An introduction to observational studies

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A clinical trial is a planned experiment designed to evaluate the benefits of a treatment for a specific medical condition. A well-designed clinical trial is the most rigorous research design for evaluating treatments. However, there several situations where it is neither possible nor ethical to conduct a clinical trial. In these situations, observational studies may be more appropriate in evaluating possible associations between a factor of interest (not necessarily treatment) and a particular disease or outcome. In observational study designs, the investigator has no control over the exposure of individuals. Study participants are observed and data are collected but nothing is done to influence either the exposure or the course of events. We will consider three main observational study designs in this article.

Aims:
To understand key concepts of observational study designs

Objectives
- Give concrete examples where clinical trials are not possible
- Explain characteristic design features, strengths and weaknesses of cross-sectional, case-control and cohort studies
- Enumerate some advantages of clinical trials as compared to observational studies

A clinical trial is a planned experiment designed to evaluate the benefits of a treatment for a specific medical condition. A well-designed trial is the most rigorous research design for evaluating treatments. However, there several situations where it is neither possible nor ethical to conduct a clinical trial. For example, consider a study to investigate the possible association between cancer and bullous pemphigoid. Individuals cannot be randomized to either condition. Alternatively, it is not ethical to randomize individuals to smoke, and therefore a clinical trial would not be possible in examining the role of smoking in the development of psoriasis. Moreover, clinical trials can be costly and both time- and resource-intensive, whereas other study designs may require less investment.

There are other study designs that can evaluate possible associations between a factor of interest (not necessarily treatment) and a particular disease or outcome. In observational studies, the investigator has no control over the exposure of individuals. Study participants are observed and data are collected but nothing is done to influence either the exposure or the course of events. For a clinical trial to provide reliable evidence of the impact of treatment, the trials need to be (i) *controlled*, (ii) *unbiased* (randomization is crucial), and (iii) large. When considering the impact of an exposure/s in observational studies, it is important to incorporate a control, or unexposed, group. For example, in assessing the impact of smoking on psoriasis, it is important that smokers are compared to non-smokers. In addition, observational studies can have large sample sizes, provided there are enough individuals with the exposure or outcome of interest. However, even if observational studies can be large, controlled studies, since participants are not randomized to the exposure of interest, these study designs are prone to bias. We will consider three main observational study designs in this article. We will start by generalizing the different types of design that observational studies fall under.

Prospective or retrospective
Prospective studies are those where data are collected from the start of the study onwards, and the trajectory of the study is to look forwards. For example, in assessing smoking and psoriasis, both smokers and non-smokers will be identified and recruited, and then followed up for the occurrence of psoriasis.
Retrospective studies are those where data are collected on information which occurred in the past (e.g. hospital records or interviews), and the trajectory of the study is to look backwards. An example might be to interview patients with psoriasis for their previous or current smoking history.

Longitudinal or cross-sectional
Longitudinal studies are those that look at information on individuals over time. In the two examples given for prospective and retrospective studies, both were longitudinal as they either followed individuals for psoriasis to occur or recorded past or current smoking history.
Cross-sectional studies collect information at a single point in time. For example, there may be interest in assessing the prevalence of cancer in patients diagnosed with bullous pemphigoid. A number of patients with bullous pemphigoid will be selected and included in the study, and their medical history checked at the same point in time as their inclusion for a previous or current diagnosis of cancer to look at the relationship between these two conditions.

Note: Clinical trials are prospective and longitudinal. Individuals are randomized to one of two interventions and then followed up prospectively over time.

I. Cross-sectional Studies

A cross-sectional study collects all information on participants at a single point in time. Data may be collected from a number of sources depending on the type of information required (e.g. interviews, questionnaires, medical examinations or hospital records). A cross-sectional study may be descriptive, analytical or a combination of both.

Descriptive

The simplest of all studies, a descriptive cross sectional study collects information on prevalence - the proportion of existing cases of a particular disease or condition in a given population at a designated time. For example, a survey might be conducted to measure the prevalence of adult-onset acne vulgaris in patients seen at the dermatology out-patient department.

Analytical

A cross-sectional study may also provide a measure of association between one or more possible risk factors and a disease or outcome of particular interest. For example, information may be collected on current dietary habits and presence of atopic dermatitis flares with the purpose of assessing the association between the two.

As abovementioned, in a cross-sectional study (and any other observational study) the exposure of interest is not allocated at random and therefore interpretation of results is more challenging, particularly because participants may differ in ways other than the exposure of interest itself. For example, suppose you were to conduct a cross-sectional study assessing the association between the use of isotretinoin and depression, and results suggest there was a greater prevalence of depression among those who are taking isotretinoin. The results could very well be because isotretinoin causes depression, however, the same results could also be due to the fact that those who take isotretinoin have severe, recalcitrant acne, and it is acne that causes the depression. This would be an example of confounding which is crucial to consider in analyzing observational studies. In large, well-designed clinical trials, randomization uses a chance process to allocate participants to one of the treatments. Any differences in outcome between the groups may then be reliably attributed to the treatment under investigation rather than other causes because randomization allows the groups to be similar at baseline in terms of known and unknown factors, and avoids allocation of subjects to treatments likely to give the most optimistic results. Moreover, because information on the exposure and outcome are collected at the same time in cross-sectional studies, it is difficult to establish whether the exposure occurred before the outcome.

