

Observational Study Design

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Summary

Much can be learned about a process by observing changes over time or by comparing two different processes under different conditions. This chapter introduces the major types of observational study designs: the longitudinal or cohort study, the comparative or case-control study, and some of their variants. It also includes examples of the key measures of relationship between factor and outcome in observational studies, the relative risk and the odds ratio. The similarity of the two measures for low incidence outcomes is illustrated, as is the use of attributable risk to assess how much of a binary outcome is due to a single factor.

Key Words: Case-control study; cohort study; cross-sectional study; matched studies; odds ratio; propensity score; prospective cohort; recall bias; retrospective cohort.

1. Introduction

Observational studies are an alternative to experimental studies. An observational study is sometimes termed a *natural experiment*. Instead of being randomized into one group or another to ensure statistical balance, subjects are classified into groups either by the *presence of an exposure*, which is called a *cohort study*, or the *presence or absence of a disease*, which is called a *case-control study*. A subject could be a cell, a bacteria, a specific cell line, a pond of environmental interest, a rat, or a person.

Some examples of the different types of groupings that are used in observational studies are

- Cohort studies (retrospective): having been exposed to asbestos in the workplace or not (or at different levels of asbestos exposure) with lung cancer as the outcome; growing up in an area with high fluoride water compared with growing up in an

area without much fluoride in the water with dental caries as an outcome; comparing the outcomes of two different treatments for acne based on a registry of clinic patients in the past 5 years; or evaluating the effect of childhood obesity on diabetes using records from 10 years of a pediatric practice.

- Cohort studies (prospective): choosing to smoke or not to smoke with the outcome being the development of lung cancer, emphysema, or heart disease; being part of an ecosystem that is high in volatile organic compounds (VOCs) compared with an ecosystem that is low in VOCs with the outcome being survival of a flora or fauna species; determining whether the apple- or pear-shaped body type (phenotype) leads to an increase in the development of heart disease, hypertension, or diabetes.
- Case-control studies: being part of a group that develops a disease such as lung cancer compared with members of the group that do not develop the disease; comparing HIV polymerase chain inhibitor-resistant HIV to nonresistant HIV in order to identify characteristics differentiating the two groups; comparing patients who have a new highly virulent infectious disease of unknown etiology to subjects without the disease but living in the same neighborhood to identify factors associated with the etiology or cause of the disease; or comparing the results of a microarray analysis applied to cells from cancer patients and noncancer patients or a microarray analysis applied to normal cells and cancer cells from the same subjects.
- Case-control (genetic association) studies: using cases that have high blood levels of methotrexate compared with controls that have low blood levels of methotrexate to identify which alleles of CYP2E1, an enzyme that affects the rate of metabolism of various compounds, relate to this phenotype; comparing severe chronic asthma (cases) to normal children of the same age, gender, and ethnicity to identify genes (or markers) that are associated with the disease; taking blood samples from cases and controls and either using a candidate gene approach or doing a genome-wide scan (1,2).

The term *subjects* could represent persons, animals, bacteria, or any other kind of experimental unit.

Because the groups in an observational study are *not randomized*, they are not necessarily equivalent for many other factors that in fact may be the real cause of the difference or may be promoters or antagonists of the effect being studied. For example, in a study comparing lung cancer patients and patients without lung cancer, the patients may be representative of different lifestyles so that many risk factors appear to differ between the groups. For example, some patients could belong to a different socioeconomic class that is exposed to some occupational risk factor that differs from the noncancer group but has no relationship to the disease process. A risk factor like this is a potential *confounder* of the relationship. A confounder is a variable that hides either a relationship or a variable that makes a relationship appear strong when it is not.

