Epidemiology series

Case-control studies: research in reverse

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Epidemiologists benefit greatly from having case-control study designs in their research armamentarium. Case-control studies can yield important scientific findings with relatively little time, money, and effort compared with other study designs. This seemingly quick road to research results entices many newly trained epidemiologists. Indeed, investigators implement case-control studies more frequently than any other analytical epidemiological study. Unfortunately, case-control designs also tend to be more susceptible to biases than other comparative studies. Although easier to do, they are also easier to do wrong. Five main notions guide investigators who do, or readers who assess, case-control studies. First, investigators must explicitly define the criteria for diagnosis of a case and any eligibility criteria used for selection. Second, controls should come from the same population as the cases, and their selection should be independent of the exposures of interest. Third, investigators should blind the data gatherers to the case or control status of participants or, if impossible, at least blind them to the main hypothesis of the study. Fourth, data gatherers need to be thoroughly trained to elicit exposure in a similar manner from cases and controls; they should use memory aids to facilitate and balance recall between cases and controls. Finally, investigators should address confounding in case-control studies, either in the design stage or with analytical techniques. Devotion of meticulous attention to these points enhances the validity of the results and bolsters the reader's confidence in the findings.

Case-control studies contribute greatly to the research toolbox of an epidemiologist. They embody the strengths and weaknesses of observational epidemiology. Moreover, epidemiologists use them to study a huge variety of associations. To show this variety, we searched PubMed for topics investigated with case-control studies (panel 1).[1–20] We identified diverse diseases and exposures, with outcomes ranging from earthquake deaths to racehorse injuries, and exposures ranging from pickled vegetables to pig farming.

The strength of case-control studies can be appreciated in early research done by investigators hoping to understand the cause of AIDS. Case-control studies identified risk groups—eg, homosexual men, intravenous drug users, and blood-transfusion recipients—and risk factors—eg, multiple sex partners, receptive anal intercourse in homosexual men, and not using condoms—for AIDS. Based on such studies, blood banks restricted high-risk individuals from donating blood, and educational programmes began to promote safer behaviours. As a result of these precautions, the speed of transmission of HIV-1 was greatly reduced, even before the virus had been identified.

By comparison with other study types, case-control studies can yield important findings in a relatively short time, and with relatively little money and effort. This apparently quick road to research results entices many newly trained epidemiologists. However, case-control studies tend to be more susceptible to biases than other analytical, epidemiological designs.[21] A notable friend of ours (David L Sackett, personal communication) told us that he would trust only six people in the world to do a proper case-control study. And, in his book, Rothman comments that: "because it need not be extremely expensive nor time-consuming to conduct a case-control study, many studies have been conducted by would-be investigators who lack even a rudimentary appreciation for epidemiologic principles. Occasionally such haphazard research can produce fruitful or even extremely important results, but often the results are wrong because basic research principles have been violated."[22]

Panel 1: **Examples of topics investigated with case-control studies**

Exposure	Outcome
Cat ownership in childhood	Schizophrenia, schizoaffective disorder, or bipolar disorder[1]
Body-mass index	Pancreatic cancer[2]
Physical disability	Earthquake mortality[3]
Hiatus hernia	Reflux oesophagitis[4]
Hair dyes	Connective tissue disorders[5]
History of shingles	Systemic lupus erythematosus[6]
Pig farming	Nipah virus infection[7]
Ghee (clarified butter) applied to umbilical cord stump	Neonatal tetanus[8]
Pickled vegetable consumption	Oesophageal cancer[9]
Turf running surface	Musculoskeletal injury in thoroughbred racehorses[10]
Digital rectal exam	Metastatic prostate cancer[11]
Statins for lipid lowering	Dementia[12]
Paracetamol use	Ovarian cancer[13]
Phyto-oestrogens	Breast cancer[14]
Overhead mirror at intersections	Forklift collision injuries[15]
Male condom use	Genital warts[16]
Physical activity	Ovarian cancer[17]
Sigmoidoscopy screening	Colon cancer[18]
Large doses of folate and iron in pregnancy	Microcephaly[19]
Influenza vaccination	Recurrent myocardial infarction[20]

