# USING CASE-CASE STUDY DESIGN: WHICH CAN BE THE PERFORMANCE?

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USING CASE-CASE STUDY DESIGN: WHICH CAN BE THE PERFORMANCE? (Abstract): The case-case studies compare groups of patients classified by the subtype of the disease they present, to identify specific risk factors for the sub-category of patients with a characteristic of interest. **Material and methods:** This analysis brings attention to the main characteristics of case-case studies, with the aim of facilitating the understanding of methodology and the adequate way of implementing it, and the interpretation of the obtained results. **Results:** Specifically, this study design identifies the differences regarding risk factors between disease's subtypes, reflecting their etiological heterogeneity. However, the association for potential risk factors that are common to comparison sub-groups cannot be identified and the risk revealed does not represent the risk level in the general population. One conducting a case-case study must consider both the characteristics of the chronic or infectious diseases category and the advantages and the limitation of this type of study. **Conclusions:** As advantages, the case-case study design helps minimizing the selection and recall bias and can be carried out for a shorter period of time, with fewer resources than conventional studies. Selection or information bias may persist, and caution is needed for the interpretation of results. **Keywords:** CASE-CASE STUDY, CASE-ONLY STUDY, BIAS.

Case-case studies are case-only epidemiological studies, a derived category from case-control studies which compares groups of patients classified by the subtype of the disease they present, in order to identify specific risk factors for the subcategory of patients with the characteristic of interest (genetic, histological etc.).

These studies are an alternative when population epidemiological studies cannot be carried out due to the unavailability of eligible participants or when resources are limited.

In general, epidemiological studies can explore only some of a disease's dimensions, having advantages and limitations in this regard. Therefore, an appropriate study design must be used to achieve the proposed objective, taking into consideration also the available resources, convenience, feasibility, costs, and ethical issues.

When none of the known epidemiological study designs allows the exploration of the disease's characteristics of interest, the design can be adapted in terms of the method (comparative groups, subject selec-

tion, statistical analysis) and measurement instruments.

The present analysis brings attention to the latest characteristics of case-case studies, with the final objective of facilitating understanding of methodology, how to efficiently perform it and how to correctly interpret the obtained results.

Case-case studies use as comparison group one of the disease's sub-category, to reflect the level of exposure in the source population, from which the cases originate. Because the comparison group also includes cases that have more frequent exposures to risk factors than the general population, it cannot represent the latter. Consequently, the measured association will not represent the risk of the disease in the general population.

As the exposure to risk factors is high in both the case and comparison groups, the potential association will be different from the one that might be revealed through classical (conventional) case-control studies. For the exposures that are very similar between cases and controls, the potential association will be masked or underestimated. However, if the risk factors are different between the comparison groups, the association can be easily identified, which suggests the existence of etiological heterogeneity.

**Studying the chronic disease category**

In the case of chronic diseases, the patients' belonging to one of the comparison groups can be identified with good accuracy by using genotyping (such as the presence of certain alleles), molecular characterization (for example the presence of cellular receptors), morphological characterization (histopathological aspects) or biomarker identification (1-4). In these studies, involving molecular tests, a gene-environment interaction (comparative analysis between genetic sub-categories) or the consequences induced by the causal factor (identification of a mutation, alteration of an intermediate marker etc.) can be revealed (4).

The errors in studies involving molecular biology data may be caused by differences in laboratory testing (laboratory method's complexity, inter-laboratory validity, working protocol), difficulty in identifying the errors, confounding factors, or misinterpretation of a biological marker significance (4). The presence of a factor associated with a disease (biomarker for molecular epidemiology) may represent an intermediate stage of a physiopathological process, or the consequence of changes induced by the causal factor and not the cause (4). At the same time, these types of studies use prevalent cases that may present a better survival, and the associated factor may be in fact a prognostic factor (4).

For the *cancer epidemiology*, the case-case studies can mainly identify risk factors, but also biomarkers of aggression (the risk of an aggressive subtype) or the risk of recurrence after treatment (1-3, 5).

For example, for *breast cancer*, a recent study identified an association between alcohol consumption and a lower risk for human epidermal growth factor 2-over expressing (H2E) receptors breast cancer compared to estrogen receptor positive (ER +) breast cancer (3). Regarding the aggressiveness of hormone receptor positive breast cancer (classified by histological grade and level of proliferation), in another study, an association was identified between nulliparity and highly proliferative (presence of K167 marker) tumors, obesity and high grade (poorly differentiated) tumors, and current use of combined hor-

mone therapy and low grade (well-differentiated) tumors (1, 5).