Risk in an observational study is often stated in terms of the *relative risk* of developing a characteristic based on exposure. If 3 out of 10 mammalian cell cultures exposed to ultraviolet (UV) radiation developed chromosomal abnormalities while 9 out of 10 mammalian cell cultures developed chromosomal abnormalities when exposed to UV radiation plus a common NSAID (nonsteroidal anti-inflammatory drug), then the relative risk (RR) of developing chromosomal abnormalities due to NSAID exposure (in the UV test system) is

$$RR = \frac{9/10}{3/10} = 3.0.$$

In a study where entities are followed over time, the relative risk is expressed in terms of the time period. For example, suppose 5% of sunbathers develop skin lesions in a year if they use a sunblock of SPF 30 or more, and 10% of sunbathers develop skin lesions in a year if they use a sunblock of only SPF 5. The relative risk of developing skin lesions in a year for using a low-value SPF sunscreen is

$$RR = \frac{10\% \text{ per year}}{5\% \text{ per year}} = 2.0.$$

Another way of expressing this is that the *protective* effect of using a high-number SPF sunscreen versus a low-number SPF sunscreen is

$$RR = \frac{5\% \text{ per year}}{10\% \text{ per year}} = 0.5,$$

and sunbathers are only half as likely to develop skin lesions. In **Section 6** of this chapter, we will discuss relative risk in more detail, as well as other measures of risk such as the odds ratio.

2. Cohort Studies

A cohort study is one where two or more groups of subjects are followed over time to see if they develop some disease or if some event occurs. In an exposure study (occupational or environmental), the effect of exposure on multiple outcomes—death, cancer, heart disease—can be observed. There are two types of cohort studies: prospective and retrospective.

2.1. Prospective Cohort Studies

Prospective cohort studies (also known as follow-up studies) follow groups of cells, animals, or patients with different exposures until some point in time where something happens or the study is terminated (3). Usually the outcomes of interest (e.g., death) are specified at the start of the study.

Example: A Prospective Cohort Study

In the British Physician study, a prospective study of smoking, 34,439 male British doctors were invited to participate in a study on the effects of smoking (5). Initially, there were two groups, smokers and nonsmokers. Eventually, a third group, those who quit smoking, was followed for 10 years, then 20 years (6), and recently the 50-year follow-up was reported (7). They were followed to observe what diseases would develop related to smoking status. The risk of lung cancer for smokers was 2.49/1000, whereas the risk of lung cancer for nonsmokers was 0.17/1000. Thus the relative risk of lung cancer for smokers over a 50-year period is

$$RR = \frac{2.49/1000}{0.17/1000} = 14.7.$$

In the same study, the risk of dying from ischemic heart disease (IHD) in smokers was 10.1/1000, and the risk of IHD in nonsmokers was 6.49/1000, giving an RR for IHD in smokers versus nonsmokers of

$$RR = \frac{10.1/1000}{6.49/1000} = 1.56.$$

The rarity of lung cancer deaths is the reason that smoking has such an effect on lung cancer. Indeed, we can quantitate how much of the lung cancer mortality is due to smoking by examining the difference in the risk in the smokers. This is called attributable risk (AR) and is a measure of how much of the condition, problem or disease is due to the risk factor.

$$\begin{aligned} AR &= \frac{\text{Lung cancer mortality due to smoking}}{\text{All lung cancer mortality}} \\ &= \frac{2.49/1000 - 0.17/1000}{2.49/1000} \times 100\% = 98.6\%. \end{aligned}$$

The same calculations give an attributable risk of 35.7% of the IHD mortality in the smokers due to smoking during the 50 years of follow-up.

2.2. Retrospective Cohort Studies

Retrospective cohort studies use historical data to make comparisons based on risk factors or exposures that occurred prior to the event. Historical records of snowfall in different continents can be used to study the effects of global warming. Historical records of bacterial prevalence in different hospitals can be used to study the effects of frequent antibiotic use. Patient records can be used to compare the effect of different treatments. Retrospective cohort designs

may also use historical data from prospective cohort studies. For example, the Framingham Heart Study (8,9) examined the effects of different partitions of the risk factors. Retrospective cohort analyses can be facilitated if the initial design of the cohort study recruits not just 1000 smokers and 1000 nonsmokers but 2000 subjects some of whom will be smokers and some of whom will be nonsmokers. Alternatively, the nonsmoking group can be studied by itself in retrospective cohort studies to examine the effect of other risk factors independent of smoking.