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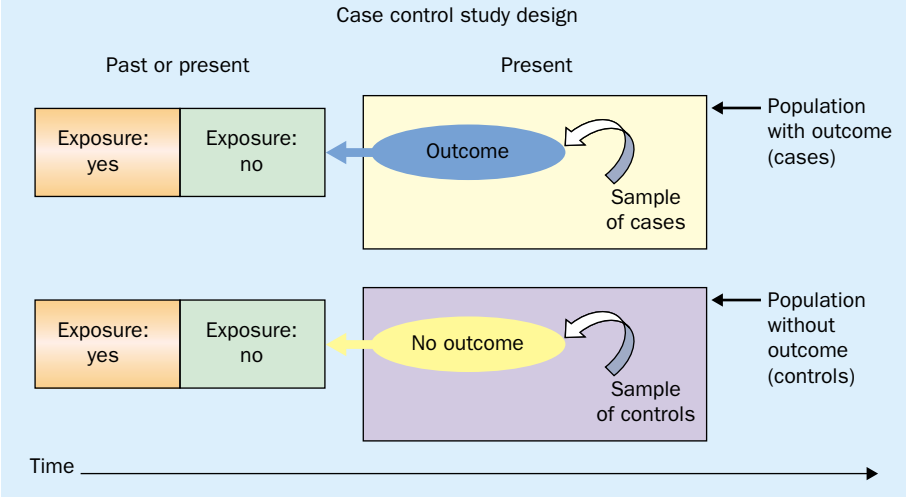
Basic case-control study design

Case-control designs might seem easy to understand, but many clinicians stumble over them. Because this type of study runs backwards by comparison with most other studies, it often confuses researchers and readers alike. In cohort studies, for example, study groups are defined by exposure. In case-control studies, however, study groups are defined by outcome (figure). To study the association between smoking and lung cancer, therefore, people with lung cancer are enrolled to form the case group, and people without lung cancer are identified as controls. Researchers then look back in time to ascertain each person's exposure status (smoking history), hence the retrospective nature of this study design. Investigators compare the frequency of smoking exposure in the case group with that in the control group, and calculate a measure of association.[21–23]



Schematic diagram of case-control study design

Unlike cohort studies, case-control studies cannot yield incidence rates.[24] Instead, they provide an odds ratio, derived from the proportion of individuals exposed in each of the case and control groups. When the incidence rate of a particular outcome in the population of interest is low (usually under 5% in both the exposed and unexposed suffices)[21] the odds ratio from a case-control study is a good estimate of relative risk.[21,23]

Advantages and disadvantages

Epidemiologists often tout case-control studies as the most efficient design in terms of time, money, and effort. This recommendation makes sense when the incidence rate of an outcome is low, since in a cohort design the researchers would have to follow up many individuals to identify one with the outcome. Case-control studies are also efficient in the investigation of diseases that have a long latency period—eg, cancer—in which instance a cohort study would involve many years of follow-up before the outcome became evident.

However, cohort studies can be more efficient than case-control studies. If the frequency of exposure is low, for example, case-control studies quickly become inefficient. Researchers would have to examine many cases and controls to find one who had been exposed. For instance, a case-control study of oral contraceptive use and transmission of HIV-1 would be impractical in parts of Africa because of the rarity of use of oral contraceptives. As a rule of thumb, cohort designs are more efficient in settings in which the incidence of outcome is higher than the prevalence of exposure.

Finally, many methodological issues affect the validity of the results of case-control studies, and two factors—ie, choosing a control group and obtaining exposure history—can greatly affect a study's vulnerability to bias.

Selection of case and control groups

Case group

All the cases from a population could, theoretically, be included as participants in a case-control study. For practical reasons, however, only a sample is frequently studied.[22] Investigators should, therefore, state how the sample was selected, providing a clear definition of the outcome being studied including, for example, clinical symptoms, laboratory results, and diagnostic methods used. Furthermore, researchers should detail eligibility criteria used for selection, such as age range and location (clinic, hospital, population-based). Finally, they should gather data preferably from incident (new) rather than prevalent (both old and new) cases;[25] since diagnostic patterns change over time, recent diagnoses are likely to be more consistent than those obtained from different periods.

Control group

The control group provides the background proportion of exposure expected in the case group. Controls should, therefore, be free of the disease (outcome) being studied, but should be representative of those individuals who would have been selected as cases had they developed the disease. In other words, controls should represent the population at risk of becoming cases.