Cross sectional studies	
Strengths	**Weaknesses**
• Relatively easy and cheap to conduct • May provide information on the distribution and burden of exposures and outcomes in a population	• Limited use in establishing causal relationships between an exposure and outcome • Prone to a number of biases • Difficulty in establishing the time-sequence of events unless exposure is fixed (e.g. gender or genetic markers)

Table 1. Strengths and weaknesses of cross sectional studies.

II. Case-control Studies

In case-control studies, a group of individuals are identified from a specified study population who have some outcome of interest (the cases), and a control group is then identified comprised of individuals without the outcome of interest (the controls). For example, in the study investigating the association of smoking and psoriasis, the cases will include individuals diagnosed with psoriasis, while the controls are individuals without psoriasis. Information is then collected from the cases and controls on their past exposure to one or more factors of interest (in our current example, their smoking history). Examples of methods collecting information include interviews or patient records. The premise of case-control studies is that if cases have higher levels of exposure than the controls, then this exposure *may possibly be* be a risk factor for the disease.

In case control studies, two important issues must be addressed: 1) the *criteria used to identify cases* (precise definitions, how cases will be selected) and 2) *selection of an appropriate control group*. Controls must be selected from the group of individuals who would have been considered for selection as cases if they had developed the disease during the study period (e.g. similar age, gender, or place of residence).

Similar to cross sectional studies, case-control studies are prone to bias, particularly recall and observer biases. Many case-control studies collect information on past exposures via interviews with the individuals concerned. Recall bias occurs when there are differences between cases and controls in recalling past exposures. Individuals who have the disease or outcome of interest may be more likely to think about possible exposures which may have led to the outcome. For example, patients with melanoma may be more likely to recall episodes of sunburn than healthy controls, which would overestimate any association. Conversely, those with melanoma would less inclined to report such exposure because of the perceived stigma that the melanoma was due to the sunburn. On the other hand, observer bias occurs when the assessment of the exposure status of an individual is affected by knowledge of whether that individual is a case or control. For example, in a case-control study assessing the impact of weight on delayed wound

healing, there may be a tendency (conscious or subconscious), to round up the measurements of the cases and round down the measurements of controls, therefore overestimating the impact of weight on wound healing.

Case control studies	
Strengths	**Weaknesses**
• Relatively easy and cheap to conduct • Suitable for rare diseases or diseases with long latent periods because participants are selected on the basis of their outcome not exposure status • Can study multiple exposures for a single outcome • Do not have losses to follow-up	• Prone to many biases • Often cannot establish the sequence of events (e.g. the exposure may be a consequence of the outcome) • Not suitable for studying rare exposures because few individuals would have the exposure of interest • Cannot be used to measure prevalence (or incidence) of disease (only the prevalence of the exposure among those with/without the outcome)

Table 2. Strengths and weaknesses of case control studies.

III. Cohort Studies

In cohort studies, individuals who are exposed or unexposed to a potential risk factor are selected and information on other characteristics and risk factors are collected. These participants are then followed up over time and the incidence (number of new cases of a disease or event in a population during a specific period of time) of the disease or outcome of interest is compared between the groups. This observational study most closely resembles a clinical trial because individuals are identified according to their exposure status and followed up for the outcome of interest. However, as all observational studies, individuals are not randomized to the exposure of interest.

In our previous example where we would like to assess the impact of smoking on psoriasis, in cohort studies, smokers and non-smokers may be followed up over time and the incidence of psoriasis compared to see whether this is higher in those who smoke. While cohort studies collect data on exposure and then follow individuals over time to document outcome development, the information can be collected prospectively or retrospectively. In the former, the exposure status is determined at the time individuals enter the study. This reduces the potential for bias, and has the added benefit of allowing the investigator to control what information is collected, ensuring its quality and completeness. However, prospective cohort studies often require long follow-up periods. On the other hand, retrospective cohort studies rely on historical records to provide information on potential exposures.

Although a well-designed cohort study is the most reliable of the observational studies, it can be costly, time-consuming and are still prone to bias. Two of the main biases are losses to follow up and observer bias. Because participants are often followed for long periods of time, the former can be a problem. Observer bias may occur when the assessment of the outcome of an individual is affected by information on his/her exposure status. Ideally, the method of ascertaining outcomes should be made without knowledge of exposure status.

Cohort studies	
Strengths	**Weaknesses**
• Unbiased in terms of disease development because exposure is measured before disease occurence • Suitable for rare exposures • Can study multiple outcomes for a single exposure • Can measure the incidence of disease in both exposed and unexposed groups • Most reliable observational design where trials are not possible	• Can be expensive and time consuming (particularly for prospective studies) • The exposure status and diagnostic criteria for outcome may change over time • Outcome ascertainment may be influenced by knowledge of exposure status • Losses to follow-up can cause bias • Less suitable for studying rare outcomes

Table 3. Strengths and weaknesses of cohort studies.

Although a well-designed and properly conducted clinical trial is the most reliable method to evaluate treatments for specific diseases, observational studies can provide insight into possible associations between exposures and outcomes. In some situations, observational studies may be the only way possible to assess such relationships. However, it must be recognized that observational study designs are prone to considerable bias. Three study designs were introduced in this article, and, in general, well-designed cohort studies are prone to less bias than cross-sectional or case-control studies.

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