studies such as case-control or cohort studies.[**5**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib5) For example, a number of “diseases of affluence” (e.g., heart disease) have been shown in the past to be associated at the national level with the sale of television sets.[**6**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib6) This association, however, does not mean that every individual who owns a television set is at a high risk of, say, heart disease. Despite some methodological issues, well-designed ecological studies play an important role in defining public health problems and in generating causal hypotheses that can be further investigated by cohort or case-control studies. For example, the international comparisons of the incidence of various cancers in different countries in the 1950s and 1960s led to causal hypotheses that were later investigated in depth by other studies.[**6**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib6)

One recent review[**2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib2) of 125 cross-sectional ecological studies found that 16% of the reviewed studies focused on cancer as the primary outcome, while 14% focused on mortality, 13% on chronic diseases, and 10% on cardiovascular disease. In terms of the unit of analysis, 38% of the studies aggregated census tract or neighborhood-level data, 18% aggregated county-level data, 12% used province or state data, and 20% used nations or nation-clusters. The authors of the review concluded that more than half of the studies had some form of ecological fallacy or used inappropriate methodologies in study design or statistical analysis and applied inferences drawn from population-level data to individuals.[**2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib2) For example, in 34% of the reviewed studies, hypotheses or conclusions clearly applied to individual-level risk factors or health outcomes.[**2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib2)

### **14.4 Example of an Ecological Study**

Modified from: Rasella D, Harhay MO, Pamponet ML, Aquino R, Barreto ML. Impact of primary health care on mortality from heart and cerebrovascular diseases in Brazil: a nationwide analysis of longitudinal data. BMJ. 2014;349:g4014. doi:10.1136/bmj.g4014

In a recent *mixed study design* ecological study, Rasella et al. (2014) investigated the impact of Brazil’s Family Health Program (FHP) on heart and cerebrovascular disease mortality across the country from 2000 to 2009. Brazil’s FHP is the largest primary care program in the world and is credited for improved population health outcomes in the country. The FHP program provides health promotion and disease prevention services, including management of cardiovascular disease risk factors, as well as secondary prevention through monitoring and management of hypertension and diabetes. The program relies on domiciliary visits and community-based interventions implemented through community health workers.

The researchers used a *mixed ecological study* model that combines *multi-group*’ and longitudinal *time trend* study designs. The unit of analysis in this study was a municipality (county). Using regression models, the researchers analyzed longitudinal vital statistics data from 1,622 Brazilian municipalities (30% of the 5,507 municipalities in Brazil) for the 10-year period. About 75% of the municipalities included in the study had less than 25,000 inhabitants. The annual FHP coverage levels and average FHP coverage level in these municipalities 4, 6, and 8 years after the implementation of the Family Health Program in 2000 were used as the main independent variables. Coverage levels were classified as “None” (0%), “Incipient” (<30%), “Intermediate” (30–69%), and “Consolidated” (≥70%). Age-standardized mortality rates from cerebrovascular diseases, ischemic heart diseases, and other heart diseases that were included in the national list of [**ambulatory care sensitive conditions**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss10) were calculated for each municipality for each year. Because deaths from accidents are not affected by the availability of primary care in a population, mortality rate from accidents was used as a control variable in these analyses.

The mean population coverage in municipalities with FHP program increased from 21% in 2000 to 68.6% in 2009—an increase of 227%. During the same period, mean cerebrovascular mortality rate in the covered municipalities fell from 40.1 to 27.0 per 100,000 population—a reduction of 32.7%. Heart disease mortality fell by 44.6% from a mean of 23.3 in 2000 to 12.9 per 100,000 in 2009. In comparison, mean mortality rate from accidents, a health status indicator largely outside the influence of access to primary care, actually increased during the same period, from 41.8 to 47.0 per 100,000 inhabitants. This variable was used in the study as a *control variable* to show the contrast between variables expected to be affected by the intervention and those not expected to be influenced by the intervention. Importantly, socioeconomic variables such as monthly per capita income and percentage of population below poverty line (examples of confounding variables) also improved between 2000 and 2009. This observation is important because it demonstrates the role of confounding variables and, in this case, raises the possibility that reduction in cerebrovascular and heart disease mortality may not be attributed entirely or even partially to increased availability of primary care, but may very well have resulted from improved living conditions. The statistical models developed by the researchers adjusted for the potential effects of these confounding variables.

The researchers calculated crude and adjusted ratios of mean mortality rates in municipalities not covered by FHP and those covered at the “Incipient,” “Intermediate,” or “Consolidated” level. For example, the adjusted cerebrovascular disease mortality rate in municipalities covered at the “Intermediate” level (≥30% to <70% coverage) was found to be 14% lower than those not covered by FHP (adjusted rate ratio = 0.86). Likewise, the adjusted mortality rate related to cerebrovascular disease in municipalities with a “Consolidated” level of coverage (≥70% coverage) was 18% lower than municipalities not covered at all (adjusted rate ratio = 0.82). However, there was no difference in accident-related mortality rates in municipalities with different levels of FHP coverage and those not covered by FHP (adjusted mortality rate ratios of 0.99, 0.97, and 1.02). In other words, the FHP did not have any effect on mortality rates from accidents.

The authors also calculated adjusted ratios of cerebrovascular disease mortality, heart disease mortality, and accident-related mortality in municipalities with no FHP coverage and those with different levels of FHP coverage 4, 6, and 8 years after the onset of the program. The results showed a clear and consistent inverse *dose-response* relationship between the extent of coverage and mortality from cerebrovascular and heart diseases 4, 6, and 8 years after the implementation of the FHP—that is, the greater the average coverage of the population by FHP and the longer the period of coverage, the lower the mortality from cerebrovascular and heart diseases. For example, municipalities that had ≥70% FHP coverage in the past 5 years had 23% lower cerebrovascular disease mortality (adjusted rate ratio = 0.77) and 25% lower heart disease mortality (adjusted rate ratio = 0.75), but almost the same rate of accident-related mortality (adjusted rate ratio = 1.02) as the municipalities with no coverage. Likewise, in municipalities that had ≥70% FHP coverage in the last 8 years, cerebrovascular disease mortality was 31% lower (adjusted rate ratio = 0.69) and heart disease mortality 36% lower (adjusted rate ratio = 0.64) than municipalities with no coverage in the same period. Again, the accident-related mortality rate in municipalities with 70% or greater coverage in the past 8 years was almost the same (adjusted rate ratio = 1.02) as those with no coverage. This is exactly what the analytical models anticipated from the use of accident-related mortality as the control variable because access to primary care in a community or lack thereof is not expected to have any bearing on mortality from accidents.

The ambulatory care sensitive subgroups of “cerebrovascular,” “ischemic heart disease,” and “other heart disease” accounted for 40% of all deaths in these categories during the 2000–2009 study period. The researchers reported that FHP coverage in Brazil was negatively associated with mortality rates from the ambulatory care sensitive subgroups of cerebrovascular and heart diseases in analytic models that were adjusted or unadjusted for demographic, social, and economic confounders. They concluded that primary care programs such as Brazil’s FHP could help reduce cardiovascular disease morbidity and mortality in developing countries such as Brazil.

The authors also pointed out that the study only provided evidence of an ecological plausibility by establishing an association between the FHP program and municipality-level reduction in cerebrovascular and cardiovascular disease mortality during the study period. As the study investigated the effectiveness of the FHP program only at the aggregated (municipality) level, no assertion can be made about the positive impact of the FHP program at the individual level. In fact, the study cannot determine whether individuals who experienced the intended impact of the FHP program (i.e., survival from cerebrovascular and cardiovascular disease) were even covered by the program or received any services.

### **14.5 Cohort Studies**

#### **14.5.1 Definition of a Cohort**

The word *cohort* is derived from Latin and traces its origin to the legions of Roman soldiers who shared the experience of staying together in an army camps and fighting together in a battle. Strictly speaking, it referred to one of the 10 divisions of a Roman legion. In common usage, the word simply refers to a group of individuals (or animals) who share an experience or effort over time. The duration of time over which the experience or effort happens is unrestricted and may vary from one cohort to another. One example might be a cohort of students at a college or university, such as the “cohort of 2018” (i.e., the class of students who graduated in 2018). Another example might be the cohort of astronauts who went on the successful Apollo 11 mission to the moon. In epidemiologic investigations, the word [**cohort**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss30) refers to a group of participants who are collectively exposed to a risk factor, substance, drug, or event and are observed over time to examine the effects, if any, of such exposure. Because of the shared experience of having been exposed to such a factor, the group of participants in the study constitutes a cohort.

#### **14.5.2 Cohort Study Design**

Typically, the cohort study design involves identification and recruitment of two groups of participants. One group comprises individuals who are or were in the past exposed to the risk factor being investigated; the other group consists of individuals not exposed to the risk factor. Both groups are then prospectively followed or observed for a duration of time to see whether they acquire the disease of interest. Because subjects are prospectively followed over time, these studies are also commonly referred to as *prospective studies*. By their very nature, [**cohort studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss32) attempt to test a hypothesis regarding the etiology of a disease. However, because of the difficulties in establishing a causal relationship between a disease and a risk factor, the goals of such a study are limited only to revealing or refuting a positive or negative statistical association between a risk factor and the disease of interest. Depending on the nature of exposure and the disease, the period of observation or follow-up can be relatively short or long. It is not uncommon for the follow-up period to span years or even decades.

There are many variations in cohort study design. In one variation, known as the *open or dynamic cohort design,* the study begins with a cohort of participants to which new recruits are added on an ongoing basis along the way. In this kind of study, the follow-up period for all participants is not exactly the same, but differs from one subject to another. Even without the addition of new participants along the way, which is the case in typical *closed cohort study design,* the period of observation for subjects who were all recruited at the same time at the onset of the study can be different. This can happen because some of the participants later opt out of the study or discontinue for one or the other reason, whereas others may be lost to follow-up because of death or migration. In another variation of cohort study design, a group of individuals (a cohort) is identified from historical record of one kind or another. Historical records can include medical records, employment records, medical claims data, or reimbursement records. In such a study, subjects are followed in time through their medical records to understand how their health status changed going forward from a point in time in the past. Such cohort studies are known as [**retrospective cohort studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss217) or [**historical cohort studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss102)*.*

Regardless of whether the study is based on a historical cohort or a prospective cohort, one feature common to all cohort studies is that study participants consist of two subgroups: One subgroup comprises those who are exposed to a risk factor that is suspected to have a causal (or protective) role in the occurrence of disease, whereas the second subgroup consists of those who are not exposed to that risk factor. The ratio of those in the cohort who are exposed to the risk factor to those who are not exposed can be predetermined to a specific level, such as one exposed participant for one unexposed individual (ratio of 1:1), or some other level, such as a ratio of 1:2 or 1:3. The ratio of exposed individuals to unexposed individuals in the study depends on several factors, including the availability of participants as well as the nature and frequency of the risk factor.

