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A review on comparative observational studies

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ABSTRACT

Observational studies are a significant type of research. Randomized controlled trials are not always necessary or ethical to answer some investigative problems in plastic surgery. Observational studies, on the other hand, may be the next best way for answering these types of questions. The outcomes of well-designed observational studies have been proven to be comparable to those of randomized controlled trials, debating the notion that observational studies are inferior. Cohort studies, Case control studies and case-control studies are three common types of observational studies used to assess disease-exposure relationships. In medical research, where feasibility and ethics are critical, observational studies are useful. The many forms of observational studies each have their own set of strengths and limitations, and a thorough grasp of these is essential for their execution and interpretation. This review comprises basic information about Cohort studies, Case control studies and case-control studies.

Keywords: Cohort studies, Case control studies, Observational studies, and randomized controlled trials

INTRODUCTION

Medical researchers are frequently interested in learning how a specific risk/therapeutic factor affects the disease/health outcome. A logical technique for producing such evidence is to compare two groups. The comparison groups might be determined by a) exposure/risk factor, b) disease/outcome, or c) intervention. The groups to be compared in observational studies are not based on the investigator's intervention or manipulation. As a result, the basis of such research projects is membership in an exposure or outcome group. An observational study might look at the influence of industrial pollution on people's health by comparing the health of persons who live in an industrial area to those who live in a nonindustrial area. [1]

Because the investigator does not intervene, these studies reflect comparative effectiveness in real-world circumstances and hence have a higher external validity. However, observational studies have some drawbacks. In observational research, the key difficulties to be considered are selection bias, information bias, and confounding. Other biases that can impair observational studies are discussed in more detail elsewhere.[2]

Rationale of using Observational studies over Clinical Trials

Despite the advantages of randomised controlled trials (RCTs), such as randomization and allocation concealment, there are times when RCTs or other interventional studies are inappropriate or not practical. Experimentation may be insufficient in circumstances where the outcome of an intervention is dictated by the care provider's activity, such as physiotherapy or surgery. Even when examining uncommon disorders, a clinical trial with a significant number of participants may not be practical. It may also be unethical to conduct an interventional study in certain circumstances, such as when researching the effects of a dangerous substance such as tobacco on health; you cannot expose someone to the harmful substance for the sake of your research.[3]

There is little difference between the results obtained from observational studies and RCTs and hence factors other than study design per se need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies. Thus a proper appraisal of the study design is critical to interpret the findings. The 'type of study design' alone, cannot be the endpoint in debates concerning the strength of the evidence generated.[4]

Types of observational studies

Crosssectional (prevalence study), case-control, and cohort studies are some of the common types of observational research.

Cross Sectional Studies

A cross-sectional study is a form of observational study design used in medical research that looks at data from a

population at a single point in time. Investigators assess outcomes and exposures of study patients simultaneously in a crosssectional study. Taking a "snapshot" of a group of people is how it's characterised.[5]
In clinical research, cross-sectional studies have primarily been employed to determine the prevalence of an illness. The proportion of people in a population who have a particular disease or attribute at any given time, regardless of when they originally developed the ailment, is referred to as prevalence. It's critical to distinguish between prevalence and incidence. The number of new cases that arise in a certain period of time is referred to as incidence. Researchers explain the distribution of variables in a population in a cross-sectional study. They can determine the prevalence of a disease or the relationship between an exposure and a specific result in a community.[6]

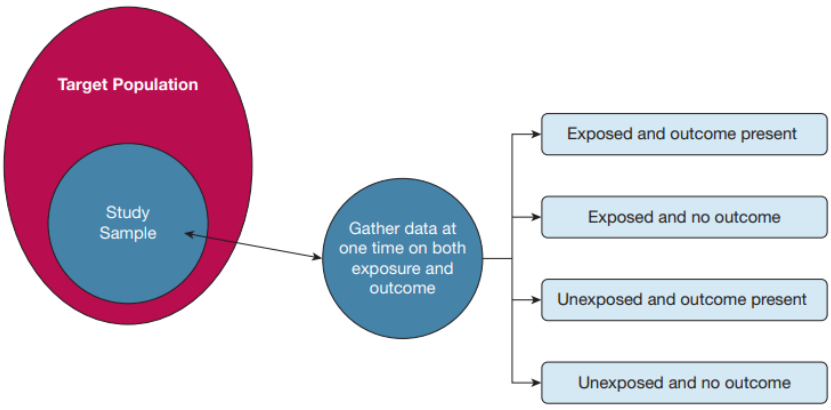

Fig 1: A schematic representation of a typical cross-sectional study. [6]

