XI. From Clinical Judgment to Case-control Design

Juan O. Talavera, Rodolfo Rivas-Ruiz

The case-control design, just as the historic cohort, is loaded with a series of potential biases resulting from reconstructing the facts once the outcome has occurred, in addition to biases generated by the selection of the control group. It is characterized by having a series of cases for which a comparative group (controls) is identified. That is, it goes from the outcome to the cause and, consequently, facts must be reconstructed in the opposite sense as to the way the causality phenomenon occurs. Nevertheless, architectural design will have to be borne in mind and in each section —baseline state, maneuver and outcome— those features necessary to demonstrate the effect of the maneuver will have to be considered, thus preventing an inadequate assembly and the susceptibility, performance and detection biases. Transfer bias can only be controlled by having a defined population, either based on general population or nested in a cohort. When a defined population is not available, this design is recommended only for rare diseases.

Key words
- case-control studies
- clinical trial

Although the case-control study is apparently a simple design for solving questions, it is without any doubt the most complex. Like the historical cohort, it is loaded with a series of potential biases resulting from the reconstruction of the events preceding the outcome, in addition to the biases in the selection of the control group. Therefore, this design should be considered only in cases where answering the clinical question through a clinical trial or a cohort study is not possible.

The collection of the information required to document the causality phenomenon —described under the concept of research architecture or clinical judgment (Figures 1, 2 and 3)— is carried out, in ideal conditions, by means of a clinical trial, whose most important characteristic is the assignment of the maneuver (experimental). When this design is not possible, the cohort is used, which preserves the opportunity of following the study population over time, with the possibility for the maneuver to be documented before the outcome occurs (longitudinal). However, the case-control design will have to be considered if the uncommonness of the phenomenon being analyzed, the difficulty to complete the sample size or the relevant use of resources, force to do so.

This design is characterized by having a series of cases for which a control group (comparative group) is identified. Unlike the clinical trial and the cohort study —where the maneuver is assigned (experimental) or identified before the outcome (observational) and a follow-up is conducted until its assessment (longitudinal)—, the case-control study tries to reconstruct the effect of the maneuver once the outcome has occurred (for the cases) or its absence documented (control group) (Figure 4). That is, it starts from the outcome and the information is reconstructed in the direction of the probable cause (figure 5); this design requires for the facts to be reconstructed in the opposite sense as to the way the phenomenon of causality occurs.

Main Characteristics

Case-control design has limits in documenting information, which are similar to those in historical cohort studies (Table 1) and, as a consequence, biases are similar.

Exposure to the Maneuver

This is an observational study that only measures the exposure to maneuver. Unlike cohort studies, the maneuver here does not divide the subjects in two groups (in the cohort, exposed and unexposed), but identification of exposure is part of the fact of being a
case or a control, which causes that within each one of these groups (cases or controls) a subgroup is generated of exposed and unexposed subjects (Figure 5). Documenting the effect of the principal maneuver in case-controls studies —conversely to what happens in clinical trials, where baseline conditions and co-maneuvers are controlled and the principal maneuver is randomly assigned— implies recording all possible confounding variables present at the baseline state (susceptibility bias) or how do co-maneuvers participate (performance bias).

**Subject Follow-up**

Some authors consider case-control studies to be longitudinal when records exist prior to the outcome, both for cases and for controls. However, it is difficult for this to happen, except for vaccine records, which are kept in the entire population, or when the study is performed in a cohort; in these situations, the quality of evidence will be higher, since exposure measurements will be known before the outcome appears.

In most cases, the reconstruction is made using interviews, whereby the record of what happened with the exposition and the outcome is simultaneous (transversal). This way of getting information is common when the control group members are related to the cases or when they agree to participate in the trial by telephone or Internet; this can even happen with hospital controls, although in these, information can occasionally be reconstructed longitudinally if previous records are available. Obtaining information in a
Figure 3 Characteristics that have to be considered in order to prevent detection and transfer bias

Cross-sectional form may produce biases due to poor data quality in all components of the causality phenomenon (baseline state, maneuver, outcome), commonly due to differential recall between the cases group and the control group members.

Directionality in Measurements

The case-control design is retrospective (retrospective). Unlike historical cohort—which is also retrospective, but whose population assembly is made based on the baseline state—, population assembly is made on the basis of the outcome (either case or control). That is, at best, the quality of information depends not only on its previous collection with purposes other than the objective of interest (e.g. the vaccination record was not designed thinking on further evaluating its association with any pathology and, similarly, a lot of confounding variables were omitted), but also transfer biases in a cohort of survivors (in a population defined according to the baseline state, it is possible to include both alive and dead cases and alive and dead controls).

Search for Association

The search for a control group for a series of cases is always carried out attempting to establish associations.

First, a series of cases is identified (AMI = acute myocardial infarction) and a control group is selected (without AMI)
The presence or not of exposition to the factor of interest is documented. Starting from the outcome, probable cause is tried to be identified.

Figure 5 Case-control study. Exposure documentation

Selection of the Control Group

Selecting the control group is the most difficult process in this type of design, and it can induce bias in all sections of the causality phenomenon, especially transfer bias.

Usually, the members of the cases group are selected among patients that in spite of being cared for in the same medical unit, they come from different geographical areas. They are pre-selected patients: in theory, they looked for medical care for different reasons; then, they had to be assessed by at least one doctor before reaching the hospital; in addition, they have to agree to participate or not in the trial and meet a series of selection criteria. Thus, it is difficult to define which population they come from or whom they represent.

