Published in final edited form as:
Plast Reconstr Surg. 2010 December ; 126(6): 2234–2242. doi:10.1097/PRS.0b013e3181f44abc.

Observational Studies: Cohort and Case-Control Studies

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Abstract

Observational studies are an important category of study designs. To address some investigative questions in plastic surgery, randomized controlled trials are not always indicated or ethical to conduct. Instead, observational studies may be the next best method to address these types of questions. Well-designed observational studies have been shown to provide results similar to randomized controlled trials, challenging the belief that observational studies are second-rate. Cohort studies and case-control studies are two primary types of observational studies that aid in evaluating associations between diseases and exposures. In this review article, we describe these study designs, methodological issues, and provide examples from the plastic surgery literature.

Keywords

observational studies; case-control study; cohort study; evidence-based medicine

Because of the innovative nature of the specialty, plastic surgeons are frequently confronted with a spectrum of clinical questions by patients who inquire about “best practices.” It is thus essential that plastic surgeons know how to critically appraise the literature to understand and practice evidence-based medicine (EBM) and also contribute to the effort by carrying out high-quality investigations.[1] Well-designed randomized controlled trials (RCTs) have held the pre-eminent position in the hierarchy of EBM as level I evidence (Table 1). However, RCT methodology, which was first developed for drug trials, can be difficult to conduct for surgical investigations.[3] Instead, well-designed observational studies, recognized as level II or III evidence, can play an important role in deriving evidence for plastic surgery. Results from observational studies are often criticized for being vulnerable to influences by unpredictable confounding factors. However, recent work has challenged this notion, showing comparable results between observational studies and RCTs.[4, 5] Observational studies can also complement RCTs in hypothesis generation, establishing questions for future RCTs, and defining clinical conditions.

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None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Observational studies fall under the category of analytic study designs and are further sub-classified as observational or experimental study designs (Figure 1). The goal of analytic studies is to identify and evaluate causes or risk factors of diseases or health-related events. The differentiating characteristic between observational and experimental study designs is that in the latter, the presence or absence of undergoing an intervention defines the groups. By contrast, in an observational study, the investigator does not intervene and rather simply "observes" and assesses the strength of the relationship between an exposure and disease variable.[6] Three types of observational studies include cohort studies, case-control studies, and cross-sectional studies (Figure 1). Case-control and cohort studies offer specific advantages by measuring disease occurrence and its association with an exposure by offering a temporal dimension (i.e. prospective or retrospective study design). Cross-sectional studies, also known as prevalence studies, examine the data on disease and exposure at one particular time point (Figure 2).[6] Because the temporal relationship between disease occurrence and exposure cannot be established, cross-sectional studies cannot assess the cause and effect relationship. In this review, we will primarily discuss cohort and case-control study designs and related methodologic issues.

COHORT STUDY

The term "cohort" is derived from the Latin word *cohors*. Roman legions were composed of ten cohorts. During battle each cohort, or military unit, consisting of a specific number of warriors and commanding centurions, were traceable. The word "cohort" has been adopted into epidemiology to define a set of people followed over a period of time. W.H. Frost, an epidemiologist from the early 1900s, was the first to use the word "cohort" in his 1935 publication assessing age-specific mortality rates and tuberculosis.[7] The modern epidemiological definition of the word now means a "group of people with defined characteristics who are followed up to determine incidence of, or mortality from, some specific disease, all causes of death, or some other outcome."[7]

Study Design

A well-designed cohort study can provide powerful results. In a cohort study, an outcome or disease-free study population is first identified by the exposure or event of interest and followed in time until the disease or outcome of interest occurs (Figure 3A). Because exposure is identified before the outcome, cohort studies have a temporal framework to assess causality and thus have the potential to provide the strongest scientific evidence.[8] Advantages and disadvantages of a cohort study are listed in Table 2.[2, 9] Cohort studies are particularly advantageous for examining rare exposures because subjects are selected by their exposure status. Additionally, the investigator can examine multiple outcomes simultaneously. Disadvantages include the need for a large sample size and the potentially long follow-up duration of the study design resulting in a costly endeavor.