Ideally, the exposed and unexposed members of the cohort are matched for age, race, sex, education, geographic area, and other factors to minimize the differences between the two groups. Sex-matched pairs of twins in which one of the twins is exposed to the risk factor while the other is not make the best matches. Other good matches include unexposed siblings or age- and sex-matched friends. [**TABLE 14.1**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab1) shows the conceptual framework of a cohort study.

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| **TABLE 14.1** A Conceptual Model of Prospective Cohort Study Design | | |
| A table shows the conceptual framework of a cohort study.  The table represents the study design in 2 rows and 3 columns whose column header reads: Start of study, Follow-up of the subject going forward in time, and End of study. The table reads the following row-wise, row 1: Study participants with risk factors (positive), a forward arrow (rightward), and number with disease (positive) and number without disease (negative). Row 2: participants with risk factors (negative), a forward arrow (rightward), and number with disease (positive) and number without disease (negative). |  |  |

#### **14.5.3 Relative Risk**

[**Relative risk**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss214), which is also known as *risk ratio*, *rate ratio*, or, more precisely, [**incidence rate ratio**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss111),[**7**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib7) is a measure of the strength of association between a risk factor and a disease and is obtained by deriving the ratio of incidence rate in the exposed population and in the unexposed population. In cohort studies, because the population of both groups—those exposed to a risk factor and those not exposed—is known and the incidence rate can be directly calculated for both groups, it is possible to derive relative risk. Essentially, relative risk indicates the excess risk of disease in the exposed group as compared with the unexposed group. In other words, relative risk is the proportion of cases in the exposed population that can be attributed to the risk factor. [**TABLES 14.2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab2) and [**14.3**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab3) are designed to demonstrate how relative risk is derived.

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| **TABLE 14.2** Relative Risk Derivation – Notational Example | | | | |
| A table show the Relative Risk Derivation to Notational Example.  The table demonstrates how relative risk is derived in 3 rows and 3 columns. The column headers: Yes, No, and Total that represents the disease. The row headers: Yes, No, and Total that represents the exposure. The data in the table reads row-wise as follows. Row 1: a, b, and a plus b. Row 2: c, d, and c plus d. Row 3: a plus c b plus d, and a plus b plus c plus d. |  |  |  |  |

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| **TABLE 14.3** Relative Risk Derivation – Numeric Example | | | | |
| A table show the Relative Risk Derivation to Numeric Example.  The table demonstrates how relative risk is derived in 3 rows and 3 columns. The column headers: Yes, No, and Total that represents the disease. The row headers: Yes, No, and Total that represents the exposure. The data in the table reads row-wise as follows. Row 1: 40, 460, 500. Row 2: 15, 458, and 500 Row 3: 55, 945, and 1000. |  |  |  |  |

In [**Table 14.2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab2), *a* represents the number of cases of disease in the group exposed to the risk factor in a cohort study, and *c* represents the number of cases in the unexposed group.

Thus, incidence rate or risk of disease among the exposed is represented by = *(a) / (a* + *b).*

The incidence rate or risk of disease among the unexposed is represented by = *(c) / (c* + *d).*

Relative risk is the ratio of the risk of disease among the exposed and the risk of disease among the unexposed. Alternatively, it is the ratio of incidence rate in the exposed group and incidence rate in the unexposed group. Therefore,

An equation reads: Relative risk equals (a over a plus b) over (c over c plus d).

[**Table 14.3**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab3) shows data from a hypothetical prospective cohort study in which 500 individuals who were exposed to a risk factor and 500 who were not exposed to the risk factor were followed over a period of time. As shown, the incidence of disease in the exposed group was 40, and in the unexposed group it was 15. The relative risk of disease in the two groups was:

An equation reads: Relative risk equals (40 over 500) over (15 over 500).An equation reads: or equals 0.08 over 0.03.Text reads: or equals 2.67.

The frequency of disease in different populations can be compared by calculating ratios such as relative risk, relative rate, risk ratio, and rate ratio. We have discussed relative risk in the preceding paragraphs in some detail because it is frequently used as an umbrella term for relative rate, risk ratio, and rate ratio. In the interest of clarity, definitions for these terms are provided below.

#### **14.5.4 Rate Ratio or Incidence Rate Ratio**

Typically, in a cohort study, all participants join the study at the same time, although they are not all followed for the full duration of the study for reasons such as death, willful discontinuation of participation, relocation, or being “lost to follow-up” for other reasons. In some variations of cohort study design, subjects can join the study at different times during the course of the study and also leave the study at different times for various reasons (such a cohort is called an *open* or *dynamic* cohort). In these situations, because different subjects are followed for different periods of time, the [**incidence rate**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss110) (IR) in each group is referred to as [**incidence density**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss109) and incidence rate is calculated in terms of person-years (PYs) of follow-up by using the aggregated follow-up time contributed by all subjects combined in that group as the denominator. For example, IR in the exposed group might be expressed as 105 per 1,000 PYs of follow-up. The 2015 prospective cohort study by Falade-Nwulia et al. discussed in section 14. 6 is an example of an open cohort study in which incidence rates in the exposed and unexposed groups were calculated in PYs. As shown in [**TABLE 14.4**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab4), the IR in the exposed group may be represented by the expression *IRe* = *a / K* and the IR in the unexposed group may be represented by the notation *IRu* *= c / L*. The subscripts *e* and *u* in these expressions refer to *exposed* and *unexposed* groups. The denominator in each group (i.e., K and L, respectively) is the sum of follow-up periods for all individuals in that group. The ratio of incidence rates in the exposed and unexposed group is therefore called a [**rate ratio**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss211) or, more accurately, incidence rate ratio.

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| **TABLE 14.4** Incidence Rate Ratio Derivation – Notational Example | | | | | |
| A tables show the Incidence Rate Ratio Derivation to Notational Example.  The table demonstrates how relative risk is derived in 3 rows and 4 columns. The column headers: Yes, No, Total follow-up in Person-years, and Incidence Rate per 1000 person-years that represents the disease. The row headers: Yes, No, and Total that represents the exposure. The data in the table reads row-wise as follows. Row 1: a, b, K, and IR subscript e equals a over K. Row 2: c, d, L, and IR subscript u equals c over L. Row 3: a plus b, b plus d, K plus L, and left empty. |  |  |  |  |  |

Incidence rate ratio, therefore, would be represented by the following expression:

An equation reads: Incidence rate ratio equals (IR subscript e) over (IR subscript a) (i.e., (a over K) over (c over L)).

A rate ratio of 1 in a cohort study suggests that there is no difference in the frequency or rate of the disease per period between the exposed group and the unexposed group. In other words, exposure to the risk factor did not increase the rate of the disease among those who were exposed to the risk factor. On the other hand, a rate ratio of greater than 1 (rate ratio >1) indicates that the frequency or rate of the disease per period was higher in the exposed group as compared with the unexposed group. Likewise, a rate ratio of less than 1 (rate ratio <1) suggests that those exposed to the risk factor (e.g., red wine or a Mediterranean diet) got the disease less frequently than those who were not exposed to the risk factor. Alternatively, we can say that exposure (e.g., to red wine) conferred some protection from the disease or reduced the likelihood of disease in the exposed group as compared with the unexposed group.

[**TABLE 14.5**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab5) provides a numeric example of the estimation of incidence rate ratio in a prospective cohort study in which 1,400 exposed individuals were enrolled in a study that lasted 10 years. The aggregated follow-up time for the 1,400 individuals totaled 12,000 PYs. The unexposed group consisted of 1,600 hundred individuals whose combined follow-up time over the 10-year period totaled 13,000 PYs. Thus, incidence rate per 1,000 PYs in the exposed group was:

An equation reads: (400 over 12000) times 1000 equals 33.3 per 1000 person-years.

Likewise, incidence rate in the unexposed group was:

An equation reads: (100 over 13000) times 1000 equals 7.7 per 1000 person-years.

The incidence rate ratio of the exposed group with the unexposed group, therefore, was:

An equation reads: Incidence rate ratio equals (33.3 over 7.7) equals 4.3. (i.e., the incidence rate in the exposed group was 4.3 times of that in the unexposed group).

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| **TABLE 14.5** Incidence Rate Ratio Derivation – Numeric Example | | | | | |
| A table shows the Incidence Rate Ratio Derivation to Numeric Example.  The table represents the Rate Ratio in 2 rows and 4 columns. The column headers: Yes, No, Total follow-up in Person-years, and Incidence Rate per 1000 person-years that represents the disease. The row headers: Yes and No that represents the exposure. The data in the table reads row-wise as follows. Row 1: 400, 1000, 12000, and IR subscript equals (400 over 12000) times 1000 equals 33.3. Row 2: 100, 1500, 13000, and IR subscript e equals (100 over 13000) times 1000 equals 7.7. The result below the table reads: Incidence Rate Ratio equals (IR subscript e) over (IR subscript u) equals 33.3 over 7.7 equals 4.3. |  |  |  |  |  |

A rate ratio of 4.3 in this example suggests that those exposed to the risk factor of interest got the disease 4.3 times more per 1,000 PYs of follow-up as those in the unexposed group.

#### **14.5.5 Risk Ratio**

Conceptually, a [**risk ratio**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss219) (RR) is slightly different from a *rate ratio* (or *incidence rate ratio*) because there is no mention of time in estimating the risk of disease in the exposed and unexposed groups. In terms of data collection and analysis, it simply means that researchers choose to disregard the issue of dropouts and “lost to follow-up” and assume that all participants were engaged for the full duration of the study. The mathematical operations for deriving a *risk ratio* or a rate ratio are practically the same. The difference lies in the fact that in risk ratio, the incidence merely represents the proportion of those in the exposed or unexposed group who got the disease. Thus, it involves a comparison of proportions rather than rates of disease in the two groups. As such, in risk ratio, the incidence of disease in the two groups is compared on the bases of [**cumulative incidence**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss54) (CI) over a period of time. Identical to [**Table 14.4**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab4) in the previous section, [**TABLE 14.6**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab6) uses the same notations and the same mathematical formulas to calculate the risk of disease (or CI) in the exposed (C*Ie*) and unexposed (C*Iu*) groups. Likewise, [**TABLE 14.7**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab7) provides a numeric example of the estimation of risk of disease or cumulative incidence in the exposed and unexposed groups and its use to derive a risk ratio. The most important point to understand about a risk ratio is that it is based on a comparison of the proportions of exposed and unexposed individuals who got the disease in an entire period and is indicative of the comparative risk of disease in the two groups. For example, the risk ratio of 1.89 shown in [**Table 14.7**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_05.xhtml#ch14-tab7) (C*Ie* */ CIu* *= 0.17 / 0.09 = 1.89*) means that the risk of disease in the exposed group was 1.89 times that of risk in the unexposed group in the same period. Note that in this example, we refer to the risk of disease, rather than the rate of disease.