Another recent study on *prostate cancer* identified the SNPs (single nucleotide polymorphism) genes CYP17A1 (gene related to the synthesis and metabolism of steroid hormones), AR (androgen receptor gene), LHCGR (luteinizing hormone chorionic gonadotropin hormone receptor gene) and ESR (estrogen receptor genes) as biomarkers of prostate cancer risk, and rs743572, rs6162, rs6163 (in CYP17A1 gene), rs1256049 (in ESR2 gene) and rs2293275 (in LHCGR gene) variants as aggressiveness biomarkers (2).

**Studying the infectious disease category**

For infectious diseases, case-case studies can identify the source of contamination (or the route of transmission) for a rapid intervention to prevent the occurrence of new cases (6-9). Thus, in an outbreak investigation, the comparison group consists of non-outbreak cases, which were previously diagnosed and identified by the in-place surveillance system. As a result, the risk factor can have different significance between comparison groups and in consequence the real contamination source may not be identified, or the exposure may be very similar (over-matching) and the association underestimated (8, 10, 11).

In the case of comparative studies of infections caused by strains differentiated through the antibiotic resistance profile, phenotypically established, there is a risk for the low-level resistance expressing strains not to be identified and to be considered sensitive, causing cases' misclassification (9, 12, 13). Also, recall bias may be an issue when the assessment of exposures is recorded through patients' self-declaration (12).

The case-case comparison of different infectious diseases surveilled through passive systems, in which only a part of cases is registered, it will use only the selected cases, which are not representative for those present in the population (6). In this comparison, a selection bias can occur, if the cases' registration in the two surveillance systems are done differently, error that can be avoided by comparing the cases with the same disease caused by different strain subtype (characterized by phage profile, antibiotic resistance, plasmid profile) (6, 8, 11, 13, 14).

At the same time, the exposures may vary over time, and if the comparison is made with a control group identified in previous periods, the difference may be due to the dynamics over time and not to a real one (6). On the other hand, etiologically different infectious diseases may have some identical risk factors, which will not be identified through these case-case studies (11, 14). Sometimes, in the surveillance systems, the reported cases can mainly originate from clusters or only the severe ones can be declared, generating differences in the disease's severity among the compared groups (14).

As an overview, in order to use cases as a comparison group in the study of infectious diseases, they must originate from a sufficiently long surveillance period or from a sufficiently large population (cumulative national data) identified by a surveillance system which is stable over time and correctly records the exposures (6, 7).

When a case-case study design is envisaged, the main advantages and inconvenient should be considered to achieve a study with valid results (tab. I).

TABLE I.

**The main advantages and limitations of case-case studies** (1, 4, 6, 15).

| Advantages | Limits |
|---|---|
| - Minimization simultaneously of the selection and recall bias<br>- Short duration in time and less resources needed than population studies<br>- Selectively identify the association between a particular exposure and a disease's sub-category<br>- Useful for biomarkers identification and for the individual disease risk assessment improvement | - The found association does not represent the risk of the disease in the population<br>- Selection or information bias may occur<br>- Possibility for the two selected groups to remain not comparable<br>- It cannot measure the association for factors that are common to both cases and the control group |

## CONCLUSIONS

The main advantage of case-case studies is the minimization of both selection and recall bias. They are useful for the rapid identification of risk factors, consuming fewer resources than other analytical studies. The method is however restrictive to study only a part of a diseases' risk factors, being appropriate for the identification of those that cannot be highlighted by population studies. The risk factors identified by these studies allow the description of a disease's etiological heterogeneity, but do not represent the risk of the disease occurring in the reference population.

The case-case study can increase the ability to exploit data collected in routine surveillance systems and complete knowledge about causality and natural history of a disease. Nevertheless, the interpretation of the results should be done with caution, considering the compared groups (aspects related to diseases or characteristics of compared patients) and the possibility of a selection and recall bias persistence.

## CONFLICT OF INTEREST AND FUNDING

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## NEWS

### BIFIDOBACTERIUM LONGUM: PROTECTION AGAINST INFLAMMATORY BOWEL DISEASE

The prevalence of inflammatory bowel disease is generally associated with the change of the immune system and gut microbiota. Bifidobacterium longum is a symbiotic bacterium existed in the human gastrointestinal tract and has been demonstrated to be capable of relieving colitis in mice and can be employed as an alternative or auxiliary way for treating inflammatory bowel disease. Bifidobacterium longum can change the structure of the gut microbiota, induce and regulate immune responses, and reduce the expression of inflammatory cytokines and reactive oxygen species in the intestine. Besides, it can also maintain the normal intestinal barrier function by increasing the expression of the tight junction protein. Therefore, Bifidobacterium longum has great potential and can be used as a prevention, replacement, or adjuvant treatment for inflammatory bowel disease. (Yao S, Zhao Z, Wang W, Liu X. *Bifidobacterium Longum*: Protection against Inflammatory Bowel Disease. *J Immunol Res* 2021; 2021: 8030297).