Comments, Opinions, and Reviews

Assessing Bias in Case–Control Studies

Proper Selection of Cases and Controls

Kim Sutton-Tyrrell, DrPH

Case–control studies are retrospective investigations in which a diseased group (cases) and a disease-free group (controls) are compared with the aim of uncovering risk factors that differ between the groups. Many times, cause–effect relationships between the risk factor and disease are inferred from the results. Many important risk factors have been identified through the use of a case–control design, including the relationship of smoking to lung cancer, the use of tampons and toxic shock syndrome, and the link between vaginal cancer and maternal use of diethylstilbestrol.

Case–control studies can be executed quickly and at a relatively low cost, even when the disease of interest is rare. Such advantages have made the case–control design popular, resulting in a progressive increase in its use.[1] The validity of a case–control study, however, is dependent on representative selection of both the case and control groups.[2] Overrepresentation or underrepresentation of either of these groups in the study sample results in a systematic error referred to as bias. Bias can cause an inaccurate assessment of the relationship between the risk factor and the disease.

Although all studies can be affected by bias, case–control studies are particularly susceptible because of the retrospective nature of the data and the resulting lack of control the investigator has over many items of interest. Case–control studies done in a clinical setting are even further prone to bias because the factors that bring patients to the clinical setting are often related to the disease or risk factor of interest. Investigators who embark on case–control studies must maintain a constant awareness of sources of potential bias that could result in invalid conclusions from the study data. This can be a difficult task because of the numerous and insidious ways that bias can exist.[1] The purpose of this paper is to illustrate how bias can result from improper selection of study patients. Specific types of bias illustrated are those particularly applicable to clinically based research.

From the Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pa.

Address for correspondence: Kim Sutton-Tyrrell, DrPH, Department of Epidemiology, University of Pittsburgh, 127 Parran Hall, 130 De Soto Street, Pittsburgh, PA 15261.

Review of the Odds Ratio

A case–control study is usually evaluated using the 2×2 table, shown in Figure 1. Case and control groups are considered either "exposed" or "unexposed," depending on whether or not the risk factor of interest is present. Using this table, one can compare the odds of disease in the exposed group (A/B) to the odds of disease in the unexposed group (C/D) to obtain the odds ratio (A/B)/(C/D). The odds ratio is most easily calculated using the algebraically equivalent formula (AD)/(BC).[3]

The odds ratio measures the strength of the association between a risk factor (exposure) and disease. A value of >1 indicates that the odds of disease are greater when exposed to the specified risk factor. For example, the interpretation of an odds ratio of 2.0 is that the odds of disease in the exposed group are two times the odds of disease in the control group. An odds ratio of <1 indicates reduced odds of disease with exposure to the risk factor, in other words, a protective effect of the exposure. A value of 1 indicates no association between exposure and disease.

The following examples illustrate how bias in the selection of cases and controls can affect the odds ratio and, hence, the conclusions of the study.

Types of Bias

Referral Bias

Referral bias occurs when the referral patterns specific to a community cause an overrepresentation or underrepresentation of exposed cases in the hospital population as compared to the general population. For referral bias to occur, referral patterns must be related to the exposure of interest. To illustrate this point, consider the following example, which is diagrammed in Figure 2.

In a defined community, patients who have diabetes have a 1.9 times greater chance of developing stroke than patients without diabetes. This community has two major hospitals, A and B. A prominent physician who specializes in the treatment and rehabilitation of diabetic patients who have suffered stroke is employed by Hospital A. Aware of the reputation of this specialist, physicians in the community refer most of their diabetic patients who manifest symptoms of stroke to Hospital A. Patients without a history of diabetes who present with stroke

Downloaded from http://ahajournals.org by on December 28, 2022

	Cases	Controls
Exposed	A Exposed Cases	B Exposed Controls
Unexposed	C Unexposed Cases	D Unexposed Controls

FIGURE 1. *Traditional 2×2 table used in the interpretation of a case-control study. From this table, the odds ratio is easily calculated using the formula AD/BC.*

and patients with diabetes who present with other health problems are referred to Hospitals A and B with equal frequency.

The specialist at Hospital A has attracted other physicians and researchers who are interested in studying stroke in diabetic patients. One investigator initiates a case–control study to assess the importance of diabetes as a risk factor for stroke. For cases, the investigator chooses all patients who are admitted to Hospital A with a diagnosis of first stroke over a period of 1 year. For controls, the investigator chooses all patients admitted to Hospital A with a diagnosis other than stroke over the same period. For each subject, the investigator identifies whether or not a history of diabetes was present before admission. The resulting data (Figure 2) lead the investigator to conclude that the odds of developing stroke for a patient with diabetes are 3.2 times that for patients without diabetes.