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| **TABLE 14.6** Incidence Rate Ratio Derivation – Numeric Example | | | | | |
| A table shows the Cumulative Incidence Derivation to Notational Example  The first table demonstrates how relative risk is derived in 3 rows and 4 columns. The column headers: Yes, No, Total, and Cumulative Incidence that represents the disease. The row headers: Yes, No, and Total that represents the exposure. The data in the table reads row-wise as follows. Row 1: a, b, a plus b, and CI subscript e equals a over a plus b. Row 2: c, d, c plus d, and CI subscript u equals c over c plus d. Row 3: a plus c, b plus d, a plus b plus c plus d, and left empty. The result below the table reads: Risk Ratio or Cumulative Incidence Ratio equals (CI subscript e) over (CI subscript u) equals ((a over a plus b) over (c over c plus d)). |  |  |  |  |  |

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| **TABLE 14.7** Cumulative Incidence Derivation – Numeric Example | | | | | |
| A table shows the Cumulative Incidence Derivation to Numeric Example.  The table demonstrates the risk of disease or cumulative incidence in 2 rows and 4 columns. The column headers: Yes, No, Total, and Cumulative Incidence that represents the disease. The row headers: Yes and No that represents the exposure. The data in the table reads row-wise as follows. Row 1: 20, 100, 120, and CI subscript e equals (20 over 120) equals 0.17. Row 2: 15, 150, 165 and CI subscript u equals (15 over 165) equals 0.09. The result below the table reads: Risk Ratio or Cumulative Incidence Ratio equals (CI subscript e) over (CI subscript u) equals 0.17 over 0.09 equals 1.89. |  |  |  |  |  |

#### **14.5.6 Considerations in the Selection of a Cohort**

There are several important considerations in the selection of subjects for *exposed* and *unexposed* groups or *index* and c*omparison* groups in a cohort study. Clearly, the availability and willingness of potential subjects to participate in a study as well as their commitment to providing or allowing researchers access to necessary information in accordance with the study protocol are the basic requirements. Beyond these basic considerations, however, many other factors also determine the suitability of individuals as potential study participants. For example, individuals whose jobs involve extensive travel or posting in different cities or states may not be suitable candidates to participate in a longitudinal cohort study either as exposed or unexposed individuals.[**7**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib7) One of the most important aspects of selecting study participants is the degree of similarity between those in the exposed group and those in the unexposed group. Except for exposure to the factor whose effects are being investigated (e.g., hypertension, alcohol, obesity), the researchers must make every effort to have subjects in the exposed and unexposed groups be as similar as possible in all other respects. This can be achieved either by matching subjects in both groups on as many demographic and socioeconomic variables as possible or by recruiting subjects from the same settings, environment, and communities. Siblings, friends, neighbors, teammates, or classmates of subjects in the exposed group can make good candidates for the unexposed group as long as they are not exposed to the variable under investigation. In these respects, both cohort and case-control studies are similar to experimental studies in which subjects being exposed to an intervention are similar to those not being exposed to the intervention whose effects are being studied. It is also important to have a sufficient number of participants in both groups to ensure adequate statistical power of the study and having approximately equal numbers of subjects in both exposed and unexposed groups. To ensure equally rigorous efforts in following subjects during the course of a prospective cohort study, at times it is useful to mask from those responsible for follow-up and continued data gathering the information as to which subjects are in the exposed group and which are in the comparison group.

#### **14.5.7 Considerations in the Measurement of Exposure**

The term *exposure* refers to a factor, behavior, or agent that plays a role in the occurrence of a disease, in preventing a disease, or in the amelioration of a disease.[**7**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib7) When the relationship of an extraneous factor or agent with a disease is causal in nature or that of facilitation, such a factor is also referred to as a *risk factor*. In a cohort or case-control study, it is important to define carefully the *exposure* or *risk factor* being investigated and deciding before the onset of the study how exposure will be assessed.

The characterization and assessment of the intensity and duration of exposure are important in both cohort and case-control studies. It is not sufficient to ask whether exposure to a particular factor or noxious agent occurred; it is necessary to fully understand the circumstances of such exposure. To make a definitive statement about an association between exposure and outcome, one must be able to develop measures of different levels of exposure and consistently apply the same definition of exposure to all subjects throughout the duration of a study.

Often the presumed or hypothesized relationship between disease and exposure requires exploration of dose–response relations—that is, it is essential to know how much exposure occurred on an hourly, daily, or weekly basis and for how long. For example, a study on the hazardous impact of radiation must determine the intensity (dose) of radiation; its frequency (hourly, daily, or weekly exposure); and its duration in weeks, months, or years. Similarly, a cohort study on the presumed protective effect of lactation on diabetes in women (see [**Case Study 14.2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#side14_2) at the end of this chapter) must carefully establish whether lactation was combined or supplemented with formula milk, as well as the frequency and duration of lactation. In [**prospective cohort studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss202), variations and changes in exposure over a period of months or years must also be carefully monitored, and analysis of data must adjust for such variations and difference in the level of exposure among different subjects.

It is also important to be clear about what sources of information will be used to ascertain exposure and how information about exposure will be verified or validated. If exposure information is based on interviews and personal reports, there can be potential for bias either because of poor recall or purposeful over- or underreporting of the intensity, frequency, and duration of exposure. For example, cases of lung cancer may underreport frequency and duration of cigarette smoking because of a “guilt complex” or “shame complex,” or possibly to hold a cigarette manufacturer liable. Alternatively, they may overreport the intensity and duration of smoking for the same ulterior motive. If medical records are used to assess exposure, there might be underestimation of exposure because of incomplete or missing information in patients’ history and physicians’ notes.

#### **14.5.8 Advantages of Cohort Study Design**

Cohort study design has several advantages over other studies such as cross-sectional studies and case-control studies. Some of these advantages are briefly discussed next.

##### **14.5.8.1 Scientific Rigor and Quality of Evidence**

As long as a study is properly designed and implemented, cohort study design is more robust in elucidating an association or the absence of an association between a risk factor of interest and a disease. This study design allows more rigorous and direct investigation of the strength of association of a disease with different levels of exposure to a risk factor as well as different durations of exposure to the same risk factor. For example, one can study the differential effects of smoking one, two, or three packs of cigarettes for 5 years, 10 years, or 20 years.

##### **14.5.8.2 Estimation of Incidence**

Cohort study design allows direct estimation of the incidence of disease in the population at risk that cannot be done with case-control studies, in which the total number of individuals exposed to the risk factor (i.e., population at risk or the denominator) is not known. Moreover, cohort study design allows estimation of incidence density in terms of the occurrence of disease per 1,000, per 10,000, or per 100,000 PYs of exposure to the risk factor or *cumulative incidence rate* in terms of the number of new cases of disease per year in the population at risk.

#### **14.5.9 Disadvantages of Cohort Study Design**

##### **14.5.9.1 Complexity of Study Design**

The design of a cohort study is complex because of the challenges involved in conceptualizing or hypothesizing a scientifically plausible and logical relationship between risk factors and the disease being investigated. These challenges increase if several different risk factors are to be explored simultaneously. A number of *a priori* procedural decisions must be made regarding the specific characteristics of individuals who will be eligible to participate in the study. Other questions that must be settled before the onset of the study include the following: (1) How will recruitment of subjects be carried out? (2) How will operational and ethical issues related to the methods of collecting data, self-selection bias, and confidentiality be handled? (3) How will a potential *Hawthorne effect* (alteration of behavior by the subjects because of their awareness of being observed or followed) be assessed and adjusted for in the final analysis? (4) How long will the follow-up period be? (5) How will a “case” be defined? (6) What clinical and laboratory tests will be done to diagnose and confirm the occurrence of disease?

##### **14.5.9.2 Difficulties in the Follow-up of Subjects**

Some degree of attrition in the number of subjects in exposed and unexposed groups is almost inevitable in all cohort studies, with the exception of historical or retrospective cohort studies that rely on previously existing historical data. The degree of attrition can be related to a number of factors, including the nature of exposure, expected duration of the study, demographic characteristics of the study population, and procedures adopted for follow-up of participants. Whether attrition happens because of migration, death, or lack of motivation on the part of subjects or failure to communicate with subjects for other reasons, it presents serious problems for the validity of study results. A bias can be introduced if participants with certain characteristics selectively discontinue their participation or attrition rates are differentially distributed between the exposed and unexposed groups or within different categories of the exposed group.

##### **14.5.9.3 Duration of Study**

For diseases that develop slowly, it can take a long time before signs and symptoms of the disease become clinically noticeable and before a definitive diagnosis can be made. Therefore, the follow-up period must be long enough for a sufficient number of new cases of disease to develop in the exposed and unexposed groups. A long follow-up period not only poses many operational challenges and increases the cost of the study, but also increases the likelihood of biased results because less-motivated individuals may drop out of the study in high numbers, leaving more motivated people in the study who may be systematically different from the less-motivated group. For example, highly motivated individuals who continue to participate in the study might be more educated, more conscientious about their health, or sicker than less-motivated subjects who dropped out of the study.

##### **14.5.9.4 Cost of Study**

Cost considerations play a major role in the design and implementation of any project. As compared with cross-sectional studies or other types of observational studies, cohort studies in general and prospective studies in particular can incur much higher costs. These costs are largely associated with the logistics of subject recruitment and ongoing follow-up. Clearly, these costs are directly proportional to the size of the cohort and the duration of follow-up, which in turn are related to the power of the study and the nature of the disease under investigation. Multicenter studies also cost more than single-center studies. The higher costs and longer time to get study results act as a counterpoint to the argument that cohort studies have greater scientific rigor and results that are more valid. Given the stiff competition for research funding and the desire on the part of researchers and funding agencies alike to see results more quickly, the issue of higher costs demands a careful consideration of alternative study designs such as case-control studies.

##### **14.5.9.5 Size of Cohort**

In the case of rare or uncommon diseases, the size of the cohort must be large enough to yield a sufficient number of cases in both exposed and unexposed groups to allow a meaningful statistical comparison. A large number of participants not only increases administrative difficulties of managing the project, but also proportionately increases the cost of the study.

### **14.6 Example of a Prospective Cohort Study**

Modified from: Falade-Nwulia O, Seaberg EC, Snider AE, et al. Incident hepatitis B virus infection in HIV-infected and HIV-uninfected men who have sex with men from pre-HAART to HAART period. Ann Intern Med. 2015;163(9):673–680.

Men who have sex with men (MSM) are at high risk of hepatitis B virus (HBV) infection. The purpose of this prospective cohort study was to identify risk factors of HBV infection among HIV-infected and HIV-uninfected MSM. Researchers used data from a multicenter (Baltimore, Chicago, Los Angeles, and Pittsburgh) AIDS longitudinal study (MAC) that had followed a cohort of MSM since 1984. The MAC included men who either already had HIV or were at risk for HIV. The participants in MAC were initially recruited from 1984 to 1985 and then again from 1987 to 1991 and from 2001 to 2003. These individuals were interviewed and tested for HIV every 6 months. At the time of enrollment into MAC, they were also tested for hepatitis B.