2.3. Analysis of Cohort Studies

Cohort studies are not subject to recall bias (defined as differential recollection of exposure because of the presence of the condition or disease) because the outcome occurs after entry to the study. However, in retrospective cohort studies, missing values for a factor that was not originally one of the primary risk factors can be a severe problem. The term *missing completely at random* means that the probability of an observation being missing does not depend on the observed or unobserved measurements. This type of missing value only affects the magnitude of the effect that the study can detect. Other types of missing values can affect the validity of the estimated risk. For example, if subjects die from a treatment effect that is not one of the primary outcomes (e.g., being hit by a car because of disorientation caused by the treatment), disease-specific mortality will be significantly biased, but all causes of mortality will not be biased (see also **Chapter 17**).

The presence of differences between the groups when the study was started is a problem with either type of cohort study. A study may show that exercise was a protective risk factor against heart disease, but it may be that the entire lifestyle is protective with regular exercise the best indicator for that protective lifestyle. Thus, when analyses of cohort data are performed, methods that group risk factors into similar classes, such as propensity scores, may be used (10,11). Differences between groups at baseline can be adjusted for by stratification (i.e., putting like hospitals together for studies of bacterial flora or putting experiments performed by the same lab technician together when studying the effect of immunoglobulins on longitudinal measures of inflammation). Regression adjustment is another method for accounting for differences between groups and is discussed in **Chapter 9**.

3. Case-Control Studies

A case-control study compares the characteristics between two groups, usually one that has a condition or disease compared with one that does not have the condition or the disease (12). These characteristics are termed *risk*

factors for the development of the disease. Some of the risk factors will be related to the development of the disease, some of them will be due to the presence of the disease but not involved in the development of the disease, and some of them will be due to chance. Statistical analysis is used to assess the probability or odds of the risk factor being related to the disease or condition.

Usually, external evidence for a mechanism of the development of the disease is also used to discriminate risk factors for the development of the disease from markers of the disease presence (13). Often, a case-control study will be followed by a cohort study to test whether the disease or condition actually develops in subjects with the risk factor.

3.1. Odds Ratios

Because the number of cases and the number of controls is predetermined in a case-control study, the relative risk cannot be used (3). An alternative way of measuring risk is in terms of the *odds ratio*. The “odds of a disease given a risk factor” is the probability of having the disease with the factor divided by the probability of not having the disease with the factor present. Thus, if the probability is 0.20 or 1 in 5, the odds is $0.2/(1 - 0.2) = 0.2/0.8 = 0.25$. It is also described as 1 : 4 (read as 1 *to* 4 and interpreted as 1 event will occur for every 4 times it does not occur). This is the same type of odds that are given at a racetrack or for a sports team. The *odds ratio* is the ratio of the odds of the disease with the risk factor present divided by the odds of the disease with the risk factor absent. It is used in case-control studies because conditional probability arguments (12) can be used to show the computation of the odds ratio as the odds of the risk factor. For example, smoking, in lung cancer patients, divided by the odds of smoking in the controls is equivalent to the odds ratio for the disease given the risk factor.

For example, if the proportion of smokers in lung cancer patients is 1 in 10 and the proportion of smokers in controls is 1 in 100, the odds ratio (OR) for lung cancer given smoking is

$$\begin{aligned} \text{OR} &= \frac{\text{Odds of smokers in lung cancer}}{\text{Odds of smokers in controls}} = \frac{\left(\frac{1}{10}\right) / \left(\frac{9}{10}\right)}{\left(\frac{1}{100}\right) / \left(\frac{99}{100}\right)} \\ &= 11.0 = \text{OR of lung cancer in smokers.} \end{aligned}$$

If the condition or disease is rare, the odds ratio and the relative risk are almost the same (see **Section 6.2**).