Study Subject Considerations

Sample size determination

The decision of sample size is a crucial stage in the design of a cross-sectional study. A descriptive cross-sectional survey and an analytical cross-sectional study have distinct sample size computations. The purpose of a descriptive cross-sectional survey is to determine the prevalence of a specific outcome. The prevalence rate, p, the desired margin of error, e (also known as the desired precision), and the significance level must all be provided by the investigators. Because statistical power only pertains to statistical comparisons, the sample size in a descriptive study does not depend on it.[7]
The generally used sample size formula for comparing two prevalence rates in an analytical cross-sectional study is the same as for planning a cohort study. The following statistical hypothesis is used to compute the sample size:H0:p1 ¼ p2 vs: H1:p1sp2. The investigators must supply a prevalence estimate, the variation of prevalence estimates, a meaningful difference between those exposed and those unexposed, the significance threshold, and the desired power to calculate the sample size..[8]

Sampling

Cross-sectional study design requires careful planning of the sample approach. In epidemiology, sampling is the process of selecting certain members or a subset of the entire population to estimate the population's characteristics. Because of the significant variation in the target population, creating a sound sample plan in a crosssectional study is crucial. There are two types of sampling methods: (1) probability sampling methods, which pick samples using a method based on probability theory, and (2) nonprobability sampling methods, which select samples based on subjective assessment. Probability sampling methods are generally favoured over nonprobability sampling methods because the former are thought to be more precise and rigorous. Random sampling, on the other hand, is not always practicable or practical in applied clinical research. In these cases, nonprobability sampling is used.[9]

Bias

When planning a cross-sectional study, researchers should keep bias in mind. Any systematic inaccuracy in a study that leads to an erroneous assessment of the true effect of an exposure on the outcome of interest is known as bias. There are various sorts of bias in clinical trials, however they can be divided into two categories for ease of understanding: selection bias and information bias. When the sample chosen or collected in a study is no longer representative of the general population, selection bias arises. It can be used if patients are chosen from a group having a higher or lower risk of developing a disease, or if the exposed and unexposed groups differ in ways that predict the result. Nonresponse bias is a typical type of selection bias that occurs in crosssectional survey studies using postal questionnaires. Nonresponse bias occurs when nonresponders' characteristics differ from those of respondents. Cross-sectional studies are especially prone to prevalence incidence bias (also known as the Neyman bias).[10]

Statistical Considerations

Confounding

When a variable is linked to the exposure and effects the outcome, confounding can occur in analytical cross-sectional studies. A variable must meet three criteria to be considered a confounder. The variable must be: (1) linked to the exposure being studied; (2) linked to the result being studied; and (3) not part of the causal chain linking exposure and outcome. Confounding could cause the relationship between exposure and outcome to be distorted.[11]
Confounding can be avoided or controlled using a variety of statistical techniques. Restriction, stratification, and matching are examples. For the sake of restriction, investigators limit research participants to those who are comparable to the

confounders. The study of the relationship between exposure and outcome within multiple strata of confounding variables is known as stratification. Propensity score matching is a statistical strategy that involves creating matched sets of two groups of people with identical propensity score values.[12]

Modeling

Investigators may create explanatory regression models or diagnostic prediction models in analytical cross-sectional investigations. Variables with a scientifically meaningful and statistically significant association with an outcome are discovered in an explanatory model. Multiple predictors are used in a diagnostic model to assess the chance that a certain illness or disease is present at the time of prediction. In cohort studies, diagnostic models differ from prognostic models, which are frequently longitudinal.[13]

Use Cases of Cross-Sectional Studies

Thomas et al conducted a descriptive cross-sectional survey on the prevalence of dysfunctional breathing in patients treated for asthma in primary care. Of the 4,381 patients aged 17 to 65 years registered with a diagnosis of asthma from the medical records of a semirural general practice, 307 (7%) met the entry criteria and were sent the Nijmegen Questionnaire for self-completion. A total of 227 questionnaires were returned after one mailing (response rate, 74%), of which 219 were suitable for analysis. The main outcome was a score $ 23 on the Nijmegen Questionnaire. In this study, the investigator found that about one-third of women and one-fifth of men had scores suggestive of dysfunctional breathing.[14]

Strengths and Weaknesses of Cross-Sectional Studies

Table 1: Strengths and Weaknesses of Cross-Sectional Studies [14]

Strength	Weakness
• Relatively quick and inexpensive to conduct No ethical difficulties • Data on all variables are only collected at one time point • Multiple outcomes and exposures can be studied • Easy for generating hypotheses • Many findings can be used to create an in-depth research study	• Unable to measure the incidence • Difficult to make a causal inference • Associations identified might be difficult to interpret • Unable to investigate the temporal relation between outcomes and risk factors • Not good for studying rare diseases • Susceptible to biases such as nonresponse bias and recall bias