If this researcher were to perform an identical study at Hospital B, he would be disturbed to find an odds ratio of 0.6, indicating a protective effect of diabetes in the development of stroke. Neither of these conclusions is valid because in both cases, the data are biased by the referral patterns in this community. The sample from Hospital A contains an overrepresentation of exposed cases, whereas the sample from Hospital B contains an underrepresentation of exposed cases. A prudent investigator could pool data from both hospitals to come up with an unbiased estimate of the relationship between diabetes and stroke.

Ascertainment Bias

Ascertainment bias occurs when there is inaccurate ascertainment of either the disease or exposure of interest. Case–control studies that rely on chart review for study data are particularly susceptible to this type of bias because the investigator has no control over how the disease and exposure variables are ascertained and recorded in the patient chart. Figure 3 illustrates the following example.

In a general population, if both the presence of a carotid bruit and the occurrence of transient ischemic attack (TIA) are ascertained with perfect accuracy, the odds of TIA among patients with a bruit are 1.6 times that of patients without a bruit. In Hospital A, interns are required to auscultate for carotid bruits as part of a standard history and physical performed on all admitted patients. Because the history is completed before the physical, the intern knows the presenting symptoms of the patient before he or she listens for bruits. In patients who present with symptoms of cerebral ischemia, the interns listen very carefully, and if a bruit is present, it is correctly diagnosed 90% of the time. In patients with symptoms of ischemia who do not have a bruit, a false positive diagnosis of bruit is made 15% of the time. The presence of bruit is less aggressively sought in patients without symptoms of cerebral ischemia, however, and a bruit is correctly diagnosed only 60% of the time. A false positive diagnosis of bruit is never made in patients without symptoms of cerebral ischemia.

An investigator at Hospital A decides to evaluate the relationship between carotid bruit and TIA using a case-control study. All patients admitted to Hospital A with a diagnosis of first TIA over a 3-month period are selected as cases. A random sample of patients admitted over the same period with a diag-

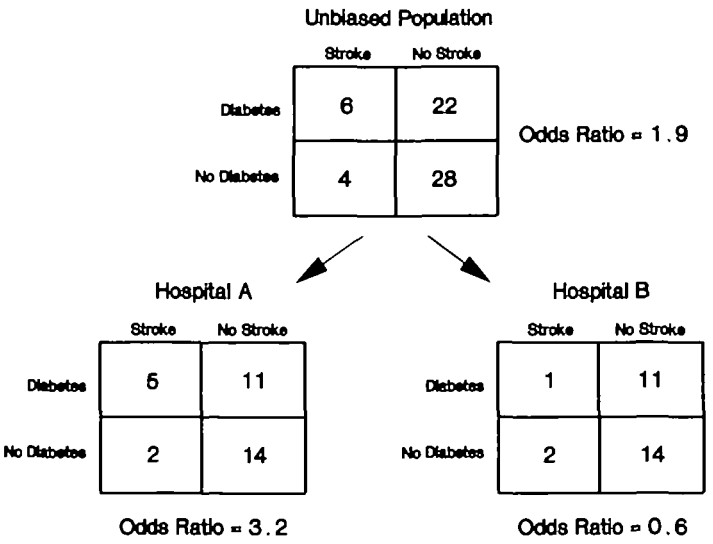

FIGURE 2. *Referral bias. Referral patterns specific to a community can cause overrepresentation or underrepresentation of exposed cases in a hospitalized population. This type of bias can be avoided by pooling results across hospitals.*