Selection of controls must be independent of the exposure being investigated. Artistic licence enters the study design at this point, sometimes for the better and, unfortunately, sometimes for the worse. When investigators consider potential control groups, they must anticipate all the potential biases that could arise, making this task one of the hardest in epidemiology.

Suppose investigators selected individuals with myocardial infarction from the cardiology ward of a large, city hospital as cases, but identified people without infarction from the emergency medicine ward of the same hospital as controls. Bias might result. The cardiology ward is used as a referral centre for the entire state, whereas the emergency medicine department primarily serves only the city. Unfortunately, the exposure history for patients from the city would not usually accurately reflect that of patients statewide. For example, the exposure of interest—eg, a new blood pressure drug—might not be available to patients in outlying areas of the state but be commonly prescribed in the city. In this example, therefore, either the controls should be chosen from the entire state, like the cases, or the investigators should exclude all individuals who lived outside the local community served by the emergency medicine ward. Moreover, controls should be selected independent of exposure. Assume that this new antihypertensive drug causes drowsiness and slows reaction time. Such side-effects might lead to automobile accidents, with injured

drivers entering the emergency medicine department. Thus, the investigator's control group would include an abnormally high proportion of individuals exposed to the new antihypertensive, a biased comparison with the case group.

Another hypothetical example could be a case-control study of whether non-steroidal anti-inflammatory drugs (NSAIDs) prevent colorectal cancer. The study measures previous NSAID use by patients admitted to hospital with (cases) and without (controls) colorectal cancer. If the control group came from the rheumatology service, then the study would be biased, since individuals with arthritis use NSAIDs more often than do the general population from which the cases were chosen. Such a high level of NSAID use in controls would result in a spuriously low risk (odds ratio) calculation. Alternatively, if the control group came from the gastroenterology service, where many ulcer patients had been advised by their doctors to avoid NSAIDs, then that control group might yield a low level of NSAID use and a spuriously high risk (odds ratio) calculation. In other words, if investigators do not select control groups independent of exposure, biases in either direction might result (panel 2).

An early case-control study in AIDS serves as a good example of how inappropriate controls can result in biased findings.[26] In this instance, the researchers compared cases of AIDS diagnosed in San Francisco, CA, USA, between 1983 and 1984 with two HIV-uninfected control groups. One control group included individuals who attended a clinic for sexually transmitted diseases (STD), and the other included people identified from the neighbourhoods of the cases. The investigators compared the risk of AIDS in individuals with more than 100 sexual partners with that in people with no to five sexual partners. The resulting odds ratios were 2·9 with STD clinic controls, but 52·0 with neighbourhood controls. The magnitude of this difference shows the potential for huge biases due to selection of improper control groups. In this study, controls from the STD clinic proved inappropriate, since their selection was not independent of exposure (more than 100 sexual partners). Acquisition of STDs is associated with number of sexual partners, thus these controls generated a highly biased odds ratio estimate.

Investigators can reduce selection bias by minimising judgment in the selection process. For example, if the case group included all affected individuals in a specified geographic region, then the control group could be chosen at random from the general population of the same area. This approach was used in a case-control study of breast cancer and oral contraceptive use.[27] All women aged 20–54 years, who had newly diagnosed breast cancer, and who lived in one of eight geographic areas in the USA formed the case group. Women of the same ages, selected by random digital telephone dialling, and from the same areas, formed the control group. Although this study represents an excellent example, such designs are not always feasible.

Readers of case-control studies should not accept results of studies without checking the appropriateness of the control group, as described in the methods section. If the researchers provide little insight into the choice of their control group, become sceptical. Examine whatever information the researcher has provided for indications about how well the control group represents the cases, independent of the exposure being studied.[25] This assessment takes time and energy, but it represents the crux of a case-control study.