The eligibility criteria for the present study that was nested in the MAC and was started in January 1985 included negative hepatitis B test results at the time of enrollment in the MAC and availability of one or more blood samples from subsequent visits to be tested for hepatitis B.

The incidence of hepatitis B was defined as seroconversion of a previously negative individual to a positive HBsAg (hepatitis B surface antigen) or anti HBc (antibody to hepatitis B core antigen) test result. The participating men in the study were followed until December 31, 2013, or the last follow-up visit or the date of incident HBV infection—whichever happened first. Data on a number of variables, including age, race, number of sexual partners, injection-drug use, and alcohol use, were abstracted at each semiannual visit.

The results of the hepatitis B cohort study showed that out of the 6,972 men enrolled in the MAC until the end of 2003, a total of 2,375 had negative test results for hepatitis B virus at the first study visit on or after January 1, 1985. Of these, 1,784 were HIV-uninfected (75%) and 591 (25%) were HIV infected. Of the 1,784 HIV-uninfected MSM at the onset of the study in January 1985, 151 (8.5%) became HIV infected (i.e., had seroconversion) during the course of the study. The 2,375 HBV-negative men accrued 25,322 PYs of follow-up period. During this time, 244 cases of HBV infection occurred in this group, resulting in an overall unadjusted HBV incidence rate of 9.6 per 1,000 PYs (95% confidence interval [CI], 8.5 to 11.0). Among the HIV-infected men, 94 cases of HBV infection occurred during the 6,301 PYs of the follow-up period, yielding an incidence rate of 14.9 per 1,000 PYs (95% CI, 12.2 to 18.3). Among the HIV-uninfected men, 150 cases of HBV infection occurred during a total follow-up period of 19,020 PYs, with an incidence rate of 7.8 per 1,000 PYs (95% CI, 6.7 to 9.3). Thus, HBV incidence rate in the HIV-infected group was significantly higher than the HIV-uninfected group with an incidence rate ratio (IRR) of 1.9 (95% CI, 1.5 to 2.4).

[**TABLE 14.8**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_06.xhtml#ch14-tab8) shows the incidence and IRR of HBV infection in HIV-infected and HIV-uninfected men stratified by various risk factors such as age, race, use of alcohol, injection-drug use, and the number of sexual partners during the last 6 months. Note that in both HIV-infected and HIV-uninfected participants, the incidence rate of HBV infection was much higher in individuals who were younger than 40 years, consumed more than 13 drinks of alcohol per week, were injection-drug users, and had two or more sexual partners in the last 6 months.

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| **TABLE 14.8** Univariate Analysis of Risk Factors Associated with HBV Infection by HIV Infection Status | | | | | | |
| A table depicts the univariate analysis of risk factors associated with HBV infection by HIV infection status.  The column headers read: Variable, HIV uninfected, and HIV infected. The rows reads as follows. HIV infected and HIV uninfected columns are sub-divided into: IR asterisk over 1000 PYs (triple asterisk) IRR (double asterisk) (95 percentage CI dagger), P Value. The rows reads as follows. Age; greater than or equal to 40 years, 4.0, 1, left empty, 7.4, 1. less than 40 years, 12.4, 3.1 (2.2 to 4.5), less than 0.001, 22.8, 3.1 (1.9 to 4.9), less than 0.001. Race; Nonwhite, 7.5, 1, left empty, 11.8, 1, left empty. White, 8.0, 1.1, (0.7 to 1.6), 0.81, 16.5, 1.4 (0.9 to 2.2), 0.150. Alcohol less than or equal to 13 drinks per week, 8.1, 1, left empty, 14.0, 1, left empty. Greater than 13 drinks per week, 8.8, 1.1 (0.6 to 1.9), 0.75, 36.0, 2.6, (1.4 to 4.8), 0.003. Ever Injection Drug Use; No, 7.7, 1, left empty, 14.4, 1. Yes 14.0, 1.8 (0.9 to 3.7), 0.100, 21.2, 1.5 (0.8 to 2.8), 0.25. |  |  |  |  |  |  |
| A table depicts the univariate analysis of risk factors associated with HBV infection by HIV infection status.  The column headers read: Variable, HIV uninfected, and HIV infected. The rows reads as follows. Sexual Exposure in Previous 6 Months; 0 to 1 partners, 3.4, 1, left empty, 8.0, 1, left empty. greater than equal to 2 partners, 12.2, 3.6 (2.4 to 5.2), less than 0.001, 21.8, 2.7 (1.7 to 4.3), less than 0.001. Note: Asterisk, Incidence rate. Double asterisk: Incidence rate ratio. Triple asterisk: Person-years (PYs). Dagger: confidence interval. |  |  |  |  |  |  |

The results of multivariate analysis of the independent relationship of factors such as age, race, injection-drug use, and the number of sexual partners with the risk of HBV infection in all MSM participating in the study and HIV-infected MSM in the study showed that MSM were more likely to have HBV infection if they were younger than 40 years, had more than one sexual partner in the last 6 months, and were HIV infected. Conversely, all MSM who had had one or more than one dose of HBV vaccine, regardless of whether they were HIV infected or HIV uninfected, were significantly less likely to get HBV infection as compared to those who had had none.

### **14.7 Example of a Retrospective Cohort Study**

Modified from: Kelley AS, McGarry K, Gorges R, Skinner JS. The burden of health care costs for patients with dementia in the last 5 years of life. Ann Intern Med. 2015;163(10):729–736.

In a 2015 retrospective cohort study in the United States, the researchers examined the end-of-life costs of dementia for Medicare beneficiaries during the 5-year period preceding death. The data for the retrospective study were obtained from a national longitudinal (prospective) cohort study called the Health and Retirement Study, which involves interviewing every 2 years a nationally representative sample of U.S. adults older than 50 years. The participants were interviewed regarding their health status and healthcare expenses paid through Medicare, Medicaid, private health insurance, and out-of-pocket, as well as an estimation of the cost of informal care provided by family members and others.

The subjects in this retrospective study were 1,702 deceased individuals 70 years or older who had died of dementia (*n =* 555), cancer (*n* = 279), heart disease (*n* = 431), and other conditions (*n* = 437) between 2005 and 2010. Longitudinal interview data from these subjects were available because, as a part of the Health and Retirement Study, they had been interviewed every 2 years prior to their death. Postdeath interviews regarding healthcare expenses before the death of each of these subjects were conducted with a spouse or some other proxy individual.

The results showed that average total costs from all sources and costs to different entities such as Medicare, Medicaid, and out-of-pocket expenses for end-of-life care for patients who had dementia were much higher than end-of-life care costs for patients who had heart disease, cancer, or some other condition. For example, average total payment from all sources combined for dementia patients was $287,038, whereas for cancer patients it was $173,383 and for heart disease patients it was $175,136. Total government payment for dementia patients on average was $121,776, but for cancer and heart disease patients it was $102,486 and $96,514, respectively. Out-of-pocket expenses for dementia patients on average were $61,522, whereas for cancer and heart disease patients, respectively, they were $28,818 and $35,294. The difference in informal care costs was even more pronounced. The authors concluded that the cost of end-of-life care is disproportionately high for families of patients with dementia as compared to patients of heart disease, cancer, and other diseases.

### **14.8 Case-Control Studies**

At the onset, it is important to clarify that all [**case-control studies**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss20) are retrospective, but not all retrospective studies are case-control studies. Cohort studies that use historical records of a cohort beginning at some specific point in the past and track changes in the health status of the cohort going forward in time are also (erroneously) considered retrospective in design but are not case-control studies; they are called retrospective cohort studies. To illustrate the point that case-control study design is the opposite of prospective cohort study design, the made-up word *trohoc* (*cohort* spelled backwards) is sometimes used for case-control studies.

As illustrated in [**TABLE 14.9**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_08.xhtml#ch14-tab9), case-control studies are retrospective because each of these studies begins with a group of people who already have the disease (cases) and another group of people who do not have the disease (controls), and compares the two groups regarding their odds of having been exposed to a potential risk factor in the past. The question being investigated in these studies is whether cases differ from control in terms of past exposure to a given risk factor. As the name suggests, the cases of a disease are identified first and then their history is traced back to discover whether these individuals had been exposed in the past to the risk factor(s) of interest and, if so, what the circumstances, intensity, and duration of such exposure were. If the history of these individuals—whether discovered through direct personal communication, an examination of past medical records, or some other means such as employment records—provides evidence of past exposure to the risk factor(s) of interest, then the strength of association between the disease and the risk factor(s) being investigated is assessed through appropriate statistical analysis.

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| **TABLE 14.9** A Conceptual Model of Case-Control Study Design | | | |
| A table shows the Conceptual Model of Case-Control Study Design.  The table illustrates the case-control studies in 2 rows and 3 columns whose column header reads: Exposure to the risk factor in the past, look back into the past of study subjects, and start of the study. The data in the table reads row-wise as follows. Row 1: Number of those who were not exposed to risk factors in the past (negative) and the number of those who were exposed to risk factors in the past (positive), a backward arrow (leftward), and study participants with disease (positive). Row 2 reads: Number of those who were not exposed to risk factors in the past (negative) and the number of those who were exposed to risk factors in the past (positive), a backward arrow (leftward), and study participants without disease (negative). |  |  |  |

In this study design, one, two, or several hypothesized risk factors can be investigated simultaneously as potential contributors or causal factors for the disease of interest as long as sources of past information or historical records provide valid and reliable information regarding exposure to such risk factors. To examine the possibility that exposure to the hypothesized risk factor(s) may have no relationship with the occurrence of the disease of interest, a parallel group of individuals who do not have the specific disease are also included in the study. The history of this group of disease-free subjects is also examined through the same mechanisms as those of the diseased individuals to discover whether these individuals too had been exposed in the past to the risk factor(s) being investigated. In conducting a case-control study, careful attention is paid to the accuracy of medical diagnosis of diseased individuals labeled as *cases*. The sources and quality of information regarding past exposure to risk factors(s) and similarities of cases with nondiseased *controls* must be carefully examined. Other than the absence of disease, controls must, as much as possible, resemble cases in terms of age, race, sex, education, and other personal characteristics. The eligibility criteria for cases and controls, such as specification of age, race, sex, education, and potential for exposure to the suspected risk factor, must be established before the onset of the study and must be applied consistently and uniformly to both groups. Some of these issues are further discussed in the following sections.

#### **14.8.1 Case-Control Study Design**

A case-control study begins with the identification and recruitment of cases of the disease of interest. The identification and recruitment of cases can occur in a healthcare setting, such as a hospital or a nursing home, or even at the individuals’ homes. It can also be done merely through medical records without ever being actually in contact with the patient. When a study is based entirely on medical, billing, employment, and other relevant records of cases and controls, no recruitment or direct communication with individuals, whether cases or controls, is needed. As long as study protocols regarding accessing and protecting confidential medical and personal records are followed, the entire study can be conducted on the bases of paper or electronic records from various sources. For each case of the disease under investigation, one or more matched controls are also included in the study. Inclusion or recruitment of cases and controls can take place over time as patients with the disease or records of patients with said disease become available. The number of cases and controls to be included in the study is specified and predetermined at the conceptual stages of the study, but can be changed as the study progresses. Typically, for common diseases, the number of cases may be large, but in the case of a rare disease, the researcher may have no choice but to limit the study to a small number of patients. However, to have a reasonable degree of confidence in the findings of the study, the number of cases and controls also depends on the desired statistical power of the study.