3.2. Choice of Controls

The key design issue in a case-control study is the *choice of the controls*. To obtain an unbiased (correct or appropriate) estimate of the risk, the controls must be comparable with the cases for factors that are not related to the disease (or outcome). For example, in the study of endometrial cancer and estrogens (14), the controls were women from the same clinic, and some of them had bleeding problems related to exposure to estrogens. Thus the odds ratio was estimated as 1.7. When the controls were not chosen from the same clinic, the odds ratio was estimated as 11.98. Usually, a *community control* is necessary in addition to clinic controls to account for common factors in the controls and cases that may also be associated with the disease. One possibility for a community control is a friend of the same gender, who will most likely be similarly aged and of similar socioeconomic status. Another possibility for a community control is to use controls from the same block, the same census tract, or from within a 1-mile radius of the control. However, if the risk factor is environmental, choosing someone within a 1-mile radius may mean that the control is exposed to the same toxic substance. These same considerations must be taken into account if the study is of the number of mutations observed in a cell selected from ponds near an environmental source compared with ponds that are not near the environmental source. The control ponds must be comparable with the “case” ponds in terms of depth, surface area, and so forth.

Because many disease conditions are rare, one design option for a case-control study is to use 2 or 3 times as many controls as cases to compensate for the shortage of cases. When the disease condition is not rare, a design option to improve the sensitivity of the study is to use 2 or 3 times as many cases as controls so that the effect of a range of exposure to the risk factor in the cases can be compared with the controls.

3.3. Case-Control Genetic Association Studies

The case-control strategy has also been adapted to genetic studies of association. The goal is to either identify the heritability of a trait or to identify the gene or the marker of a gene that is associated with the phenotypic trait. Usually, “cases” represent the presence of some phenotype (e.g., hypertension, curly fruit fly wings, differential pharmacokinetic and pharmacodynamic response, or polymerase inhibitor resistance in the HIV retrovirus). In a genetic association study, the controls are chosen not to have that phenotype. However, the controls again need to be similar to the cases in general genetic background; otherwise false-positive genes will be identified because of admixture (differences between the groups that are unrelated to the outcome of interest). More on genetic association studies will be found in **Chapter 21**.

3.4. Matching and Case-Control Studies

In some studies, the controls are *matched* to the cases to eliminate confounders (e.g., age or gender) that can affect the presence of the disease but are not directly related to the development of the disease. For example, each control may be chosen to be within 2 years of age of the corresponding case. Evaluations of the effects of an intervention on two different cell lines would be done by the same lab technician or with the same batch of chemicals. Another type of matching often found in genetic studies is to match siblings that are specifically chosen to be either affected by the disease or unaffected by the disease. Environmental studies often match on nonenvironmental factors that may predispose to the disease. For example, one might match the cigarette smoking status of parents in a case-control study of leukemia due to exposure to power line radiation.

In another example of a case-control study using matching, researchers examined pemphigus foliaceus, which is an adolescent/early adult autoimmune disease that has both genetic susceptibility and suspected environmental risks (possible insect carriers, etc.). Both family controls and community controls were used in the study (15). The disease was studied in a remote Indian community in Brazil with one to four age-matched family controls over age 18 matched and one to five age-matched community controls. The goal was to be able to identify differences within the “house,” as well as differences in the location of the house, exposures by occupation, pets, different types of insects, and several other factors. Family controls were required to be over 18 to reduce the chance that they would become cases.

One disadvantage of matching by age is that it may be difficult or impossible to find controls close enough in age to participate in the study. Sometimes a group-matching strategy is used to approximately balance age without matching one-to-one.

Another disadvantage of matching is that it is possible to *overmatch* by choosing a matching variable that is part of the causal pathway of the disease or condition. Overmatching tends to mask the relationship between the risk factor and the disease. For example, if obesity causes hypertension, which causes strokes, then matching on hypertension status would be overmatching because it would be removing part of the effect of obesity on strokes.