Cohort studies can be prospective or retrospective (Figure 2). Prospective studies are carried out from the present time into the future. Because prospective studies are designed with specific data collection methods, it has the advantage of being tailored to collect specific exposure data and may be more complete. The disadvantage of a prospective cohort study may be the long follow-up period while waiting for events or diseases to occur. Thus, this study design is inefficient for investigating diseases with long latency periods and is vulnerable to a high loss to follow-up rate. Although prospective cohort studies are invaluable as exemplified by the landmark Framingham Heart Study, started in 1948 and still ongoing,[10] in the plastic surgery literature this study design is generally seen to be inefficient and impractical. Instead, retrospective cohort studies are better indicated given the timeliness and inexpensive nature of the study design.

Retrospective cohort studies, also known as historical cohort studies, are carried out at the present time and look to the past to examine medical events or outcomes. In other words, a cohort of subjects selected based on exposure status is chosen at the present time, and outcome data (i.e. disease status, event status), which was measured in the past, are reconstructed for analysis. The primary disadvantage of this study design is the limited control the investigator has over data collection. The existing data may be incomplete, inaccurate, or inconsistently measured between subjects.[2] However, because of the immediate availability of the data, this study design is comparatively less costly and shorter than prospective cohort studies. For example, Spear and colleagues examined the effect of obesity and complication rates after undergoing the pedicled TRAM flap reconstruction by retrospectively reviewing 224 pedicled TRAM flaps in 200 patients over a 10-year period.11 In this example, subjects who underwent the pedicled TRAM flap reconstruction were selected and categorized into cohorts by their exposure status: normal/underweight, overweight, or obese. The outcomes of interest were various flap and donor site complications. The findings revealed that obese patients had a significantly higher incidence of donor site complications, multiple flap complications, and partial flap necrosis than normal or overweight patients. An advantage of the retrospective study design analysis is the immediate access to the data. A disadvantage is the limited control over the data collection because data was gathered retrospectively over 10-years; for example, a limitation reported by the authors is that mastectomy flap necrosis was not uniformly recorded for all subjects. 11

An important distinction lies between cohort studies and case-series. The distinguishing feature between these two types of studies is the presence of a control, or unexposed, group. Contrasting with epidemiological cohort studies, case-series are descriptive studies following one small group of subjects. In essence, they are extensions of case reports. Usually the cases are obtained from the authors' experiences, generally involve a small number of patients, and more importantly, lack a control group.[12] There is often confusion in designating studies as “cohort studies” when only one group of subjects is examined. Yet, unless a second comparative group serving as a control is present, these studies are defined as case-series. The next step in strengthening an observation from a case-series is selecting appropriate control groups to conduct a cohort or case-control study, the latter which is discussed in the following section about case-control studies.[9]

Methodological Issues

Selection of Subjects in Cohort Studies—The hallmark of a cohort study is defining the selected group of subjects by exposure status at the start of the investigation. A critical characteristic of subject selection is to have both the exposed and unexposed groups be selected from the same source population (Figure 4).[9] Subjects who are not at risk for developing the outcome should be excluded from the study. The source population is determined by practical considerations, such as sampling. Subjects may be effectively sampled from the hospital, be members of a community, or from a doctor's individual practice. A subset of these subjects will be eligible for the study.

Attrition Bias (Loss to follow-up)—Because prospective cohort studies may require long follow-up periods, it is important to minimize loss to follow-up. Loss to follow-up is a situation in which the investigator loses contact with the subject, resulting in missing data. If too many subjects are loss to follow-up, the internal validity of the study is reduced. A general rule of thumb requires that the loss to follow-up rate not exceed 20% of the sample.[6] Any systematic differences related to the outcome or exposure of risk factors between those who drop out and those who stay in the study must be examined, if possible, by comparing individuals who remain in the study and those who were loss to follow-up or dropped out. It

is therefore important to select subjects who can be followed for the entire duration of the cohort study. Methods to minimize loss to follow-up are listed in Table 3.

CASE-CONTROL STUDIES

Case-control studies were historically borne out of interest in disease etiology. The conceptual basis of the case-control study is similar to taking a history and physical; the diseased patient is questioned and examined, and elements from this history taking are knitted together to reveal characteristics or factors that predisposed the patient to the disease. In fact, the practice of interviewing patients about behaviors and conditions preceding illness dates back to the Hippocratic writings of the 4th century B.C.[7]

Reasons of practicality and feasibility inherent in the study design typically dictate whether a cohort study or case-control study is appropriate. This study design was first recognized in Janet Lane-Claypon's study of breast cancer in 1926, revealing the finding that low fertility rate raises the risk of breast cancer.[13, 14] In the ensuing decades, case-control study methodology crystallized with the landmark publication linking smoking and lung cancer in the 1950s.[15] Since that time, retrospective case-control studies have become more prominent in the biomedical literature with more rigorous methodological advances in design, execution, and analysis.