Downloaded from http://ahajournals.org by on December 28, 2022

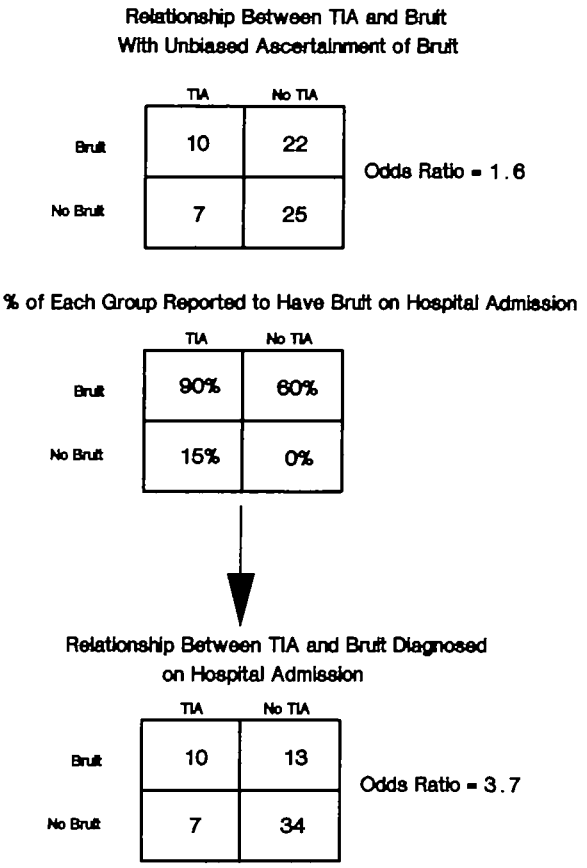

FIGURE 3. *Ascertainment bias. Incomplete ascertainment of the risk factor of interest can result in underrepresentation of exposed patients in the control group. To avoid this type of bias, the risk factor of interest must be sought with equal vigor in both the case and control populations. Note: Numbers in the bottom table result after taking into account true positive, false positive, true negative, and false negative results. Cell A results from nine true positives plus one false positive; cell B results from 13 true positives plus zero false positives; cell C results from six true negatives plus one false negative; cell D results from 25 true negatives plus nine false negatives. TIA, transient ischemic attack.*

nosis other than stroke or TIA are selected as controls. Patients with a history of stroke or TIA are excluded. For all study patients, the standard physical the intern performs at admission is reviewed to obtain data on the presence or absence of a carotid bruit. The results of this study indicate that the odds of TIA are 3.7 times higher among patients with a carotid bruit than among patients without a carotid bruit.

This overestimate of the true odds ratio occurred because of bias in the ascertainment of bruit, which resulted in an underrepresentation of exposed patients in the control group. A similar spurious increase in the odds ratio could occur if there were a bias in the ascertainment of TIA. Consider the following scenario.

In this same population, patients with known carotid bruits receive education about the symptoms of cerebral ischemia and are told to report immediately to the hospital if such symptoms occur. Thus, in the group with carotid bruits, patients experiencing TIA are hospitalized almost 100% of the time. Patients without bruits, however, receive no such warnings, and consequently 40% of the time they fail to even report TIA symptoms to their physician. If symptoms are reported, it may be months later, and hospitalization never occurs. Ascertainment bias would result in a hospital-based case–control study because there would be an underrepresentation of unexposed cases in the sample.

To avoid ascertainment bias, the investigator must make sure that both the exposure and disease of interest are sought with equal vigor in both the case and control populations. If the investigator does not have direct control over ascertainment, then selecting patients on the basis of the biasing factor can be done. In the above example, bias in the ascertainment of TIA could be eliminated by selecting for study only patients without a known carotid bruit before hospital admission. Both exposed and unexposed cases then would have an equal probability of having their TIA diagnosed at hospital admission.

Berkson Bias

Berkson bias, also called admission rate bias, was first described in 1946.[4] The concept underlying this bias is that patients with more than one disease or condition are more likely to be hospitalized than patients with only one disease or condition. If a case–control study is exploring the relationship between two diseases, this bias can cause an overestimation of exposed cases in the hospital population. Figure 4 illustrates the following example.

In a defined population of 160 people, 10 people develop both stroke and some form of cancer, 30 people develop cancer alone, 30 people develop stroke alone, and 90 people develop neither disease. If one were to evaluate the relationship of cancer and stroke in this population, the odds ratio would be 1.0, indicating no association. At a given point in time, the hospitalization rates for each of the four groups are as follows: 50% for those with both a history of stroke and cancer, 10% for those with only one of the two diseases, and 5% for those with neither disease.

A neurologist working in Hospital A notices during her rounds that many of her patients who have suffered stroke also have a history of some form of cancer. To determine whether there is a relationship between stroke and cancer, the neurologist decides to conduct a case–control study. As cases, the neurologist chooses all patients on the medical service who have a history of stroke. As controls, she chooses all patients on the medical service who do not have a history of stroke. The charts then are reviewed for a history of any form of cancer. The results of the study (Figure 4) lead the neurologist to conclude that for patients with cancer, the odds of also having a stroke are 2.8 times higher for patients with cancer than for patients without cancer. But this conclusion is invalid