3.5. Biases in Case-Control Studies

In a case-control study, *selection bias* refers to the problem that people who agree to participate in a study may be different from people who do not agree to participate. Sometimes the nonparticipants can be compared with the participants in terms of gender and age to test comparability of the participants and the

nonparticipants. An alternative is to use a *capture-recapture* strategy by acquiring data from a separate registry to characterize cases with the condition (16).

Unlike cohort studies, case-control studies are subject to *recall bias*. Recall bias refers to differential recall between the cases and the controls about exposure to the risk factor(s). For example, a questionnaire survey of mothers of babies with birth defects will likely recover much more detail on exposure compared with mothers of normal children. In some cases, access to the medical records will allow equal ascertainment of the exposure if the medical records are complete enough to have the information.

3.6. Cross-Sectional Studies

The *cross-sectional* study design is a unique kind of case-control study. This type of design is used if cases cannot be identified a priori or if the prevalence of the disease or condition needs to be determined. Subjects are sampled randomly and then classified according to whether or not they have the condition. From this point on, everything proceeds as if the study were a typical case-control study. Even the odds ratio can be determined from prevalence data, called the prevalence odds ratio. An example of a cross-sectional study is drawing blood samples from a population of interest and then cross-classifying them by biochemical or genetic markers after assays have been performed on the blood.

4. Outcomes

Outcomes in an observational study depend on the type of study. In a case-control study, the “disease” outcome is binary (present or absent) or ordinal (healthy, preclinical, clinical, and advanced). If the outcome is ordinal, the relationship is usually examined by comparing two states at a time.

Several types of outcomes are possible in a cohort study. As with a case-control study, the outcome may be binary. For example, the grouping factors may be smokers and nonsmokers and the outcome is the development of cardiovascular disease. If the key outcome is rare, like lung cancer, the study may need to be much larger to have sufficient disease events to allow comparisons of the two groups (see **Chapter 14** and **Chapter 19**). The outcome variable(s) also usually includes the binary disease event and the time to occurrence of the disease. In this case, survival analysis statistical methods are used (see **Chapter 15**).

Outcomes in a cohort study may also be continuous. For example, a cohort study may look at the level of PSA (prostate-specific antigen) or a lung function measure. The advantage of this type of study is that changes may be detected before they are irreversible.

The outcome of a cohort study may also be a counting variable, such as the number of genetic abnormalities (breaks in the chromosomes). For example, in a study of the effect of human growth hormone (HGH) in children of very small stature compared with normal-height children, a retrospective cohort study was used with the outcome being a count of the number of chromosomal defects (17).

Each type of outcome requires a different type of statistical analysis: logistic analysis or survival analysis for binary data (see **Chapter 14** and **Chapter 15**, respectively), Poisson regression for counts of the number of events (3), and mixed model regression and analysis of variance (see **Chapter 11**) for continuous observations over time. When the outcomes are continuous, the effect of a discrete risk factor may be expressed as a difference in means. If the risk factor is continuous, it may be expressed as a correlation.

5. More on Odds Ratios and Relative Risks

5.1. Relative Risks

If the outcome is binary, then the probability of the event occurring is based on some risk factor being present. This is more often presented in terms of a *relative risk*: the ratio of the probability of the event with the factor present compared with (divided by) the probability of the event occurring with the factor absent. In general, the relative risk requires a time frame for the event to occur (e.g., a month, a year, 10 years). A secondary infection from someone who has a cold may only take a few days to develop, whereas the development of emphysema from cigarette smoking may take decades. Another example might be the probability of an anticancer drug achieving a 95% in vitro effective reduction of cancer cell activity. Clearly, in this case the probability of the drug being effective depends on the individual cell response.