Study Design

Case-control studies identify subjects by outcome status at the outset of the investigation. Outcomes of interest may be whether the subject has undergone a specific type of surgery, experienced a complication, or is diagnosed with a disease (Figure 3B). Once outcome status is identified and subjects are categorized as cases, controls (subjects without the outcome but from the same source population) are selected. Data about exposure to a risk factor or several risk factors are then collected retrospectively, typically by interview, abstraction from records, or survey. Case-control studies are well suited to investigate rare outcomes or outcomes with a long latency period because subjects are selected from the outset by their outcome status. Thus in comparison to cohort studies, case-control studies are quick, relatively inexpensive to implement, require comparatively fewer subjects, and allow for multiple exposures or risk factors to be assessed for one outcome (Table 4).[2,9]

An example of a case-control investigation is by Zhang and colleagues who examined the association of environmental and genetic factors associated with rare congenital microtia,16 which has an estimated prevalence of 0.83 to 17.4 in 10,000.[17] They selected 121 congenital microtia cases based on clinical phenotype, and 152 unaffected controls, matched by age and sex in the same hospital and same period. Controls were of Hans Chinese origin from Jiangsu, China, the same area from where the cases were selected. This allowed both the controls and cases to have the same genetic background, important to note given the investigated association between genetic factors and congenital microtia. To examine environmental factors, a questionnaire was administered to the mothers of both cases and controls. The authors concluded that adverse maternal health was among the main risk factors for congenital microtia, specifically maternal disease during pregnancy (OR 5.89, 95% CI 2.36-14.72), maternal toxicity exposure during pregnancy (OR 4.76, 95% CI 1.66-13.68), and resident area, such as living near industries associated with air pollution (OR 7.00, 95% CI 2.09-23.47).[16] A case-control study design is most efficient for this investigation, given the rarity of the disease outcome. Because congenital microtia is thought to have multifactorial causes, an additional advantage of the case-control study design in this example is the ability to examine multiple exposures and risk factors.

Methodological Issues

Selection of Cases—Sampling in a case-control study design begins with selecting the cases. In a case-control study, it is imperative that the investigator has explicitly defined inclusion and exclusion criteria prior to the selection of cases. For example, if the outcome is having a disease, specific diagnostic criteria, disease subtype, stage of disease, or degree of severity should be defined. Such criteria ensure that all the cases are homogenous. Second, cases may be selected from a variety of sources, including hospital patients, clinic patients, or community subjects. Many communities maintain registries of patients with certain diseases and can serve as a valuable source of cases. However, despite the methodologic convenience of this method, validity issues may arise. For example, if cases are selected from one hospital, identified risk factors may be unique to that single hospital. This methodological choice may weaken the generalizability of the study findings. Another example is choosing cases from the hospital versus the community; most likely cases from the hospital sample will represent a more severe form of the disease than those in the community.[2] Finally, it is also important to select cases that are representative of cases in the target population to strengthen the study's external validity (Figure 4). Potential reasons why cases from the original target population eventually filter through and are available as cases (study participants) for a case-control study are illustrated in Figure 5.

Selection of Controls—Selecting the appropriate group of controls can be one of the most demanding aspects of a case-control study. An important principle is that the distribution of exposure should be the same among cases and controls; in other words, both cases and controls should stem from the same source population. The investigator may also consider the control group to be an at-risk population, with the potential to develop the outcome. Because the validity of the study depends upon the comparability of these two groups, cases and controls should otherwise meet the same inclusion criteria in the study.

A case-control study design that exemplifies this methodological feature is by Chung and colleagues, who examined maternal cigarette smoking during pregnancy and the risk of newborns developing cleft lip/palate.18 A salient feature of this study is the use of the 1996 U.S. Natality database, a population database, from which both cases and controls were selected. This database provides a large sample size to assess newborn development of cleft lip/palate (outcome), which has a reported incidence of 1 in 1000 live births,[19] and also enabled the investigators to choose controls (i.e., healthy newborns) that were generalizable to the general population to strengthen the study's external validity. A significant relationship with maternal cigarette smoking and cleft lip/palate in the newborn was reported in this study (adjusted OR 1.34, 95% CI 1.36-1.76).18

Matching—Matching is a method used in an attempt to ensure comparability between cases and controls and reduces variability and systematic differences due to background variables that are not of interest to the investigator.[8] Each case is typically individually paired with a control subject with respect to the background variables. The exposure to the risk factor of interest is then compared between the cases and the controls. This matching strategy is called individual matching. Age, sex, and race are often used to match cases and controls because they are typically strong confounders of disease.[20] Confounders are variables associated with the risk factor and may potentially be a cause of the outcome.[8] Table 5 lists several advantages and disadvantages with a matching design.