Downloaded from http://ahajournals.org by on December 28, 2022

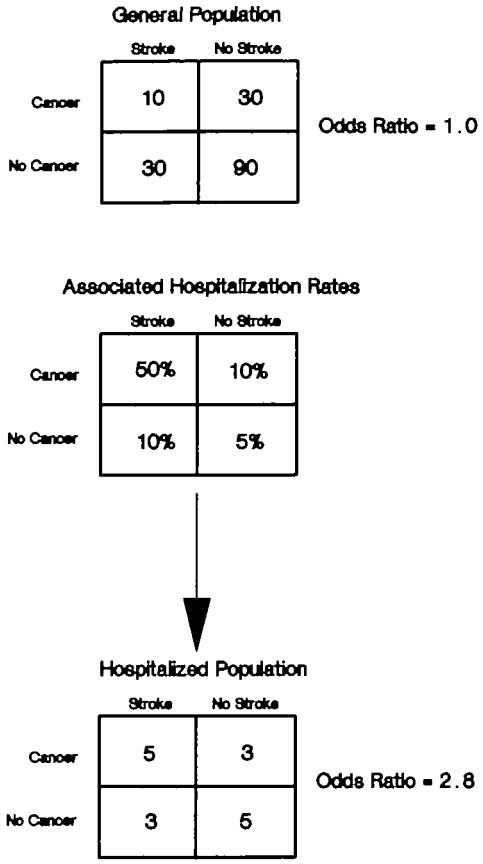

FIGURE 4. *Berkson bias. Patients with more than one disease or condition are more likely to be hospitalized than patients with only one condition. This can cause overrepresentation of exposed cases in a hospitalized population when the exposure of interest is another disease. Berkson bias can be avoided by limiting all study subjects to those with a certain number of major conditions.*

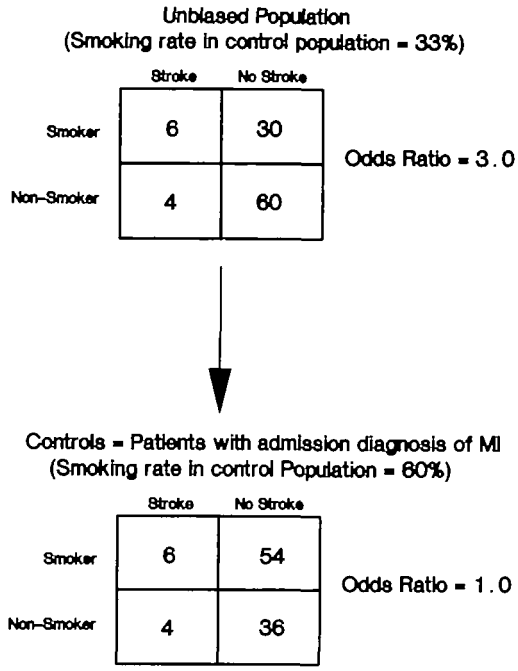

FIGURE 5. *Hospital control bias. If the disease among the control group is related to the exposure of interest, then an overrepresentation of exposed controls can result. This type of bias can be prevented by selecting patients with a variety of admission diagnoses for use as controls. MI, myocardial infarction.*

because the group of patients with both cancer and stroke (the exposed cases) were overrepresented in the study population. Patients with both diseases were more likely to be hospitalized and thus chosen for study than patients with only one or neither disease.

If the investigator had understood Berkson bias, she could have designed her study to avoid this bias by selecting for study only patients with two major health problems. This would cause the hospitalization rates to be approximately equal for the exposed, unexposed, case, and control groups. The investigator then would have found that cancer occurs just as often among patients with other major illnesses as among those with stroke.

Hospital Control Bias

For hospitalized patients to be an adequate control group, the disease that resulted in hospitalization cannot be related to the exposure of interest. If the prevalence of the exposure is higher in the control group than in the general population, then a true relationship between the exposure and the disease of interest could be masked. Likewise, if the exposure is protective against the disease causing hospitalization of the control group, then the relationship could be spuriously increased. Figure 5 illustrates the following example of hospital control bias.

Suppose that in the general population the odds of suffering stroke are three times higher in smokers than nonsmokers, and the smoking rate among those who do not develop stroke is 33%. An investigator working in Hospital A wishes to investigate the relationship between smoking and stroke and decides to do a case–control study. As cases, the investigator chooses all patients admitted to Hospital A with a diagnosis of embolic stroke over a 3-month period. As controls, he selects all patients admitted with a diagnosis of myocardial infarction over the same period. The results of this study yield an odds ratio of 1.0, and the investigator concludes that there is no relationship between smoking and embolic stroke.