Cohort Studies

The term "cohort" in modern epidemiology refers to "a group of people with defined characteristics who are followed up to determine the incidence of, or mortality from, some specific disease, all causes of death, or some other outcome."[15]
In clinical research, cohort studies are appropriate when there is evidence to suggest an association between an exposure and an outcome, and the time interval between exposure and the development of outcome is reasonable. Cohort studies are the design of choice for determining the incidence and natural history of a condition. Due to their longitudinal design feature, one can look at disease progression and natural history.[16]

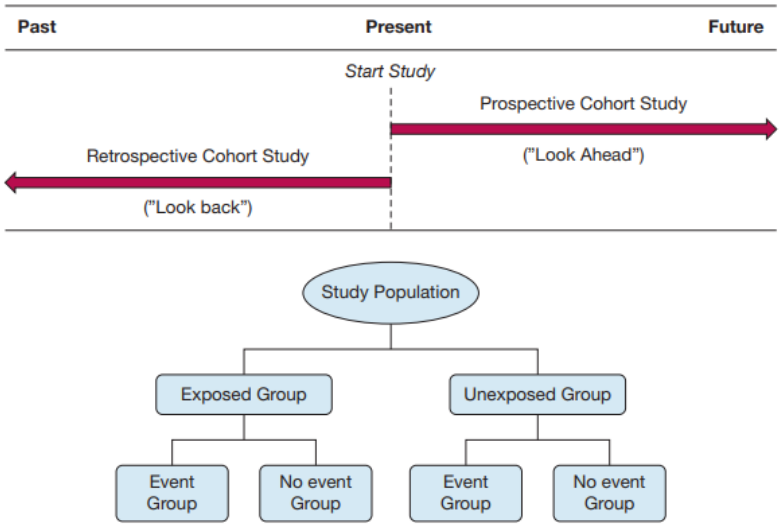

Fig 2: Graphical representation of the timeline in a prospective vs a retrospective cohort study design.[16]

Study Subject Considerations

A cohort study's subjects must be taken into account in numerous ways. These include choosing an acceptable sample of the population of interest, the sampling procedure to be employed, availability to longitudinal data for the participants chosen, and the sample size needed to power the study properly. The inclusion and exclusion criteria should be defined at the study design stage. The study subjects chosen should be appropriate for the research question and generalizable to the target population.[17]

A comparison of incidence rates is usually the major aim of a cohort study. Assume that and p1are the incidence rates of the end point of interest in the exposed and unexposed samples. The sample size is typically calculated based on the following statistical hypothesis: H0 : p1 ¼ p2 vs H1 : p1sp2 [18].

Statistical Considerations

Cohorts are frequently used by researchers to examine the relationship between various exposures and numerous outcomes over time and to develop prognostic/prediction models. In cohort studies, the modelling and analytic method could be more sophisticated. A few key aspects of statistical analysis are highlighted below.

Bias

Any systematic inaccuracy in a clinical trial that leads in an erroneous assessment of the true effect of an exposure on the outcome is referred to as bias. Loss to following is a key source of possible bias in cohort studies. Dropouts or death, which are common in trials with long follow-up periods, cause this. A typical rule of thumb is that no more than 20% of the sample should be lost to follow-up.[19]It is recommended that investigators examine any systematic differences related to the outcome and/or exposures between those who completed the study and those who were lost to follow-up. Methods of minimizing loss to follow-up in a prospective cohort study have been comprehensively discussed by Hulley et al.[20]

Confounding

In cohort studies, confounding is common. A variable must meet three criteria to be considered a confounder: (1) it must be linked with the exposure being studied; (2) it must be connected with the outcome being studied; and (3) it must not be in the causal route between exposure and outcome. Confounding can cause effects to be distorted; it might cause an effect to be overestimated or underestimated, or even reverse its direction. Alcohol consumption, for example, was linked to lung cancer in one study. Alcohol use increases the likelihood of smoking, which is a risk factor for lung cancer. Taking into account the potential confounding effect of smoking, there may be no link between alcohol use and lung disease.[21]

Model Building

In cohort studies, model creation is frequently required. Explanatory or predictive models may be required by investigators. In explanatory modelling, the goal is to find factors that have a scientifically relevant and statistically significant relationship with a given outcome. The purpose of predictive modelling is to forecast the likelihood of or risk of an individual's existence (diagnosis) or future occurrence (prognosis) of a particular event. The variables chosen for inclusion in a model (explanatory or predictive) should be based on critical assessment of relevant literature or medical expert knowledge. Stepwise selection should only be used in a few situations, such as during the early stages of constructing a model or when there is a lack of understanding of what is needed. [22]