Multiple Controls—Investigations examining rare outcomes may have a limited number of cases to select from, whereas the source population from which controls can be selected is much larger. In such scenarios, the study may be able to provide more information if multiple controls per case are selected. This method increases the “statistical power” of the

investigation by increasing the sample size. The precision of the findings may improve by having up to about three or four controls per case.[21-23]

Bias in Case-Control Studies—Evaluating exposure status can be the Achilles heel of case-control studies. Because information about exposure is typically collected by self-report, interview, or from recorded information, it is susceptible to recall bias, interviewer bias, or will rely on the completeness or accuracy of recorded information, respectively. These biases decrease the internal validity of the investigation and should be carefully addressed and reduced in the study design. Recall bias occurs when a differential response between cases and controls occurs. The common scenario is when a subject with disease (case) will unconsciously recall and report an exposure with better clarity due to the disease experience. Interviewer bias occurs when the interviewer asks leading questions or has an inconsistent interview approach between cases and controls. A good study design will implement a standardized interview in a non-judgemental atmosphere with well-trained interviewers to reduce interviewer bias.[9]

The STROBE Statement: The Strengthening the Reporting of Observational Studies in Epidemiology Statement

In 2004, the first meeting of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) group took place in Bristol, UK.[24] The aim of the group was to establish guidelines on reporting observational research to improve the transparency of the methods, thereby facilitating the critical appraisal of a study's findings. A well-designed but poorly reported study is disadvantaged in contributing to the literature because the results and generalizability of the findings may be difficult to assess. Thus a 22-item checklist was generated to enhance the reporting of observational studies across disciplines.25›26 This checklist is also located at the following website: www.strobe-statement.org. This statement is applicable to cohort studies, case-control studies, and cross-sectional studies. In fact, 18 of the checklist items are common to all three types of observational studies, and 4 items are specific to each of the 3 specific study designs. In an effort to provide specific guidance to go along with this checklist, an “explanation and elaboration” article was published for users to better appreciate each item on the checklist.[27] Plastic surgery investigators should peruse this checklist prior to designing their study and when they are writing up the report for publication. In fact, some journals now require authors to follow the STROBE Statement. A list of participating journals can be found on this website: http://www.strobe-statement.org./index.php?id=strobe-endorsement.

Conclusion

Due to the limitations in carrying out RCTs in surgical investigations, observational studies are becoming more popular to investigate the relationship between exposures, such as risk factors or surgical interventions, and outcomes, such as disease states or complications. Recognizing that well-designed observational studies can provide valid results is important among the plastic surgery community, so that investigators can both critically appraise and appropriately design observational studies to address important clinical research questions. The investigator planning an observational study can certainly use the STROBE statement as a tool to outline key features of a study as well as coming back to it again at the end to enhance transparency in methodology reporting.

Acknowledgments

Supported in part by a Midcareer Investigator Award in Patient-Oriented Research (K24 AR053120) from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (to Dr. Kevin C. Chung).

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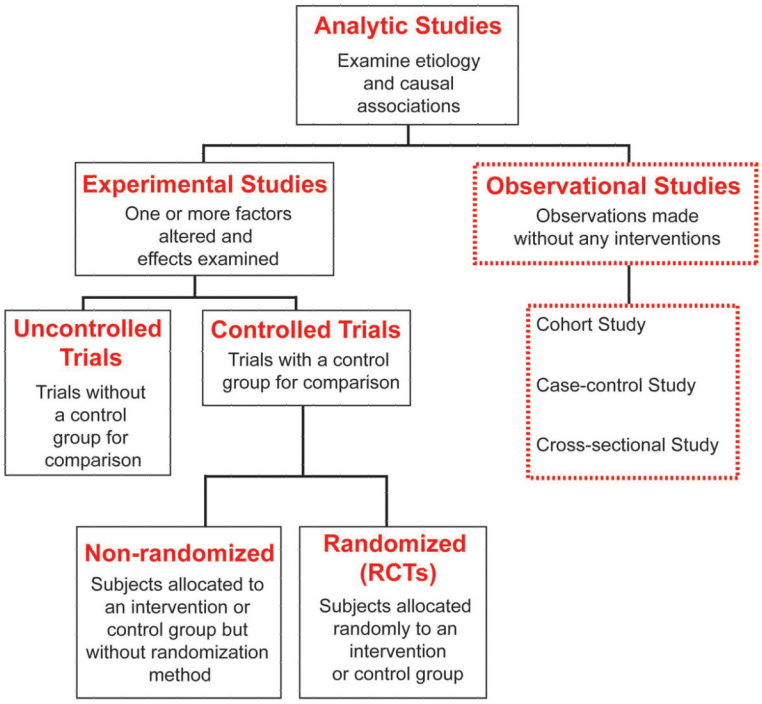