#### **14.8.2 Definition of a Case**

The word *case* refers to a person who had already been diagnosed with the disease whose relationship with a suspected risk factor is being investigated. The diagnostic criteria on which the determination is made regarding whether a person has the disease in question must be established carefully and explicitly before the onset of the study. The decision to include or exclude individuals in a case-control study depends on such criteria. The definition of a case must be developed on the bases of established clinical guidelines and standard laboratory tests that provide the grounds for diagnosing and treating patients of the disease. In the event there is confusion, controversy, or ambiguity in published literature regarding the criteria for diagnosing cases of a disease, researchers must establish explicit evidence-based criteria from the existing body of literature and diligently adhere to these criteria throughout the course of the study. Validity of such criteria can be tested on a few known cases of the disease or checked against the medical records of known patients before the onset of the case-control study to see if the criteria accurately fit the disease in question. Changing the definition of a case in the middle of a study can cast serious doubts about the findings of the study because not all the cases included in the study were based consistently and uniformly on the same criteria.

What follows is an example of a precise definition of a case in a case-control study. In a study to investigate the potential risk of pituitary tumor associated with cellphone use, Shrestha et al.[**8**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib8) defined a case as “an individual between 20 to 69 years of age with either a histologically confirmed pituitary tumor (ICD oncology code C75.1) or unequivocal brain scan-based identification of a space occupying lesion during the study period.”

#### **14.8.3 Definition of a Control**

The criteria to define a control must also be carefully developed before the onset of the study and then consistently applied throughout the study. The number of controls for each case, whether one, two, or three, can be altered during the course of the study without compromising the findings of the study as long as each control meets the same uniform definition and eligibility criteria. For example, if the criteria for recruiting controls in the study state that same-sex siblings will be used as controls, then using same-sex neighbors or schoolmates of the opposite sex as controls would violate the study protocol.

As an example of selecting case-matched controls, in a study to understand risk factors for ischemic and intracerebral hemorrhagic stroke,[**9**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib9) age-, sex-, and ethnicity-matched hospitalized individuals, outpatient clinic patients, or relatives of hospitalized individuals with no previous history of stroke were recruited as controls. One control was recruited for each case of ischemic stroke and one for each case of hemorrhagic stroke.

#### **14.8.4 Sources, Identification, and Recruitment of Cases**

The setting or geographic location for recruiting cases should also be determined and specified before the onset of the study. For example, cases can be all patients of the disease of interest admitted to a specific hospital during a specified period or admitted to a group of hospitals in a county or metropolitan area. Patients can also be recruited from other healthcare settings, such as ambulatory care clinics, nursing homes, or assisted living facilities, or from within a community. If subjects are identified through a nonclinical setting such as an insurance plan or a disease registry, they can be recruited directly from homes or institutional settings, such as retirement homes and assisted living facilities, in a predefined geographic area. Whether all or some of the eligible individuals are recruited depends on the nature of the disease as well as the sampling methodology employed in the study. In the case of a commonly occurring disease, a random or systematic sample of cases identified in a clinical setting or reported at a registry during a given period may be used. On the other hand, if the disease being investigated is rare, then all diagnosed or reported cases in the past can be recruited.

#### **14.8.5 Purpose of Controls**

The purpose of controls is to provide a comparison group for cases in the study and to shed light on the frequency of exposure to a given risk factor in the entire population from which cases emerged. For that reason, it is important that controls should be representative in their characteristics of the general population from which they are drawn. Having a control group in the study is of critical importance because many diseases have a multifactorial etiology. A given chemical, physical, or biologic agent may be just one of the factors that contribute to the development and occurrence of a disease. If such is the case, then estimation of exposure to a given risk factor can provide only limited information regarding the underlying causes of a disease. It is worth noting that a vast majority of noninfectious diseases cannot be attributed to a single causal agent, as is the case with infectious disease such as HIV, tuberculosis, or malaria. For such diseases, exposure to a risk factor does not always lead to disease (i.e., the disease does not occur despite exposure). On the other hand, a multifactorial disease can occur in the absence of a given risk factor—in other words, exposure to a risk factor may be neither necessary nor a sufficient condition for the disease of interest to occur. Whereas cases in a case-control study provide information about the extent to which a disease occurred with or without exposure to a given risk factor, controls allow researchers to understand the extent to which a disease may not occur despite exposure.

#### **14.8.6 Sources, Identification, and Recruitment of Controls**

Controls in a case-control study are usually recruited from the same source population from which the cases emerged. For example, if cases of a cancer are identified and recruited through a statewide cancer registry, the controls should also be from the same state and should be as similar to the cases as possible in terms of demographic and socioeconomic characteristics. If cases are recruited throughout the state or from specific ZIP codes, counties, or neighborhoods, so should be the controls. The controls should also be similar to cases in terms of the potential for past exposure in the same period as the cases. However, researchers should have no knowledge of the history and potential past exposure of controls to the risk factor, and selection of controls should be strictly without any reference to past risk exposure. Likewise, if any exclusionary criteria are applied to cases, the same criteria must also be applied to the controls.

If recruited from the general population, the controls should be selected through a random sampling protocol. However, controls can also be selected from the same clinical settings as cases, such as patients in the same hospital admitted for reasons unrelated to the disease being studied. In such an instance, care must be taken to ensure that the condition or malady for which controls are admitted to the hospital is unrelated to the disease for which cases are admitted. This would also mean exclusion of individuals admitted to the hospital for diseases etiologically related to the risk factor being investigated. Further, the referral and admission process for controls and their medical conditions should be the same as cases in the study. The diagnoses or list of medical conditions for which controls are admitted to the hospital need not be limited to only one or two as long as they are unrelated to the disease for which cases are admitted in the same facility.

#### **14.8.7 Methods to Obtain Information Regarding Past Exposure**

A variety of methods, such as personal interviews; abstraction of data from medical, employment, pharmaceutical, or laboratory records; or direct measurement of the variable of interest, can be used to obtain information regarding past exposure to a risk factor and the current health status of both cases and controls. The suitability and availability of any of these sources of data can vary from one study to another and depend entirely on the circumstances and nature of the specific case-control study. As much as possible, it is paramount that the validity and reliability of data regarding the current medical diagnosis and past exposure to the risk factor are carefully established and cross-checked from various sources. None of the mentioned methods of information gathering can be guaranteed to be 100% accurate. Each can pose its own challenges, and each is vulnerable to contamination from a variety of sources. For example, information obtained through personal interviews may be impossible to verify and can suffer from problems related to poor memory (*recall bias*) or deliberate over- or underreporting by the subject (errors of omission and commission). Likewise, data obtained from medical records can pose difficulties such as incomplete or unavailable medical records, lack of clarity regarding primary or secondary diagnoses, verification of the date of diagnosis, and the timing of the first appearance of signs and symptoms.

#### **14.8.8 Considerations in the Measurement of Exposure**

For both cases and controls, several important points should be considered in the assessment of exposure to the risk factor. The timing, duration, and degree of exposure should be carefully established and, for cases, it must precede the occurrence or manifestation of disease—that is, the temporal sequence of events should be logical for an assertion to be made that the risk factor played a role in the occurrence of the disease. The question that must be clearly answered in a case-control study is: When did exposure occur in relation to the appearance of signs and symptoms or diagnosis of the disease? For controls, an arbitrary but carefully thought out reference date in the past can be used to discover whether they had been exposed to the risk factor before that date and what the duration and level of exposure were. The quantification of exposure in terms of both duration and level of exposure is necessary to assess a dose–response relationship between exposure and the disease.

#### **14.8.9 Calculation and Interpretation of Odds Ratio**

In cohort studies, the relative risk (also known as risk ratio, rate ratio, or incidence rate ratio) of disease associated with exposure to a risk factor is calculated by directly comparing the proportions of new cases of a disease in the exposed and unexposed groups of people. Because the total number of exposed and unexposed people from which new cases of disease emerged is not known in case-control studies, direct estimation of relative risk is not possible. Consequently, case-control studies are limited to an indirect estimation of relative risk by comparing the odds of past exposure in diseased and disease-free individuals. Estimation of the odds of past exposure in the diseased and disease-free individuals and calculation of relative odds of exposure in the two groups (*odds ratio*) provides an acceptable measure of the strength of association between a disease and the risk factor being examined.

In [**TABLE 14.10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_08.xhtml#ch14-tab10), the odds of exposure among the cases can be obtained by dividing the number of cases of disease with past exposure (*a*) by the number of cases without a history of past exposure (*c*). So, the odds of exposure among the cases can be represented as follows:

An equation reads: Odds of exposure among the cases equals (a over c).

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| **TABLE 14.10** Odds Ratio Derivation – Notational Example | | | | |
| A table show the Odds Ratio Derivation to Notational Example.  The table shows the odds of exposure in 3 rows and 3 columns whose column header reads: Yes, No, and Total that represents the disease. The row headers: Yes, No, and Total that represents the exposure. The data in the table reads row-wise as follows. Row 1: a, b, and a plus b. Row 2: c, d, and c plus d. Row 3: a plus c, b plus d, and a plus b plus c plus d. |  |  |  |  |

Similarly, the odds of past exposure among the controls are obtained by dividing the number of controls with a history of past exposure to the risk factor (*b*) by the number of controls who did not have a history of past exposure to the risk factor (*d*). Again, the odds of exposure among the controls can be represented as:

An equation reads: Odds of exposure among the controls equals (b over d).

The ratio between the odds in the two groups (odds ratio) is obtained simply by dividing the odds of exposure among the cases (*a / c*) by the odds of exposure among the controls (*b / d*).

Thus,

An equation reads: Odds ratio (OR) equals (a over c) over (b over d).An equation reads: or equals ad over bc.

An odds ratio of 1.0 means that the odds of having been exposed to a risk factor in the past are equal for both groups—cases and controls. In other words, it is likely that there is no association between the risk factor and the disease in question. An odds ratio of greater than 1.0 (i.e., >1.0) suggests a positive link between a risk factor and a disease (i.e., a possible causal link), whereas an odds ratio of less than 1.0 (i.e., <1.0) suggests a negative association (i.e., a possible protective effect conferred by the risk factor). [**TABLE 14.11**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_08.xhtml#ch14-tab11) shows the results of a hypothetical case-control study. The estimation of odds ratio in this case would be as follows:

An equation reads: Odds ratio (OR) equals (80 times 530) over (70 times 220); or equals (42000 over 15400); or equals 2.75.