Reporting Considerations

We recommend that investigators record their cohort studies using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, which includes a checklist of 22 items that are considered essential for observational study reporting. We recommend that investigators consult the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement if multivariable prognostic prediction models are developed in a cohort study to be used in predicting future outcomes in individuals at risk.[23]

Use Cases of Cross-Sectional Studies

Short et al performed a retrospective cohort study to examine the effect of b-blockers in the management of COPD. They searched a disease-specific database of patients with COPD and linked to the Scottish morbidity records of acute hospital admissions, the Tayside community pharmacy prescription records, and the General Register Office for Scotland death registry. A total of 5,977 patients aged > 50 years with a diagnosis of COPD were identified and divided into two groups according to b-blocker use. The study found that b-blockers might reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt cardiovascular disease and cardiac drugs, and with no adverse effects on pulmonary function.[24]

Strengths and Weaknesses of Cross-Sectional Studies

Table 2: Advantages and Disadvantages of Cohort Studies [23]

Strength	Weakness
• Can investigate multiple outcomes that may be associated with multiple exposures • Able to study the change in exposure and outcome over time • Good for examining rare exposures • Can measure incidence of outcome May be able to infer causality	• Susceptible to loss to follow-up compared with cross-sectional studies • Confounding variables are the major problem in analyzing the data compared with RCTs

Case Control Study

Case-control studies begin with case and control subjects (i.e., the outcome of interest is known) and look back retrospectively at the subjects' exposures to find an association. This differs from prospective cohort studies, which involve observing a cohort of subjects with variable levels of the exposure of interest over time to relate the occurrence of the outcome of interest to the exposure. We estimate the prevalence of health outcomes in a community at a given time point or over a very short period of time using data collected from persons who are similar in all factors save the health outcome under study in a final observational design, cross-sectional research. [24]

Finding an acceptable research base from which to pick the control group is the main problem in a case-control study. The simplest way to choose a control group is to take a random sample from the research population, with control participants chosen irrespective of the case subjects' characteristics. Another option for selecting the control group is to divide the study population into separate strata based on stated matching criteria, then randomly choose case and control group subjects from each stratum so that case and control subjects are comparable in terms of those matching criteria. The matching criteria are based on prior knowledge of a link between the outcome of interest and the matching criteria.[25]

Case-Control Study Subtypes

The case-control study can be subcategorized into four different subtypes based on how the control group is selected and when the cases develop the disease of interest.

Nested Case-Control Study

A nested case-control study is one in which a case-control study is conducted within a cohort study. Cohort subject exposures and characteristics are examined at the start of the cohort study in a nested case-control research. At a later point in time, case and control subjects are identified. The control group is made up of cohort members who do not satisfy the case definition at a later point in time. Case subjects are the remaining individuals of the cohort who fulfil the definition of a case at a later time point. In a nested case-control study, the difficulty of selecting control individuals in a traditional case-control study is lessened. The control group should be made up of a random sample of people from the general population, which is not always practicable in practise. [26]

Case-Crossover Study

The influence of transient exposures on the risk of acute event onset is studied using a case-crossover methodology. Because the individual belongs to the control group at the start of the trial and before the onset of the acute event, each case acts as its own control in a case-crossover study. There is a period when a person was a case, known as the "case window," and a period when the person was not a case, known as the "control window," for each individual. We compare the risk of exposure during the case window to the risk of exposure during the control window after collecting data throughout time. [27]

Matching in Case-Control Studies

Subject traits or other exposures may be linked to both the risk exposure and the study outcome in a case-control study. These factors may alter the association being explored if they are not taken into consideration. These confounding factors should be controlled for in the study design and/or analysis. Selecting participants using "matching" principles is one technique to control the effect of confounding circumstances. In a matched case-control study, subjects in the control group are chosen in such a way that they share some features (possible confounders) with those in the case group. The matching variables can be categorical or continuous.[28]