Figure 1.
Analytic Study Designs. Adapted with permission from Joseph Eisenberg, Ph.D.

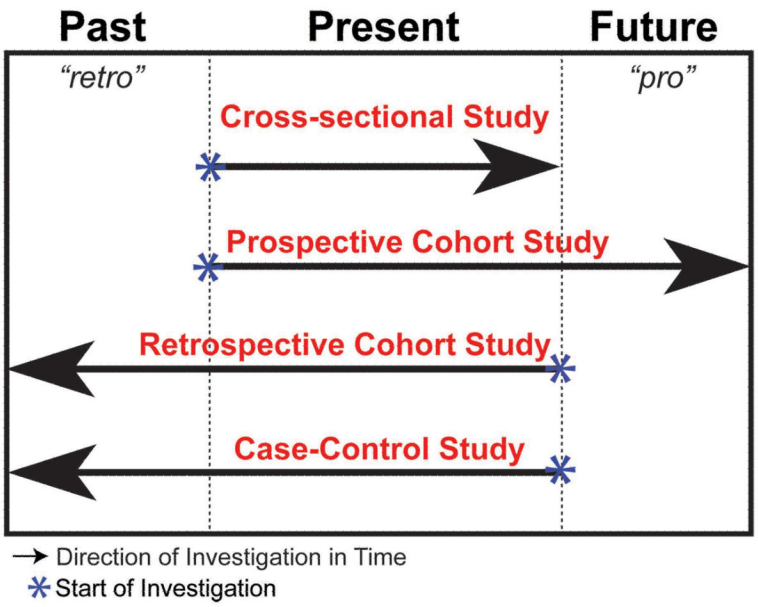

Figure 2.

Temporal Design of Observational Studies: Cross-sectional studies are known as prevalence studies and do not have an inherent temporal dimension. These studies evaluate subjects at one point in time, the present time. By contrast, cohort studies can be either retrospective (latin derived prefix, "retro" meaning "back, behind") or prospective (greek derived prefix, "pro" meaning "before, in front of"). Retrospective studies "look back" in time contrasting with prospective studies, which "look ahead" to examine causal associations. Case-control study designs are also retrospective and assess the history of the subject for the presence or absence of an exposure.

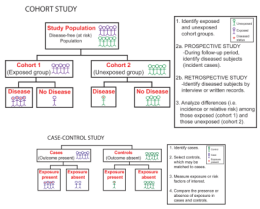

Figure 3.
Cohort and Case-Control Study Designs

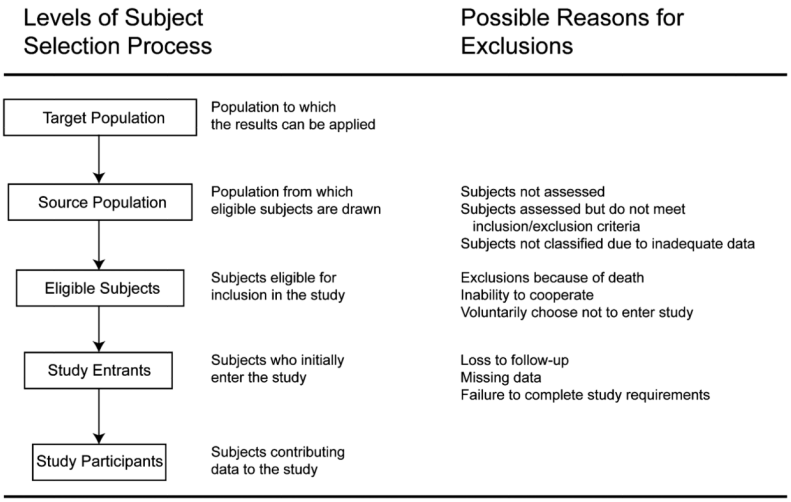

Figure 4.
Levels of Subject Selection. Adapted from Ref [9].