The results of this hypothetical study would indicate that the cases of disease were 2.75 times more likely than the controls to have been exposed to the risk factor in the past.

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| **TABLE 14.11** Odds Ratio Derivation – Numeric Example | | | | |
| A table show the Odds Ratio Derivation to Numeric Example.  The table shows the odds of exposure in 3 rows and 3 columns whose column header reads: Yes, No, and Total that represents the disease. The row headers: Yes, No, and Total that represents the exposure. The data in the table reads row-wise as follows. Row 1: 80, 70, and 150. Row 2: 220, 530, and 750. Row 3: 300, 600, and 900. |  |  |  |  |

#### **14.8.10 Advantages of Case-Control Study Design**

Case-control studies have several advantages over cohort studies, including the fact that they are relatively easier to conduct and require less time, money, and other resources to complete. Because there is no long-term follow up of subjects, they are not prone to attrition of study participants over time and potential self-selection bias resulting from the possibility that those who continue to participate in a cohort study over a period of time might be more motivated or different in some other ways from those who decide to drop out. For the same reason, case-control studies can be completed with relatively small numbers of subjects and do not require participant samples as large as those for cohort studies. Case-control studies also allow the opportunity to simultaneously explore the relationship of several different risk factors with the disease being investigated. Therefore, multiple etiologic hypotheses can be tested in the same study, and the interaction of several risk factors with one another can be conveniently explored. Finally, an important advantage of case-control studies is their suitability to investigating the etiology of relatively uncommon or rare diseases as well as those disorders that have a long latent period. Data on rare diseases can be found from national or regional registries, large medical centers, or insurance companies. Suitable historical controls can also be found through the same sources. In a case-control study, even with a few cases of a rare disease, meaningful results can be obtained with the help of advanced statistical techniques.

### **14.9 Example of a Case-Control Study**

Modified from: Friis S, Riis AH, Erichsen R, Baron JA, Sorensen HT. Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: a population-based case-control study. Ann Intern Med. 2015;163(5):347–355.

This 2015 population-based case-control study used data from northern Denmark to assess whether there was an association between past use of low-dose aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) and subsequent risk of colorectal cancer (CRC). Some studies in the past have shown a lower risk of colorectal cancer associated with at least 5 years’ use of low to moderate doses of aspirin or use of nonaspirin NSAIDs. Data on drug use, comorbid conditions, and history of colonoscopy for 10,280 patients (cases) with colorectal cancer and 102,800 controls were obtained from a prescription database and three patient registries.

Data from these four sources were linked by using the unique identification number assigned to each Danish resident by the government. In Denmark, low-dose aspirin (75 mg, 100 mg, or 150 mg tablets) is almost exclusively (>90%) sold with a prescription, whereas high-dose aspirin (500 mg tablets or more) is largely sold over the counter. All nonaspirin NSAIDs, with the exception of 200 mg tablets of ibuprofen, are sold only with a prescription. Therefore, data on over-the-counter purchase of high-dose (500 mg) aspirin and low-dose (200 mg) ibuprofen were not available. Cases comprised all individuals in northern Denmark with a histologically verified first diagnosis of CRC between 1994 and 2011 and at least 5 years of prescription drug coverage before diagnosis of CRC (*n* = 10,280). All cases were between 30 to 85 years of age at the time of CRC diagnosis and lived in one of the four counties in northern Denmark. The case definition also excluded all individuals with previous history of cancer (other than nonmelanoma skin cancer), inflammatory bowel disease, or history of familial adenomatous polyposis before being diagnosed with CRC. For each case of CRC, 10 controls matched for birth year, sex, and county of residence were included in the study (*n* = 102,800).

The researchers used logistic regression analysis to estimate age-, sex-, and area-matched odds ratios (ORs) as well as multivariable (e.g., high-dose aspirin, hormone replacement therapy, antidepressants, and statin drugs, plus a number of other variables) adjusted ORs and 95% CIs for the association of CRC with use of low-dose aspirin or nonaspirin NSAIDs such as ibuprofen. They created multiple statistical models to estimate ORs based on the dose, frequency, duration, and continuity of use of low-dose aspirin. For example, they estimated adjusted ORs for CRC among “ever users,” “recent users,” and “former users*”* of low-dose aspirin and nonaspirin NSAIDs (see [**TABLE 14.12**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_09.xhtml#ch14-tab12)). In all analyses, nonuse of aspirin or nonuse of nonaspirin NSAIDs was used as the reference category.

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| **TABLE 14.12** Use of Low-Dose Aspirin or Nonaspirin NSAIDs and Risk of Colorectal Cancer | | | |
| A table depicts the use of low-dose aspirin or nonaspirin NSAIDs and the risk of colorectal cancer.  The column headers of the table read as follows. NSAID use, case-patients, control patients, and multivariate-adjusted OR (95 percent CI) dagger. Low-dose aspirin; Nonuse double dagger, 7984, 79807, reference; Ever use (dollars), 2296, 22993, 1.03 (0.98 to1.09); Recent use (superscript double vertical bar), 2058, 20652, 1.03 (0.97 to 1.09); Former use (superscript pilcrow sign), 238, 2341, 1.06 (0.92 to 1.22). Model 2: Cumulative Duration of Use (double asterisk two single daggers); less than 5 years, 1321 13,133, 1.04 (0.97 to 1.11); 5 to less than 10 years, 595, 6187, 1.00 (0.91 to 1.10); greater than or equal to 10 years, 142, 1332, 1.13 (0.94 to 1.35). Model 3: Tablet Dose With Cumulative Duration of Use greater than 5 Years (double asterisk, two single daggers, and two double daggers); 75 to 100 mg, 243, 2450, 1.03 (0.90 to 1.19); 150 mg, 200, 2085, 0.99 (0.85 to 1.15). Model 4: Continuous Use (superscript double dagger double dollar); Continuous use greater than 5 years, 45, 634, 0.73 (0.54 to 0.99). |  |  |  |
| A table depicts the use of low-dose aspirin or nonaspirin NSAIDs and the risk of colorectal cancer.  The column headers of the table read as follows. NSAID use, case-patients, control patients, and multivariate-adjusted OR (95 percent CI) dagger. Nonaspirin NSAIDs; Nonuse (dagger), 5647, 54748, Reference; Ever use (section sign), 4633, 48052, 0.94 (0.90 to 0.98). Model 2: Duration of Use (quotation mark); less than 5 years, 2331, 22935, 0.99 (0.94 to 1.04); 5 to less than 10 years 1414, 15590, 0.89 (0.83 to 0.94); greater than10 years, 888, 9527 0.90 (0.83 to 0.98). Model 3: Intensity of Use with Duration of Use greater than or equal to 5 Years (double quotation); <0.1 DDD (pilcrow sign), 1459, 14836, 0.96 (0.90 to 1.02); 0.1 to less than 0.3 DDD (pilcrow sign), 505, 5515, 0.89 (0.81 to 0.98); greater than 0.3 DDD (pilcrow sign), 338, 4766, 0.70 (0.62 to 0.78). Model 4: Consistent Use; Consistent use greater than or equal to5 years (three asterisk), 93, 1426, 0.64 (0.52 to 0.80). Note: NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; DDD: defined daily dose. Dagger: In addition to age, sex, and area; adjusted for a number of additional variables, such as use of high-dose aspirin, hormone replacement therapy, use of antidepressants, statins, plus other variables. Double dagger less than 2 prescriptions, more than 1 year before the date of CRC diagnosis (index date). Pilcrow sign greater than or equal to prescriptions, more than 1 year before the date of CRC diagnosis (index date). Double vertical line greater than 2 prescriptions for low-dose aspirin and greater than or equal to 1 prescription within 1 to less than 3 years before the index date. Pilcrow sign greater than or equal to 2 prescriptions for low-dose aspirin but no prescription within 1 to less than 3 years before the index date. Double asterisk Analysis restricted to recent users and nonusers of low-dose aspirin. Two single daggers, Cumulative treatment periods were defined according to the number of dispensed tablets and grace periods of 30 days. Two double daggers, Exclusive use of 75 to 100 mg or 150 mg. Mixed-use not included. Double section sign, One continuous treatment period defined according to the number of dispensed tablets and grace periods of 30 days. Double vertical line, Time period between the first and last filled prescriptions (disregarding the last year before the index date). Double (pilcrow sign) Cutoff values of estimated average dose per day in DDDs, defined by approximate tertiles of estimated average dose per day among control participants. Asterisk greater than or equal to 2 prescriptions per consecutive years of nonaspirin NSAID use until 1 year before the index date. |  |  |  |

The results showed that ORs for colon cancer associated with ever using aspirin (≥2 prescriptions) and nonaspirin NSAIDs were 1.03 (95% CI 0.98–1.09) and 0.94 (95% CI 0.90–0.98). Continued long-term use (≥5 years) of 75 mg to 150 mg of aspirin (Model 4 in [**Table 14.12**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_09.xhtml#ch14-tab12)) was associated with a 27% reduction in the risk of CRC (OR 0.73; 95% CI 0.54–0.99). On the other hand, no reduction of CRC risk was observed with overall long-term use of low-dose aspirin. Five years or longer high-intensity use of nonaspirin NSAIDs was associated with 30% to 38% reduced risk of colorectal cancer. The possibility of confounding factors such as diet and physical activity affecting the results of the study could not be completely ruled out because the authors did not look into those factors. Overall, the authors concluded that unless taken regularly, low-dose aspirin did not seem to confer protection consistently against colorectal cancer.

### **14.10 Risk Factor and Exposure in Cohort and Case-Control Studies**

In epidemiology, the term *risk factor* refers to any factor, whether external or intrinsic to the subject, that directly or indirectly increases or decreases the likelihood of death, disease, or disability in a person. External factors can include chemical, physical, or biologic agents. Internal factors can be related to genetic makeup and personal characteristics, including age, race, sex, or behavioral characteristics. The term *risk factor* generally implies a causal relationship of one or more such factors with a disease. Because a cause-and-effect relationship is difficult to prove, evidence of a statistically significant association between a risk factor and a disease can be considered an appropriate objective for an epidemiological study. In other words, based on the strength of statistical association, both cohort and case-control studies provide an estimation of the risk of disease associated with a given factor. Alternatively, we can state that cohort and case-control studies are *risk assessment* studies.

