Research Methodology and Biostatistics Series VI - Observational Studies

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Abstract:

Studies on antecedent-outcome relationships in naturally occurring events are called observational studies. Hazardous 'interventions', such as smoking and anaemia, are particularly suitable for observational studies because these cannot be intentionally introduced but occur naturally.

In a prospective observational study, subjects with specific antecedents or exposure are followed up for the occurrence of the outcome. This design yields more valid results because the subjects are monitored over time. A retrospective study starts with the outcome — for example, individuals with and without a disease — and investigates previously occurring events that might have led to the disease in some and not in others. This type of study can be completed more quickly but may involve biased assessment of the antecedents. A cross-sectional study requires a carefully chosen, adequately representative sample and gives valid results when both antecedents and outcomes are properly assessed at the same time. The merits and demerits of these designs are discussed in this article.

This article also describes some other observational study designs such as case-control, nested case-control, and retrospective cohort studies, which are sometimes misunderstood.

Key words: Prospective Studies, Retrospective Studies, Cross-Sectional Studies, Analytical Studies, Case-Control Studies, Retrospective Cohort Studies, Nested Case-Control Studies.

What is an Observational Study?

In clinical trials, we intentionally administer an intervention to human subjects and study how it affects them. Thus, this forms a stimulus-response experimental setup in human beings. Such studies typically offer good control over the selection of subjects, allocation between the case and the control groups, and blinding — thus providing credible evidence for or against a cause-effect relationship, or at least a stimulus-response relationship.

However, in many situations, feasibility, cost, or ethical considerations prevent us from conducting a trial. Smoking is a well-known example. We cannot ethically ask people to smoke for 10 years to study its effect on pulmonary functions. Instead, we assess the pulmonary functions of people who already smoke, across various durations and intensities. Similarly, we cannot ask pregnant women to become anaemic to study how different grades of anaemia affect birth outcomes such as gestational age, intrauterine growth retardation, or birth weight. Instead, we observe naturally occurring cases of anaemia in antenatal women to study its effects on birth outcomes.

When the 'intervention' is a naturally occurring factor that is already present in some individuals but not in others, and we simply observe the outcomes, the study is referred to as an observational study. While observational studies are a natural choice for investigating the effect of adverse factors, they are sometimes preferred for beneficial interventions too, due to convenience, cost and speed. For example, in studying dietary supplementation, we may observe outcomes such as liver and kidney functions in those already taking specific supplements for a defined period and compare these with individuals not taking the supplementation. This strategy could be more efficient than conducting a trial in which some participants are asked to take supplements while equivalent controls are asked not to. However, in observational studies, several other factors, such as age, nutritional status, and comorbidities can play spoil sport as confounders. Confounders are factors whose effects are so closely intertwined that their individual effect cannot be separated. They typically affect both the antecedents and the outcomes of interest, thereby contaminating the results.

The term 'observational study' associated with the study of antecedent-outcome relationships. While the underlying question may relate to cause and effect, observational studies rarely meet the strict conditions required to meet causality.[1] These conditions are numerous and beyond the scope of this article. Therefore, observational studies can only confirm or refute associations, not causality — unless those strict conditions are met.

To understand observational studies, it is necessary to understand the terms 'antecedents' and 'outcomes.' Antecedents are factors that are precursors and contribute to the outcome of interest. These may include risk factors (e.g., metabolic syndrome for cardiovascular diseases), exposures (e.g., radiation leading to illness), or protective factors (e.g., a healthy diet reducing risk of certain cancers). Outcomes are the consequences of interest, such as the onset of a disease, survival duration, or improvement in the condition. In the smoking–pulmonary function example, smoking is the antecedent and pulmonary function is the outcome. In the anaemia–birth outcome example, anaemia is the antecedent and birth characteristics are the outcomes. A factor may be an antecedent in one study and outcome in another; for example, obesity is an antecedent for diabetes but an outcome for sedentary behaviour.

Since the aim is to assess the antecedent-outcome relationship, an observational study is an analytical study as explained in an earlier article.[2] If the aim is not to examine this relationship but to merely describe characteristics of the population or estimate exposure levels, the study is descriptive rather than analytical. Such descriptive studies, sometimes referred to as prevalence studies, might focus on the proportion of subjects who are non-smokers, mild, moderate, or heavy smokers, or assess smoking intensity using indices, or describe demographics such as age, sex, socio-economic status, and stress levels.

Observational studies can be carried out using different designs. One design is the ecological study, in which population-level rather than individual-level data are used. For example, Moreira-Soto *et al.*[3] analysed the relationship between severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) laboratory testing capacity and socio-economic factors across 109 countries in 2020-21 to identify potential determinants of global disparities in testing capacity, without using individual-level data.

More commonly, observational studies involve individual-level data and can be prospective, retrospective, or cross-sectional. Note that these classifications apply only to analytical studies (which assess antecedent-outcome relationships) and not to descriptive studies. Some researchers mistakenly refer to descriptive studies as observational studies. For example, Maposse *et al.*[4] studied the prevalence of cell phone use while driving and erroneously called it an observational study instead of a descriptive study.

Prospective, Retrospective, and Cross-Sectional Studies

The natural design of an observational study follows a direction from antecedent to outcome. This requires selecting subjects with and without the antecedent of interest and following them up for the occurrence or non-occurrence of outcomes. The two groups — those with and without the antecedent — must otherwise be equivalent at baseline. A study evaluating the use of a cemented dual mobility cup for primary total hip arthroplasty in terms of quality of life[5] will yield valid results only if the patients receiving the cemented cup have the same clinical condition at baseline as those treated with alternative procedures.