Defined Population

If the population where the cases come from is known and, in turn, it is clearly defined, the biggest difficulty

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**Table I Main characteristics of the case-control studies**

<table>
<thead>
<tr>
<th>Design</th>
<th>Observational/Experimental</th>
<th>Longitudinal/Transversal</th>
<th>Prolective/Retrolective/Retro-prolective</th>
<th>Comparative/Descriptive</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>Observational</td>
<td>Longitudinal</td>
<td>Prol/Retro/Rp</td>
<td>Comparative</td>
<td>Incidence</td>
</tr>
<tr>
<td>Case-control</td>
<td>Observational</td>
<td>Long/Cross</td>
<td>Retrolective</td>
<td>Comparative</td>
<td>Case/control ratio</td>
</tr>
</tbody>
</table>

The methodological approach considers four features: 1. Imposition or not of the maneuver for investigational purposes: experimental or observational study. 2. Patient follow-up (longitudinal) or not (cross-sectional) over time. 3. Directionality in the collection of information: prolective, retrolective and retro-prolective. 4. Search or not for association of two or more variables: comparison or description. Measurement of outcome occurrence is determined by incidence, prevalence or case-control ratio.
of the study design is solved. This happens when the case-control study is population-based or when it analyzes a group nested in a cohort. In both situations, the total population where the cases come from is available and, evidently, this is where the controls will be selected from. It is even possible to determine which group the deaths (if any) correspond to. When the number of subjects in the population exceeds the size calculated for the sample, it is also possible to make a random selection of cases, as well as of controls.

Given that generally in cohort studies the information of the population under analysis is documented—which was measured before the occurrence of the outcome that will be examined in the case-control study—, errors are avoided in the documentation of such information. Cohort-nested case-control studies have additional characteristics: they usually are restricted to the analysis of elements of interest obtained during the initial assessment of the cohort (which would correspond to the baseline state from the case-control study), instead of addressing elements of the total cohort. This way, only the subjects who have developed the outcome and a control group are examined. This allows for resources to be optimized and to preserve the elements under study in the rest of subjects in the cohort (blood samples, tissues, etc.).

Undefined Population or from a Secondary Source

Since it is common for a defined population not to be available, there are different strategies to obtain control subjects likely to belong to the same population of the cases. The most usual is to include neighbors or friends of the cases, individuals invited by telephone or Internet (previously identified as coming from the same geographic region as the cases) and, in other occasions, hospital-based controls. Whichever the situation, usually there is a sub- or over-representation of the exposure that will alter the results.

Phenomenological Reconstruction of the Facts

Facts must be reconstructed according to the causality phenomenon, regardless of their own limitations on how the population is assembled (from outcome to exposure) and how the data are collected (retrospectively and transversally). For this, a series of recommendations exist:

- To clearly establish the criteria for integrating the population to be studied, applicable both to cases and controls (Figure 1). The questioning or search for information on records has to be transferred to the period that for each case or control would correspond to the baseline state, and the following should be attempted for the entire population:
  
  a) Restrict as much as possible the scope of the research only to subjects belonging to the same region.
  
  b) Define the diagnostic criteria, i.e., the population to be analyzed.
  
  c) Define the selection criteria, i.e., requirements to be met by subjects in which the outcome has not occurred or, if the interest is to assess its progression rather than its manifestation, in those in which it still is incipient. Although this might sound obvious, care should be taken to avoid that these criteria do not include subjects with indication or contraindication for the maneuver, but do include those in which the outcome is likely to occur. It is important to remember that the baseline state, even in the group of cases, must be free of the outcome. In fact, criteria are equal for both.
  
- Document all baseline state variables that are likely to modify the effect of the maneuver on the outcome, or that regardless of the maneuver contribute to the onset of the outcome (Figure 1).
  
- Clearly define the exposure and, if possible, graduate it for magnitude and time, as well as for all possible co-maneuvers (Figure 2).
  
- Specify the criteria defining the case and the control.
  
- Try to select recently diagnosed cases, in order to ensure that the exposition to the maneuver has not been modified after the diagnosis.
  
- Determine which will be the documentation sources to obtain data for the cases. These must be the same as for controls (figure 3).
  
- Standardize the way to reconstruct the information for both cases and controls, whether based on previously obtained data or by means of questioning. It would be erroneous obtaining the information for the cases from the record and for controls by means of questioning.
  
- Assign the tasks of facts reconstruction to different people. Ideally, those who obtain the baseline state information should have no contact with those documenting the exposure to the maneuver and, in turn, both should be different of those who document the outcome.
  
- Obtain the information in the order at which the causality phenomenon occurs (baseline state, maneuver and outcome).
Comments

Without a doubt, in addition to the mentioned errors, the reconstruction of events based on the outcome entails transfer biases, since in cases and controls only survivors are usually assessed.

It is advisable to avoid the case-control design as a strategy to document the causality phenomenon when the answer can be obtained by means of a clinical trial or a cohort. What this design has in common with the other research designs is that it is only a tool to document the causality phenomenon; therefore, the most important suggestion is to always maintain the mental structure of clinical judgment, by means of which three well-known elements are conceptualized: a baseline state where the distinctive characteristics of a group of subjects lead to their distribution in sub-groups according to their likelihood to suffer the outcome even before the exposure to any maneuver (prognostic demarcation); a principal maneuver with characteristics of its own, accompanied by a series of actions around it (co-maneuvers); and measurement of the changes in the baseline condition or the onset of new characteristics, known as the outcome.

That phenomenological structure, usual for clinicians—clinical judgment/research architecture—is universal and is not modified by the way the information is obtained, either in a clinical trial or an observational study. When performing a structured evaluation of an article or when trying to answer a question by means of a research study, the causality phenomenon should always be thought of from the clinical point of view.

Recommended readings