It is not sufficient to make a claim of exposure to a risk factor in a cohort or case-control study; rather, it is necessary to substantiate and report the exact circumstances, nature, degree, and duration of exposure. Exposure to a factor that has a positive or negative effect on the likelihood of getting a disease in the future can be short or long in duration and mild or severe in intensity. Exposure to a risk factor, whether malicious or protective in nature, can occur in the following three forms: (1) exposure occurs in the form of a bolus (i.e., large amount of exposure as a single event of a short duration), (2) continued low-dose exposure over an extended period of time with cumulative effects, and (3) intermittent or sustained high-level exposure over a period of time. Naturally, the effects of exposure to a risk factor depend not only on the amount and duration of exposure but also, and most important, on the nature of the risk factor itself. It is also important to point out that not all individuals exposed to a risk factor will necessarily respond in the same manner and may or may not develop disease. Even with the same dose and duration of exposure, some individuals will develop the associated disease (or immunity if exposure confers protection), whereas others may show little or no effect at all. Likewise, because of the multifactorial etiology of many diseases, some individuals who have had no exposure whatsoever may still develop a disease frequently associated with a risk factor. In other words, absence of disease does not rule out past exposure, and absence of exposure does not rule out the occurrence of disease. Of course, evidence of a dose–response relationship between exposure to a risk factor and a disease adds exponentially to the credibility of both case-control and cohort studies.

A dose–response relationship means that there is a direct statistical correlation between the amount, duration, and intensity of exposure and the intensity of disease or the degree of protection against the disease conferred by the exposure to a risk factor. Although the term *risk factor* has a negative connation, it also refers to a factor, such as a vaccine, that has a protective effect against a disease. The term *dose–response relationship* in the context of a vaccine or a therapeutic agent refers to the efficacy of such an agent in generating antibodies or mounting resistance against disease.

The term *exposure assessment* refers to the steps, procedures, and protocols by which the level, frequency, and duration of exposure to a risk factor are estimated. In both cohort and case-control studies, it is necessary to carry out exposure assessment in a careful manner to determine who was exposed to the risk factor. Therefore, exposure assessment must clarify as to when, where, how, and how much exposure occurred.

### **14.11 Comparison of Cohort and Case-Control Study Design**

Cohort and case-control studies are sometimes referred to as the studies of “natural experiments” because, in both kinds of studies, individuals are “naturally” exposed to some risk factor(s) rather than being deliberately or intentionally exposed by the researcher to a chemical, physical, biologic, or psychological agent or stressor. The use of the word *natural* is intended to be in contrast with *intentional*, *deliberate*, or *manipulative*, in which case the researcher selectively introduces, controls, and manipulates the nature, amount, and duration of exposure to one or more risk factors for one or more groups of individuals (or laboratory animals).

Although both kinds of studies are valuable epidemiologic tools, each has its advantages or disadvantages. [**TABLE 14.13**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_11.xhtml#ch14-tab13) is designed to help the reader understand these advantages or disadvantages in a comparative context only. To test a hypothesis about the association of a risk factor with a disease, researchers can begin by first conducting a case-control study. If the results of the case-control study support their hypothesis, they may choose to invest further time and resources in conducting a cohort study to see if the results of the case-control study are validated.

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| **TABLE 14.13** Comparison of Case-Control and Prospective Cohort Study Design | | |
| **Consideration**[**\***](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_11.xhtml#fn_ch14-tab13_1) | **Case-Control Study** | **Prospective Cohort Study** |
| Duration of study | Relatively short (months) | Much longer (years) |
| Number of participants | Relatively smaller | Much larger |
| Cost of study | Relatively inexpensive | Much more expensive |
| Need for other resources | Relatively less | Much greater |
| Logistics and organization | Less complicated | Complicated or challenging |
| Study design | More straightforward | Complex |
| Potential for bias | Possibly greater | Somewhat easier to avoid |
| Quality of data | May be less than optimal | Usually superior |
| Confidence in results | Relatively less | Much greater |
| Scientific rigor | Somewhat lesser | Much greater |
| [**\***](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_11.xhtml#fn_ch14-tab13_1a)The considerations listed are only in comparative and relative terms between the two study designs rather than absolute. | | |

### **14.12 Association and Causality**

Our thinking about the causation of diseases has evolved since the time of Hippocrates in the 4th century BCE, and especially since the identification of *Mycobacterium tuberculosis* by Koch in 1882 and the identification between 1897 and 1900 of microbial organisms responsible for 22 different infectious diseases. Before the identification of microbial organisms in the second half of the 19th century, diseases such as tuberculosis (also called “consumption” or “phthisis” in older literature), malaria, and cholera were not seen as specific and separate diseases distinct from one another. Rather, they were all seen as the health effects of poor environmental and sanitary conditions lumped under the title “miasmas.” The identification of microbial organisms such as tubercle bacillus and *Vibrio* *cholerae* led to the belief that every disease is caused by one and only one specific causative agent or substance. This belief in the existence of a single underlying causative agent is known as the theory of *mono-causal* etiology of diseases. The implications of this theory were that each disease is caused by a single underlying factor that does not cause any other disease, and a particular disease cannot be caused by any other agent or factor.[**10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib10) Consequently, the theory ruled out the possibility that diseases can result from a complex interaction of multiple biologic and socioeconomic factors—that is, diseases can have a *multifactorial* etiology or can be *multicausal* in nature. The mono-causal theory of disease etiology is clearly reflected in Koch’s postulates formulated in the late 19th century that have fallen out of favor in modern times.

Recognition of the fact that not all individuals exposed to a microbial agent such as *Vibrio cholerae* contract acute symptomatic disease and that not all those exposed to the microbe *Salmonella typhi* suffer from typhoid fever led to the concept of an *epidemiologic triangle*. The idea of an epidemiologic triangle suggested that diseases result from a dynamic interaction among the causative agent, the host, and the environment in which both the agent and the host exist. The causative agent can be a specific biologic, chemical, or physical entity whose presence is necessary to produce the disease. However, the presence of such an agent may not be a sufficient condition to produce the disease of interest. Favorable host characteristics such as susceptibility or weak constitution, and environmental conditions such as appropriate temperature and humidity may be essential for the agent to cause disease.

In addition to the role of a specific causal agent, the epidemiologic triangle model explicitly recognizes the role of the environment in which the agent and host interact. The presence of an agent such as a microbe, a chemical agent, or a physical factor is necessary but not always sufficient for a disease to occur.

With new developments in science and increasing incidence and prevalence of noninfectious chronic disorders, such as a variety of cancers, hypertension, and diabetes, it was recognized that the epidemiologic triangle model applies predominantly, if not exclusively, to infectious diseases. The epidemiologic triangle fails to incorporate the role played by coexisting multiple factors—such as age, race, gender, diet, occupation, and lifestyle—in determining whether an illness occurs and the extent, severity, and course of disease.

In the last 50 years or so, there has been a growing emphasis on multifactorial etiology of diseases. In recognition of the fact that chronic disorders such as coronary artery disease, stroke, cancer, and arthritis result from a complex interplay of a number of different factors, a new etiologic model called the *web of causation* has emerged with widespread acceptance. The web of causation explicitly recognizes that the occurrence and severity of a disease is a function of a complex interaction among biologic, social, and environmental factors such as genetic predisposition, employment, social support, and access to various services to support a healthy lifestyle. While the web of causation emphasizes the role that multiple intrinsic and extrinsic variables play to affect the probability of a disease occurring in an individual or groups of people, it does not address the fact that certain social, racial, or ethnic groups may be inherently at a higher or lower risk of a disease.

A number of philosophic and conceptual objections have been leveled against both the mono-causal and web of causation perspectives. The criticism of the web of causation model is largely on the grounds that it assigns a causal role to one or more factors based on a statistical association with the disease. The critics argue that statistical association of factors such as marital status, poverty, unemployment, or housing with a disease (e.g., diabetes or hypertension) merely constitutes identification of risk factors or increased probability of the occurrence of disease rather than a causal relationship. The critics also object to the interchangeable use of the terms *exposure* and *risk factor*. They argue that the term *exposure* should be reserved for factors or agents that have a clearly causal relationship with a disease, whereas *risk factors* merely increase the probability of acquiring a disease but are not a part of the causal pathway. They point out that factors such as age, poverty, or low levels of immunity, as implied by the word *risk*, only increase the likelihood of getting a disease but, in and of themselves, have no pathophysiologic role in causing the disease. Frequently, these factors are associated with both the causal factor(s) and the disease and therefore, as discussed later in this chapter, are referred to as [**confounder variables**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss42).

The theory of *general susceptibility*, which has gained some ground in the last two or three decades, specifically makes the point that, all else being equal, certain ethnic or demographic groups, per se, are more prone to some diseases than other groups. Rather than focusing on causality, the theory of general susceptibility emphasizes the role of socioenvironmental factors. Before the theory of general susceptibility, most medical thinkers and social scientists believed in the principles of necessary cause and disease specificity. Necessary cause meant that a particular disease could not occur in the absence of a particular agent or factor; disease specificity meant that each disease is unique in being caused by a specific agent and none other, and the causative agent of one disease could not cause another disease.[**10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib10)

The theory of general susceptibility is rooted in the idea that each individual is an open system that survives only through adaptation to the changes taking place in its surroundings or external environment. This also means that to cope with the changes taking place in the external environment, the individual should maintain a stable internal environment. Therefore, the occurrence of a disease is viewed as a failure of the individual’s adaptive struggle to cope with the changes taking place in his/her physical and social environment.[**10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib10) Conversely, healthy individuals are seen as those who have successfully adapted to their external environment. The ability to adapt successfully to changes in one’s physical and social environment is a function of the individual’s own constitution as well as the severity and nature of changes occurring in the external environment.[**10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib10)

The theory of general susceptibility draws support from examples of infectious diseases caused by opportunistic organisms that are ubiquitous in our surroundings or exist in the body but do not cause harm under ordinary circumstances, only when the individual is exposed to physical and social stressors.[**10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib10) For example, studies[**11**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib11)–[**13**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib13) have shown that stressful experiences or events increase the risk of streptococcal infections. Similarly, a strong association of stressful life events is observed with mental disorders such as depression and suicide.

In contrast to the theory of general susceptibility, the necessary cause and disease specificity beliefs couched in the mono-causal model of disease etiology view the individual as a closed system impervious to, immune to, or isolated from the effects of the stressors in the physical and social environment. Viewing the individual as a closed system was useful to understanding the interaction between agent and host in the context of infectious diseases. For contemporary multiple-cause chronic diseases such as hypertension, stroke, and diabetes, the open system perspective is much more useful. An important aspect of the open system perspective is its recognition of the fact that a stressful life event, such as divorce or loss of employment, can have a variety of health effects. Conversely, a health outcome may have multiple stressful stimuli as its antecedents.[**10**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib10)

### **14.13 Bias**

The Dictionary of Epidemiology[**14**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib14) provides the following definition of [**bias**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss13):

Systematic deviation of results or inferences from truth. Processes leading to such deviation. An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from truth.