Measurement of exposure information

Another difficulty in case-control studies involves the measurement of exposure information. Participants, both cases and controls, might inaccurately remember past exposures, especially those that happened a long time ago. Furthermore, cases often remember exposures to putative risk factors differently than controls. This differential recall (recall bias) causes information bias.[25]

In the study of breast cancer and oral contraceptive use,[27] for example, investigators asked participants about previous exposure to oral contraceptives. Women with breast cancer might have searched their minds for what could have caused their cancers, identifying oral contraceptives as a risk because of stories in the media about the postulated relation between contraceptives and breast cancer. Thus, although some women in each group might have used a particular oral contraceptive 20 years ago, the case might remember taking it whereas the control might not. Such recall bias would generate an exaggerated relation between oral contraceptives and breast cancer. Information bias is especially pernicious because analytical techniques, irrespective of their sophistication, cannot moderate or eliminate it.

In a Swedish study,[28] investigators examined the potential link between induced abortion and later development of breast cancer. They gathered information about exposure (previous abortion) from cases and controls by means of personal interviews and by looking through national medical records. When interviewed, fewer controls admitted to having had an abortion than was evident in vital statistics. This discrepancy did not arise among cases. Differential recall between cases and controls led to a biased estimate of risk.

Bias from data gatherers presents further difficulties. If the individuals gathering information know the case or control status of the participants they can elicit information differently, again leading to potential information bias. A data gatherer might delve more deeply into a case's background than a control's to obtain a hypothesised exposure. When possible, data gatherers—eg, interviewers—should be unaware of the case or control status of the respondents. When blinding is not possible, investigators should keep the main hypothesis from the data gatherers. Furthermore, researchers should train data gatherers to elicit information similarly for cases and controls. Obtaining exposure information from records, as

Panel 2: **Introduction of bias through poor choice of controls**

Cases	Control selection	Non-representativeness	Selection bias
Colorectal cancer patients admitted to hospital	Patients admitted to hospital with arthritis	Controls probably have high degrees of exposure to NSAIDs	Would spuriously **reduce** the estimate of effect (odds ratio)
Colorectal cancer patients admitted to hospital	Patients admitted to hospital with peptic ulcers	Controls probably have low degrees of exposure to NSAIDs	Would spuriously **increase** the estimate of effect (odds ratio)

NSAIDs=non-steroidal anti-inflammatory drugs.

a solution to information bias, rarely suffices, since such information does not always exist, and, if it does, is usually insufficient to control adequately for confounding factors in the analysis.[22]

Investigators who do case-control studies must be aware of the potential for information bias. They should address it in their study design and describe in their report approaches used to avoid such bias. Memory aids, such as photographs, diaries, and calendars can help participants remember exposures. For example, in the case-control study of oral contraceptives,[27] the investigators used an album with colour photographs of every oral contraceptive marketed over the preceding decades and a blank calendar grid to help recall major life events and contraceptive use. Those colour photographs stimulated memories, both in cases and controls, to past exposure use, and thus reduced recall bias. Reports of case-control studies that do not detail use of memory aids, &c, should make readers sceptical.

Control for confounding

Case-control studies need to address confounding bias.[21,22,29] This type of bias can be dealt with in the design phase by restriction or matching, but researchers generally prefer to handle it in the analysis phase with analytical techniques such as logistic regression or stratification with Mantel-Haenszel approaches.[21,22,25] If this second approach is used, investigators should plan carefully in advance what potentially confounding variables to obtain data for; irrespective of the analytical approach used, researchers cannot control for a variable for which they have no data. Moreover, invalid measurement of potential confounding factors leads to residual confounding, even after adjustment.[22]

Conclusion

Case-control studies that are well designed and carefully done can provide useful and reliable results. Investigators must, however, devote meticulous attention to the selection of control groups and to measurement of exposure information. Awareness of these key elements should help readers to identify the strengths and weaknesses of a properly reported study. Accurate and thorough description of methods by investigators will result in reader confidence in their results.

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References

1 Fuller Torrey E, Rawlings R, Yolken RH. The antecedents of psychoses: a case-control study of selected risk factors. *Schizophr Res* 2000; **46:** 17–23.

2 Silverman DT. Risk factors for pancreatic cancer: a case-control study based on direct interviews. *Teratog Carcinog Mutagen* 2001; **21:** 7–25.

3 Osaki Y, Minowa M. Factors associated with earthquake deaths in the great Hanshin-Awaji earthquake, 1995. *Am J Epidemiol* 2001; **153:** 153–56.