Usually, relative risk is determined for two different levels of the risk factor. If the risk factor is continuous, the two levels must be chosen. For example, use the level of exposure to cotton dust in a cotton processing plant; the levels might be chosen to be $10\mu\text{g}\cdot\text{ms}/\text{m}^3$ and $200\mu\text{g}\cdot\text{ms}/\text{m}^3$ (a level that equals the National Institute of Occupational Safety and Health level of permissible exposure). The relative risk of a $200\mu\text{g}\cdot\text{ms}/\text{m}^3$ compared with a $10\mu\text{g}\cdot\text{ms}/\text{m}^3$ exposure, if the coefficient of the odds ratio per $\mu\text{g}\cdot\text{ms}/\text{m}^3$ is 0.00346 from a logistic regression (see **Chapter 14**), is

$$\text{RR} = \exp[0.00346 \times (200 - 10)] = 1.93.$$

If the variable were age, the choice of the two levels is often a decade apart. If the risk factor were discrete, for example, such as managers, foremen, and

weavers in the cotton processing plant, the relative risk is determined pairwise. For example, if the risk of byssinosis (disease of the lungs caused by inhalation of cotton dust or dusts from other vegetable fibers) in a 5-year period is 3% for managers, 15% for foremen, and 30% for weavers, the relative risk of byssinosis of weavers to managers is $30\% \div 3\% = 10.0$, for weavers to foremen is $30\% \div 15\% = 2.0$, and for foremen to managers is $15\% \div 3\% = 5.0$.

5.2. Odds Ratios

As discussed earlier, an alternative way of measuring risk is in terms of the odds ratio. To compare relative risk and the odds ratio, suppose the incidence of lung cancer in smokers is 1/1000 in a 5-year period and 1/10,000 in non-smokers in the same time period. Then the relative risk is

$$RR = \frac{1/1000}{1/10,000} = 10.0.$$

The odds for smokers is $1/999 = (1/1000) / (999/1000)$ and the odds for the nonsmokers is $1/9999$; thus the odds ratio is

$$OR = \frac{1/999}{1/9999} = 10.01.$$

If the disease is rare, the odds ratio is essentially the relative risk (**12**). If the disease is common, for example, 1/10 of children have colds compared with 1/100 adults, the relative risk is 1/10 divided by 1/100 = 10.00. However, the odds for children is 1/9 and for adults is 1/99, which gives an odds ratio of $99/9 = 11$. Most diseases are rare in the population as a whole but may not be rare in a high-risk subgroup. For example, recurrence of breast cancer may be common in women who originally had breast cancer.

One advantage to using the odds ratio is the ability to calculate the odds ratio of *not* getting the disease given the risk factor. This is calculated as $1/\{\text{odds ratio of getting the disease given the risk factor}\}$. For example, if the odds of heart disease given a good exercise program is 0.5, the odds of not getting heart disease with a good exercise program is $1/0.5 = 2.0$. Using the odds ratio also gives us the ability to determine the odds ratio of getting the disease with the risk factor *not* present. This is calculated as $1/\{\text{odds ratio of getting the disease given the risk factor}\}$. For example, if the odds ratio of heart disease in a non-smoker is 0.4, then the OR in a smoker is $1/0.4 = 2.5$. A final advantage is that the odds ratio can be computed from a case-control study even though the relative risk cannot (**12**). Using the odds ratio rather than the relative risk makes it easier to describe the relationship between the risk factor and the disease. In addition, the coefficients of many of the regression models—logistic, Poisson,

and proportional hazards regression analysis—can be directly interpreted in terms of the odds ratio (see **Chapter 14** and **Chapter 15**).

6. Conclusion

Observational studies are useful when randomization cannot be used to divide exposure into groups. Observational designs can also be used to compare factors when the groups are defined by the values of the outcome. Observational studies are not a replacement for randomized designs but allow formulation and testing of hypotheses in cases where experimental interventions are not possible. Experimental interventions are not possible when the characteristics of interest are innate parts of the experimental units or when using historical data. Each type of observational study—cohort and case control—can be used to characterize abnormal versus normal cells, mutant versus wild genes, or diseased versus nondiseased patients.

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