The dictionary lists dozens of different forms and sources of conscious or unconscious bias in epidemiologic research. As indicated by the preceding definition, bias can get introduced in a study through multiple sources, including (1) flaws in study design, (2) procedures and criteria for selection of subjects, and (3) inadequate methods of data collection and analysis.[**14**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib14),[**16**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib16)

The impact of a bias in epidemiologic studies can be overestimation or underestimation of whatever is being measured and unwarranted conclusion based on the findings of the study. For example, in case-control studies, erroneous conclusions regarding a statistical association between a risk factor and a disease can be drawn and causal assertions can be made because of a bias in the selection of subjects or poor recall of participants regarding past exposure to a risk factor. Conversely, a valid association between a risk factor and disease can be missed because of an underestimation resulting from biased study design, data collection, or statistical analysis. Put another way, biased results of a study can lead to either a [**Type I error**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss241) or a [**Type II error**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/22_Gloss.xhtml#gloss242) (i.e., erroneous rejection of a null hypothesis or erroneous acceptance of a null hypothesis). It is useful to recall that, in statistics, a null hypothesis states that there is no statistical relationship between the two variables being examined (i.e., risk factor and disease). In case-control studies, Type I and Type II errors can occur because of erroneous assignment of cases and controls to the wrong group—that is, misclassification of cases to the control group and vice versa, or erroneous assignment of exposure (i.e., assignment to the exposed group when there was no exposure to the risk factor, or to the unexposed group when there had been exposure). Likewise, in screening programs discussed elsewhere in this text, bias associated with the administration of a test or interpretation of test results can lead to erroneous assignment of many individuals to the disease-positive group or the disease-negative group. Such a situation can result in over- or underestimation of the magnitude of the problem and cause unnecessary confusion, concern, and avoidable follow-up investigations.

Case-control studies are more prone to interviewer bias, observation bias, recall bias, or misclassification bias because of the methods used for selecting cases and controls and for collecting necessary information. For example, bias can be introduced if individuals with certain characteristics (e.g., age, sex, ethnicity, and income) are over- or underselected or excluded altogether. In case-control studies, bias can also be introduced because of a difficulty in establishing an appropriate temporal relationship between the alleged causal factor and the disease being studied. A causal relationship can only be alleged if exposure to the risk factor can be shown to have preceded the occurrence of disease. If exposure to the risk factor occurred after the appearance of disease, then clearly the risk factor being examined could not have contributed to the development of the disease. For example, if someone starts drinking heavily because he or she is depressed, then occurrence of depression cannot be attributed to the consumption of alcohol.

It is critically important to avoid any sources of bias in study design and data collection because such problems are difficult to detect and nearly impossible to correct after the completion of data collection. To avoid the possibility of bias or systematic error in an epidemiologic study, researchers must understand potential sources of bias, such as those related to the selection of participants and collection of data, whether in the form of direct observation, personal interviews, or administration of surveys. To address the issue of bias after the conclusion of a study, researchers not only need to look into the sources of bias but also must assess the degree or seriousness and the direction of bias to determine its impact in terms of over- or underestimation of the strength of association between variables. A small degree of bias may not seriously affect an observed association between variables, but a strong bias can totally invalidate the findings of a study.

### **14.14 Confounding**

The word *confound*, derived from the Latin word *confundere*, means to cause confusion or to mix up one thing with something else.[**15**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib15) In any observational study, whether case control or cohort, the operative assumption is that there is a direct cause-and-effect relationship between Risk Factor A (or exposure, such as smoking) and the Disease of Interest B. The situation, however, can be muddied if a third variable or factor exists, such that it is related to both—the risk factor and the disease. This third variable or factor is called a confounder variable. The relationship of the confounder variable with the risk factor and with the disease is independent of the relationship between the risk factor and the disease. The value of the risk factor can increase or decrease as the value of the confounder increases or decreases. Similarly, the occurrence and intensity of the disease also varies with a change in the value of the confounder variable. Thus, a confounder variable can account for, partly or fully, an apparent relationship between exposure and disease.

Many authors consider confounding to be a form of bias because it systematically distorts the measurement or assessment of the relationship between exposure to a risk factor and disease.[**17**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib17),[**18**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib18) To be a confounder, a variable must fulfill the following three conditions: (1) it must be associated with the disease of interest; (2) it must be associated with the risk factor and should be unequally distributed between the exposed and unexposed groups or between different levels of exposure; and (3) it should not be the result or effect of the risk factor—that is, it should not be a part or intermediate step in the causal pathway between exposure and disease.[**17**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib17),[**18**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib18) [**FIGURE 14.2**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#ch14-fig2) illustrates the relationship of a confounder variable with the risk factor (exposure) and the disease or health outcome.

An illustration shows a block, Risk factor (A) on the left points to another block, Disease (B) on the right. A block from the bottom, Confounder variable (C) points to the blocks (A) and (B). 

**FIGURE 14.2** Illustration of the relationship of a confounder variable with the risk factor and the disease or health outcome.

In both observational and experimental studies (i.e., cohort and case-control studies and clinical trials), researchers employ various techniques during planning, implementation, and analytic stages to prevent or control the effects of confounder variables. These techniques include matching of exposed and unexposed subjects or cases and controls on potentially confounding variables such as age, race, sex, ethnicity, and other demographic and socioeconomic variables. In experimental studies, random assignment of subjects to experimental and control groups is also done to avoid the distortion of study results by various confounding variables. During analyses, data can be stratified, for example, by age groups to deal with the effect of age on the degree of exposure (e.g., hypertension) and the disease (e.g., stroke).

[**FIGURE 14.3**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#ch14-fig3) provides an example of a confounder variable in a case-control study by O’Donnell et al.[**9**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_16.xhtml#ch14-bib9) The study, described more in detail later in this chapter, was conducted to investigate the relationship of a number of risk factors with stroke. During the design stage, cases were matched with controls on age, sex, and ethnicity. The multivariate analysis to examine the relationship of a given risk factor with stroke also adjusted for a number of confounder variables. For example, the multivariate model for the relationship of hypertension with stroke was adjusted for age, race, sex, diet, smoking, alcohol intake, and several other variables. [**Figure 14.3**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#ch14-fig3) shows the relationship of hypertension with stroke. In this case, stress is shown as a confounder variable that, unless adjusted for in statistical analysis, could have distorted the estimation of the role hypertension plays as a causal factor in the occurrence of stroke.

An example of a confounder variable in a case-control study shows three blocks, which are labeled hypertension, stroke, and stress. In which, stress points to hypertension and stroke, and hypertension points to stroke.

**FIGURE 14.3** An example of a confounder variable in a case-control study (See [**Case Study 14.4**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#side14_4) at the end of the chapter).

### Search icon ***CASE STUDY 14.2: Prospective Cohort Study***

Modified from: Gunderson EP, Hurston SR, Ning X, et al. Lactation and progression of type 2 diabetes mellitus after gestational diabetes mellitus: a prospective cohort study. Ann Intern Med. 2015; 163(12):889–898.

Gestational diabetes mellitus (GDM) is a disorder of glucose tolerance that affects 5%–9% of all U.S. pregnancies (approximately 250,000 pregnant women). Women who experience GDM have a 7 times greater risk of subsequent diabetes mellitus (DM) than women who do not. Breastfeeding or lactation is a modifiable postpartum behavior that improves glucose and lipid metabolism and has favorable metabolic effects that persist after weaning.

The purpose of this study was to examine whether breastfeeding had any effect on or a relationship with the occurrence of DM in the 2-year period following delivery among women who had GDM during pregnancy. A total of 1,035 pregnant women who had been diagnosed with GDM and who delivered a baby after 35 weeks or more of pregnancy were enrolled and followed from August 2008 to December 2011. Three in-person examinations of these women from 6 to 9 weeks after delivery were conducted to collect baseline data. Thereafter, annual follow-ups included anthropometric measurements, personal interviews, and glucose tolerance testing 2 hours after oral administration of 75 grams of glucose.

Of the 1,035 women initially enrolled, 25 were excluded from the study because they either had DM 6–9 weeks after delivery or delivered a baby before 35 weeks of pregnancy. Out of the remaining 1,010 women who delivered a baby after 35 or more weeks of pregnancy and did not have DM 6–9 weeks after delivery, the researchers were able to follow 959 (95%) for up to 2 years, and 113 (11.8%) of them were noted to have developed DM during the course of this time.

Data were analyzed using advanced statistical methods, including regression analysis, to examine the independent association of different levels and durations of breastfeeding with the incidence of DM after adjusting for potential confounding factors such as age, race, and weight.

*Crude* incidence rate of Type 2 DM within 2 years of follow-up of women with GDM by lactation intensity groups at 6 to 9 weeks after delivery showed that women in the “exclusively formula milk” group had an incidence rate of 8.79 per 1,000 person-months of follow-up, those in the “mostly formula milk” group had an incidence rate of 6.47, those in “mostly lactation” group had an incidence rate of 4.88, and those in the “exclusively lactation” group had an incidence rate of 3.95 per 1,000 person-months of follow-up. [**TABLE 14.14**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#ch14-tab14) shows lactation intensity groups 6–9 weeks after delivery and adjusted hazard ratios (representing the risk of DM) of the incidence of DM within the 2-year follow-up period among women who had GDM during pregnancy.

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| **TABLE 14.14** Lactation Intensity Groups 6–9 Weeks After Delivery and Adjusted Hazard Ratios of the Incidence of Diabetes Mellitus Within the 2-Year Follow-Up Period Among Women Who Had Gestational Diabetes During Pregnancy |
| A table depicts the lactation intensity groups.  In the table, the column header reads: Types of the regression model and Adjusted hazard ratio of Incidence of diabetes Mellitus Within 2 years of follow-up by lactation Intensity. The second column header is divided into "Exclusively Formula n equals 153, (95 percent CI asterisk), Mostly Formula and Inconsistent Lactation n equals 214, (95 percent CI asterisk), Mostly Lactation n equals 387, (95 percent CI asterisk), and Exclusively Lactation n equals 205, (95% CI asterisk). The rows read as follows. Age-adjusted, 1.00 (reference group), 0.72 (0.43 to 1.23), 0.54 (0.33 to 0.89) 0.43 (0.23 to 0.82); Maternal risk factors (A), 1.00 (reference group) 0.64 (0.37 to 1.12), 0.54 (0.32 to 0.92) 0.46 (0.24 to 0.88). A + newborn outcomes (B), 1.00 (reference group), 0.65 (0.37 to 1.13) 0.53 (0.31 to 0.91), 0.47 (0.25 to 0.91). A + B + postpartum lifestyle, 1.00 (reference group), 0.66 (0.38 to 1.14), 0.56 (0.32 to 0.95), 0.48 (0.25 to 0.92). Asterisk represents 95% confidence interval. |

**Questions**

**Question 1.** What research question was addressed in this study, or what hypothesis was tested?

**Question 2.** Why are incidence rates of DM in this study reported per 1,000 person-months rather than per 100 or per 1,000 women, and what does person-months mean?

**Question 3.** What do hazard ratios in [**Table 14.14**](https://jigsaw.vitalsource.com/books/9781284174403/epub/EPUB/xhtml/20_Chapter14_14.xhtml#ch14-tab14) indicate? Are these results statistically significant? Explain your answer with the help of data from the table.

**Question 4.** Why in this study were the estimates of the health outcome (DM) statistically adjusted for variables such as age, maternal risk factors, neonatal outcomes, and postpartum maternal lifestyle?