4 Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. Risk factors for erosive reflux esophagitis: a case-control study. *Am J Gastroenterol* 2001; **96:** 41–46.

5 Freni-Titulaer LW, Kelley DB, Grow AG, McKinley TW, Arnett FC, Hochberg MC. Connective tissue disease in southeastern Georgia: a case-control study of etiologic factors. *Am J Epidemiol* 1989; **130:** 404–09.

6 Strom BL, Reidenberg MM, West S, Snyder ES, Freundlich B, Stolley PD. Shingles, allergies, family medical history, oral contraceptives, and other potential risk factors for systemic lupus erythematosus. *Am J Epidemiol* 1994; **140:** 632–42.

7 Amal NM, Lye MS, Ksiazek TG, et al. Risk factors for Nipah virus transmission, Port Dickson, Negeri Sembilan, Malaysia: results from a hospital-based case-control study. *Southeast Asian J Trop Med Public Health* 2000; **31:** 301–06.

8 Traverso HP, Bennett JV, Kahn AJ, et al. Ghee applications to the umbilical cord: a risk factor for neonatal tetanus. *Lancet* 1989; **1:** 486–88.

9 Cheng KK, Day NE, Duffy SW, Lam TH, Fok M, Wong J. Pickled vegetables in the aetiology of oesophageal cancer in Hong Kong Chinese. *Lancet* 1992; **339:** 1314–18.

10 Hernandez J, Hawkins DL, Scollay MC. Race-start characteristics and risk of catastrophic musculoskeletal injury in thoroughbred racehorses. *J Am Vet Med Assoc* 2001; **218:** 83–86.

11 Friedman GD, Hiatt RA, Quesenberry CP, Selby JV. Case-control study of screening for prostatic cancer by digital rectal examinations. *Lancet* 1991; **337:** 1526–29.

12 Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000; **356:** 1627–31.

13 Cramer DW, Harlow BL, Titus-Ernstoff L, Bohlke K, Welch WR, Greenberg ER. Over-the-counter analgesics and risk of ovarian cancer. *Lancet* 1998; **351:** 104–07.

14 Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. *Lancet* 1997; **350:** 990–94.

15 Collins JW, Smith GS, Baker SP, Landsittel DP, Warner M. A case-control study of forklift and other powered industrial vehicle incidents. *Am J Ind Med* 1999; **36:** 522–31.

16 Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of genital warts: are condoms protective? *Sex Transm Infect* 1999; **75:** 312–16.

17 Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE. Physical activity and breast cancer risk in women aged 20-54 years. *J Natl Cancer Inst* 2000; **92:** 128–35.

18 Slattery ML, Edwards SL, Ma KN, Friedman GD. Colon cancer screening, lifestyle, and risk of colon cancer. *Cancer Causes Control* 2000; **11:** 555–63.

19 Abdel-Salam G, Czeizel AE. A case-control etiologic study of microcephaly. *Epidemiology* 2000; **11:** 571–75.

20 Naghavi M, Barlas Z, Siadaty S, Naguib S, Madjid M, Casscells W. Association of influenza vaccination and reduced risk of recurrent myocardial infarction. *Circulation* 2000; **102:** 3039–45.

21 Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in observational epidemiology. New York: Oxford University Press, 1996.

22 Rothman KJ. Modern epidemiology. Boston: Little, Brown and Company, 1986.

23 Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. *Lancet* 2002; **359:** 57–61.

24 Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet* 2002; **359:** 341–45.

25 Schlesselman J. Case-control studies: design, conduct, analysis. New York: Oxford University Press, 1982.

26 Moss AR, Osmond D, Bacchetti P, Chermann JC, Barre-Sinoussi F, Carlson J. Risk factors for AIDS and HIV seropositivity in homosexual men. *Am J Epidemiol* 1987; **125:** 1035–47.

27 Stadel BV, Rubin GL, Webster LA, Schlesselman JJ, Wingo PA. Oral contraceptives and breast cancer in young women. *Lancet* 1985; **2:** 970–73.

28 Lindefors-Harris BM, Eklund G, Adami HO, Meirik O. Response bias in a case-control study: analysis utilizing comparative data concerning legal abortions from two independent Swedish studies. *Am J Epidemiol* 1991; **134:** 1003–08.

29 Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002; **359:** 248–52.