Invalid results were obtained in this case because the exposure (smoking) was associated with both the disease of interest (embolic stroke) and the disease causing hospitalization in the control group (myocardial infarction). This caused an overrepresentation of exposed patients in the control group. The investigator should have chosen a control group that had a smoking rate comparable to the general population. This error may seem obvious because of the well-known association between smoking and myocardial infarction. The real problem manifests itself when

Downloaded from http://ahajournals.org by on December 28, 2022

the association between the exposure and the disease among the control group is unsuspected. One way to guard against this type of bias would be to select a control group from hospitalized patients with a variety of different conditions.

Consequences When Bias Goes Unrecognized

In 1929 Raymond Pearl, a noted professor at Johns Hopkins University, published results of a case–control study that revealed a strong negative correlation between evidence of cancer at autopsy and the presence of active tuberculous lesions.[5] Cases were patients autopsied in the Johns Hopkins Hospital and found to have a malignant tumor. Control patients without malignant tumors on autopsy were age-, sex-, and race-matched to the cases. Active tuberculous lesions were found in 16% of patients without malignant tumors but in only 7% of patients with malignant tumors. Pearl thus concluded that "there is a definite and marked incompatibility or antagonism between the two diseases, cancer and tuberculosis."[5] Researchers at Johns Hopkins were so impressed by these findings that they began treating terminal cancer patients with tuberculin and published preliminary results in the *Lancet*.[6] Elation over a cure for cancer was short-lived, however, as it was soon discovered that this case–control study suffered from bias that invalidated the results. The study sample contained an overrepresentation of exposed controls (many control subjects had died from tuberculosis), causing a spurious negative correlation between cancer and tuberculosis. When the study was replicated using a representative control group (patients who died from heart disease), the prevalence of tuberculous lesions was found to be the same in both cancer and control groups.[7] Pearl then was obligated to publish a retraction, which appeared in *Science*.[8] Thus, failure to select a proper control group and failure to identify the resulting bias led to a major embarrassment for Pearl, as well as the journals in which his initial papers were published. Pearl subsequently lost a prestigious appointment to Harvard, and funding for his Institute of Biological Research was not renewed.[9]

Concluding Comments

Bias can produce spurious associations as well as mask true associations, leading to invalid study conclusions. The process of recognizing bias can be difficult and has been described as an intuitive process rather than an exact science.[10] This is because measures needed to prevent bias are often specific to the study circumstances. For example, the mechanism of subject selection appropriate for one study may be inappropriate for another.

Researchers must conduct an evaluation of potential bias during the design phase of a case–control study. If sources of potential bias are identified, then measures can be undertaken to control or eliminate them. If one waits until the data have been collected, there is often little one can do to repair the damage.

Although bias is a particular problem with case–control studies,[11,12] it can affect any type of research. Researchers must be trained to understand bias by reviewing examples and applying the concepts to different research scenarios. The alternative is for researchers to become victims of bias, as in the case of Professor Pearl. The Pearl example also underscores the importance of the editorial review process. This process must include reviewers who have an understanding of how bias can affect study results. Finally, the investigator or clinician reviewing the literature may also suffer consequences if the validity of published research is not continuously scrutinized. Thus, in the design and evaluation of case–control studies as well as all research, an awareness of bias is essential.

References

1. Sackett DL: Bias in analytic research. *J Chron Dis* 1979;32:51–63
2. Schlesselman JJ, Stolley PD: *Sources of Bias in Case-Control Studies.* New York, Oxford University Press, Inc, 1982, pp 125–143
3. Kahn HA, Sempos CT: Relative risk and odds ratio, in *Statistical Methods in Epidemiology.* New York, Oxford University Press, Inc, 1989, chap 3
4. Berkson J: Limitations of the application of fourfold tables to hospital data. *Biometrics Bull* 1946;2:47–53
5. Pearl R: Cancer and tuberculosis. *Am J Hyg* 1929;9:97–159
6. Pearl R, Sutton AC, Howard WT Jr: Experimental treatment of cancer with tuberculin. *Lancet* 1929;216:1078–1080
7. Carlson HA, Bell ET: A statistical study of the occurrence of cancer and tuberculosis in 11,195 post-mortem examinations. *J Cancer Res* 1929;13:126–135
8. Pearl R: Discussion: A note on the association of diseases. *Science* 1929;70:191–192
9. Fee E: *Disease and Discovery: A History of the Johns Hopkins School of Hygiene and Public Health.* Baltimore, Johns Hopkins University Press, 1987, pp 136–143
10. Feinstein AR: Methodologic problems and standards in case-control research. *J Chron Dis* 1979;32:35–41
11. Cornfield J, Haenszel W: Some aspects of retrospective studies. *J Chron Dis* 1960;11:523–534
12. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–748

KEY WORDS • case–control studies • selection bias

Downloaded from http://ahajournals.org by on December 28, 2022