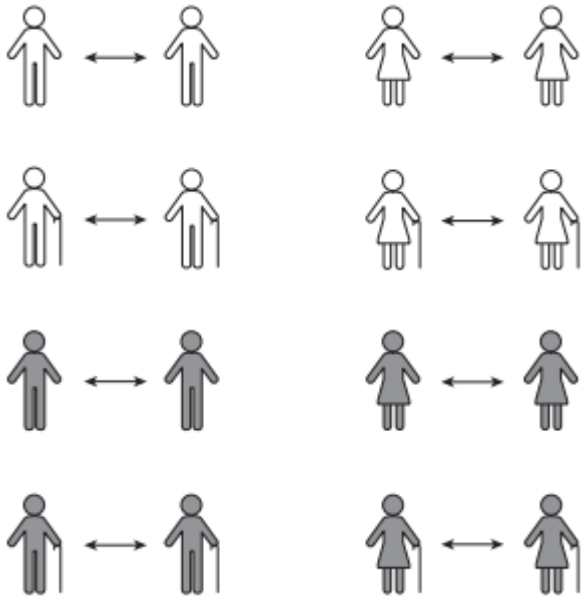

Fig3: Graphical representation of matching in a case-control study

Sample Size Selection in Case-Control Studies

Choosing an appropriate sample size is critical in any observational study since having the right number of samples assures the study's findings are reliable. Many studies have insufficient sample sizes, making negative outcomes difficult to interpret. The chance of identifying an effect when it is statistically significant is the power of a test. The basic rule is

that the larger the sample size, the more precise or powerful a study will be in detecting an impact of a given size. The sample size needed to appropriately power a study is determined by the effect size we want to detect, the data variability (SD), and the test size.[29]

Odds Ratio vs Relative Risk

It is critical to determine how much the link between the exposure or risk factor explains for a health result in any clinical investigation. The odds ratio (OR) and relative risk (RR) are two measurements that quantify this relationship. In a cohort research, the investigator separates the individuals into two groups based on whether they were exposed or not, and then tracks them over time to see who develops the outcome. The ratio of the number of persons who develop the result to the total number of individuals in the group can be used to calculate the risk or incidence of developing the outcome in that group. In this scenario, a natural measure of association may be calculated by dividing the risk of developing the outcome in the exposed group by the risk of developing the outcome in the unexposed group. The relative risk is defined as this ratio. Another way to quantify the link is to calculate the outcome's OR, which is defined as the ratio of the odds of an exposed person developing the outcome to the odds of an unexposed person developing the outcome. [30]

A typical observational study design can be simply expressed in tabular form as follows:

	Case Subjects	Control Subjects
Exposed	a	b
Unexposed	c	d

From this study design table, the relative risk and OR can easily be expressed as: [31]

$$\text{Relative Risk (RR)} = \frac{a/(a+b)}{c/(c+d)}$$

$$\text{Odds Ratio (OR)} = \frac{a/b}{c/d} = \frac{ad}{bc} \textbf{ for outcome}$$

When OR ¼ 1, odds of the outcome are the same for exposed and unexposed, whereas OR > 1 indicates that the odds of the outcome are higher for those exposed, and an OR < 1 indicates that odds of the outcome are reduced for those exposed. Relative risk has a similar interpretation.[30]

In contrast to this scenario, in case-control studies, the investigator groups the participants based on the presence or absence of the health result, then determines the risk factor of interest exposure in these two groups retrospectively. Risks cannot be computed to measure relative risk due to a lack of knowledge about the prevalence of the result. Comparing the distribution of the exposure, on the other hand, aids in quantifying the relationship between the exposure and the outcome. The OR for exposure is defined as the ratio of the odds of a person with the outcome being exposed to the odds of a person not having the outcome being exposed. This OR can be found in the design table previously indicated as:[32]

$$\text{OR} = \frac{a/c}{b/d} = \frac{ad}{bc} \text{ for exposure}$$

For rare diseases or outcomes, case-control studies are the most efficient design. They require fewer study samples than cohort studies. Also, in large cohort studies, there are several challenges of having a large sample to follow up over time. If correctly sampled with sufficient sample size, a case-control study can provide similar information to what can be obtained from a more expensive and labor-intensive cohort study. Case-control studies cannot be used to determine an estimate of rate or risk, as the denominator of these measures is not available. Any type of case-control study may have some bias because it is retrospective, and thus patients may fail to correctly recall details about their exposures. There can also be a selection bias due to a faulty selection of an appropriate source population.[33]

CONCLUSION

Study design forms a core component of research, mainly determined by the study objectives, and it in turn further decides the type of statistical analyses to be carried out. Observational studies are devoid of the investigator's control over assignment of a subject to the treated or control group, in contrast to interventional studies Even though randomized controlled trials are seen as the best study design, evidence shows that properly conducted observational studies give similar results, and is relevant in medical research where ethics and feasibility concerns assume great significance. Observational studies point out towards possible causal associations, are less resource intensive than trials and have a better external validity.Observational studies are relevant in medical research where feasibility and ethics are indispensable components. The various types of observational studies have their own merits and limitations and a proper understanding of these is required for implementation and interpretation of such study designs.

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