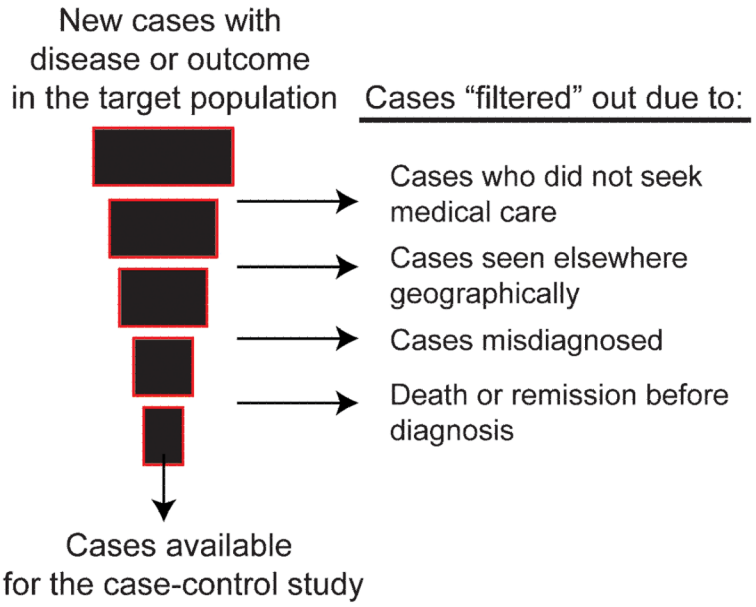

Figure 5.
Levels of Case Selection. Adapted from Ref [2].

Table 1

Levels of Evidence Based Medicine

Level of Evidence	Qualifying Studies
I	High-quality, multicenter or single-center, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser quality, randomized controlled trial; prospective cohort study; or systematic review of these studies
III	Retrospective comparative study; case-control study; or systematic review of these studies
IV	Case-series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research, or “first principles”

From REF [1].

Table 2

Advantages and Disadvantages of the Cohort Study

Advantages
Gather data regarding sequence of events; can assess causality
Examine multiple outcomes for a given exposure
Good for investigating rare exposures
Can calculate rates of disease in exposed and unexposed individuals over time (e.g. incidence, relative risk)
Disadvantages
Large numbers of subjects are required to study rare exposures
Susceptible to selection bias
Prospective Cohort Study
May be expensive to conduct
May require long durations for follow-up
Maintaining follow-up may be difficult
Susceptible to loss to follow-up or withdrawals
Retrospective Cohort Study
Susceptible to recall bias or information bias
Less control over variables

Table 3

Methods to Minimize Loss to Follow-Up

During enrollment
Exclude subjects likely to be lost
Planning to move
Non-committal
Obtain information to allow future tracking
Collect subject's contact information (e.g. mailing addresses, telephone numbers, and email addresses)
Collect social security and/or Medicare numbers
During follow-up
Maintain periodic contact
By telephone: may require calls during the weekends and/or evenings
By mail: repeated mailings by e-mail or with stamped, self-addressed return envelopes
Other: newsletters or token gifts with study logo

Adapted from REF [2].

Table 4

Advantages and Disadvantages of the Case-Control Study

Advantages
Good for examining rare outcomes or outcomes with long latency
Relatively quick to conduct
Relatively inexpensive
Requires comparatively few subjects
Existing records can be used
Multiple exposures or risk factors can be examined
Disadvantages
Susceptible to recall bias or information bias
Difficult to validate information
Control of extraneous variables may be incomplete
Selection of an appropriate comparison group may be difficult
Rates of disease in exposed and unexposed individuals cannot be determined

Table 5

Advantages and Disadvantages for Using a Matching Strategy

Advantages	Disadvantages
Eliminate influence of measurable confounders (e.g. age, sex)	May be time-consuming and expensive
Eliminate influence of confounders that are difficult to measure	Decision to match and confounding variables to match upon are decided at the outset of the study
May be a sampling convenience, making it easier to select the controls in a case-control study	Matched variables cannot be examined in the study
May improve study efficiency (i.e. smaller sample size)	Requires a matched analysis
	Vulnerable to overmatching: when matching variable has some relationship with the outcome

Adapted from REF [2].