The essential feature of a prospective design is follow-up. This can be short, lasting a few hours or days, or long, spanning several years. For instance, a study investigating anaemia in pregnant women and birth outcomes is prospective if women with different grades of anaemia (none, mild, moderate, and serious) are enrolled and followed up for outcomes such as birth weight. It becomes retrospective if researchers examine the records of mothers of newborns with different weights (low, normal, high) to determine their haemoglobin (Hb) levels during the antenatal period, say in the first trimester. In this case, this investigation moves from outcome (birth weight) to antecedent (Hb level).

The anaemia-birth outcome study becomes cross-sectional when all births within a specified period are included, and Hb levels of the mothers and the birth weights of the infants are recorded at a single point in time.

Variations of Observational Studies

Colloquially, the prospective-retrospective classification is based on the time frame. A study is considered retrospective if based on records of cases no longer available, and prospective if based on subjects enrolled from a specified date moving forward. However, this time-based classification does not align with the correct scientific usage, which classifies studies based on the direction of enquiry: from antecedent to outcome (prospective), or from outcome to antecedent (retrospective), regardless of the time frame.

For more clarity on the time aspect, consider a study on mortality among COVID-19 patients admitted to the intensive care unit (ICU).[6] The study was based on records, but the direction of investigation was from antecedent (ICU admission) to outcome (mortality). Therefore, despite using retrospective data, it qualifies as a prospective study in terms of design. Nevertheless, the authors referred to it as a "retrospective cohort study."

This brings us to the term 'cohort study'. A cohort is a group of people with defined, shared characteristics. There may be a cohort of specific cases to be admitted over the next year (a prospective cohort) or cases admitted over the past 3 years (a retrospective cohort). However, the term "retrospective cohort" does not automatically imply a retrospective study. The direction of the investigation in a cohort study, whether prospective or retrospective, is typically from antecedent to outcome, such as from the admission to discharge.

However, Li *et al.* retrieved records of patients with coronary heart disease (CHD), categorised them into mild, moderate, and severe stenosis groups using Gensini score, and analysed the role of remnant cholesterol (RC) in predicting stenosis severity.[7] Here, the direction of investigation was from outcome (severity of stenosis) to antecedent (RC), which is a retrospective design. Yet, the authors referred to it as a "retrospective cohort study." Such variations in usage are common in the literature, although scientifically, a cohort study should ideally follow a prospective direction from antecedent to outcome. A prospective study may also be longitudinal, where subjects are observed at several time points rather than at just the endpoint.

A case-control study, in which the case group comprises individuals with a disease (or another outcome) and the control group includes those without it, is also retrospective in design. It begins with subjects who have (case group) and do not have (control group) the outcome and investigates the antecedents. This design provides valid results only if the case and control groups are equivalent at baseline apart from the antecedents under study. Otherwise, differing antecedents may act as confounders and bias the results. In the anaemia-birth weight example, potential confounders include parental weight, calorie intake, and intake of nutritional supplements. If the case group has specific comorbidities that the control group does not, the results may be invalid because of baseline inequivalence. A type of observational study is the nested case-control study, in which cases and controls are drawn from a cohort already being investigated for another purpose. Wu *et al.*[8] reported such a study, selecting cases with gestational diabetes mellitus (GDM) and controls without GDM from a birth cohort. They studied the role of maternal plasma concentrations of trimethylamine N-oxide and its precursors — choline, betaine, and carnitine — in the risk of developing GDM.

Merits and Demerits of the Different Types of Observational Studies

An in-depth consideration of the various designs within the observational study paradigm reveals that each design has advantages in some situations and disadvantages in others. Since individuals with outcomes are already identified and the investigation looks backwards to assess antecedents, retrospective studies can be completed quickly and require fewer resources. Multiple antecedents can be investigated simultaneously. These studies can begin with an adequate number of cases and controls, and there is minimal risk of dropouts. However, the demerits include the potential for recall lapse, especially when subjects are asked to recall past events — milder events are often forgotten, while severe ones are more easily remembered. Some participants may intentionally withhold information, leading to biased results. This design cannot assess risk directly, as risk has future implications; instead, odds ratios are calculated. Establishing a cause-effect relationship is more difficult in a retrospective design because the temporal sequence of events can be ignored easily.

Conversely, these precisely are the merits of a prospective design. A prospective observational study can assess risk, and both negative and positive predictive values of the antecedents for an outcome can be calculated. This design can come closer to establishing a cause-effect relationship. These are the two major strengths of prospective studies. They provide greater confidence in the results because all events are observed in real-time as they occur. However, if the outcome of interest is rare, the final number of cases may be low, which reduces the statistical power to detect an effect. Moreover, prospective studies are expensive due to the need for follow-up. Dropouts can occur, and some subjects may change their status during the follow-up period, introducing a potential bias.

Cross-sectional studies can provide credible results when the chosen sample adequately represents a full spectrum of the target population, and both antecedents and outcomes are properly assessed. This design has minimal risk of recall bias or similar errors, as data collection occurs at a single point in time. In conclusion, the choice of study design in observational research should be guided by a careful consideration of the various merits and demerits discussed in this article.

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