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Case-control studies

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"If the best you can find is a case-control study, you must recognize that this is a weak design that often has led to erroneous conclusions..."
D.L. Sackett, et al. (1985) [1]

"The sophisticated use and understanding of case-control studies is the most outstanding methodological development of modern epidemiology"
K.J. Rothman (1986) [2]

1. Introduction

Few issues in epidemiology have led to more controversy than the validity of case-control studies. This is illustrated by the above statements, drawn from two widely read textbooks in the field [1,2]. Some epidemiologists go as far as to strongly advise against reading, let alone conducting, a case-control study, especially when the study objective is to assess causality or treatment efficacy [1]. They believe that bias inherent to this type of study makes the interpretation of its results virtually impossible. Others have taken a less extreme point of view and emphasize both the limitations and the potential of case-control studies [3,4]. Notwithstanding these opposing views, there can be no doubt that, since the publication of the first case-control study in 1920 [5], these studies have played an important role in the development of knowledge about the determinants of a variety of diseases. Important examples of their contribution to clinical medicine include the studies on the causal relationship between blood transfusions and hepatitis, smoking habits and cancer of the lip or lung, the use of diethylstilbestrol during pregnancy and clear-cell adenocarcinoma of the vagina in offspring, exposure to radiation and leukaemia, and ABO blood type and venous thromboembolism.

2. Essentials of the case-control study

In essence, the case-control study is a formalisation of the natural search for determinants of

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disease as it occurs in day-to-day medical practice [4]. A physician wonders what may be the factor underlying the occurrence of a particular disease, and will attempt to identify common characteristics in patients with the condition ("cases") which are not or less often present among those without the condition ("controls"). The design of a case-control study is shown in Fig. 1. As in all types of clinical epidemiological research the objective is to study the relationship between certain determinants and the occurrence of a disease. In the empirical situation of the actual research, the data on the exposure to the determinant and the outcome are then collected. The main difference between a follow-up study and a randomized controlled trial (RCT) on the one hand, and a case-control study on the other, lies in the way in which information is obtained. In the former types of study, a group of subjects with and without the determinant, but not yet having experienced the outcome under study, are identified and followed over time to establish whether they develop the particular outcome. In case-control studies the information on exposure is collected in all patients who develop the outcome ("cases") and in a sample of the population from which the cases emerge. It simply aims at abstracting the information on determinants in the whole of the study population from which the cases came, by sampling from that population. Thus, a case-control or case-referent study may be viewed as an efficient study design in which the level of exposure to the determinant is measured in cases and controls only, whereas in a follow-up study or RCT the determinant is measured in the entire population. This is further illustrated in the Appendix. As a consequence, a case-control study is highly attractive when the outcome is rare. For instance, a follow-up study on the association between exposure to ultrasound during preg-

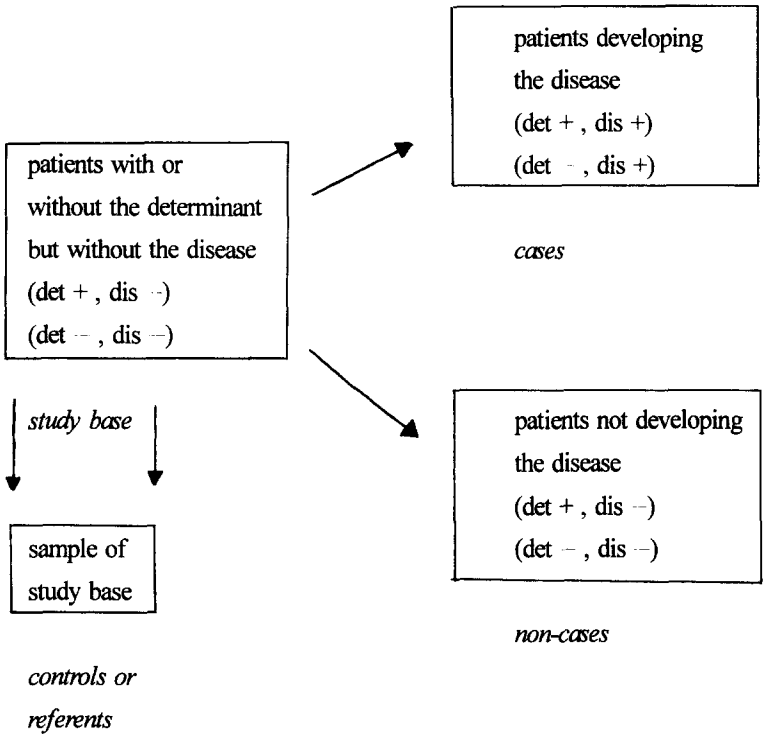

Fig. 1. Study design of a case-control study. In a case-control study the information on exposure on the determinant (det) is collected in the cases, i.e. those who develop the disease (dis) under study, and in the controls, i.e. a sample of the study base from which the cases and non-cases emerge, only. Thus, in essence, the controls are not necessarily non-cases, but may become cases during the study period.

nancy and the occurrence of childhood leukaemia in the Netherlands would constitute unsurmountable logistic problems in terms of following all pregnant Dutch women for a period up to 15 years. The alternative, namely to identify all children with the diagnosis of leukaemia, and a control group, and collecting information on exposure to ultrasound during pregnancy in these two groups only, is clearly more feasible. In contrast to a follow-up study and RCT, a case-control study, in general, does not provide absolute measures of disease frequencies. The relationship between determinant and outcome is quantified by the odds ratio, which is the ratio of the odds of exposure to the determinant in the cases, and the corresponding odds in the controls. Under certain assumptions the odds ratio equals the incidence ratio, i.e. the disease rate (incidence) among exposed subjects relative to the disease rate among those not exposed to the determinant, and thus may be interpreted as a relative risk. The odds ratio can be easily derived from a two-by-two contingency table by calculating the cross-product. As an example, the odds ratio of lung cancer in smoking men and women is computed in Table 1, using data from a case-control study published in 1952 [6].

Table 1
Calculation of the odds ratios of lung cancer per category of smoking behaviour in men and women.

Men	1,357 cases	1,357 controls	odds ratio
Smoking status			
One or more cigarettes/day	99.5% (a)	95.5% (b)	9.0
Non-smoking	0.5% (c)	4.5% (d)	1.0
Women	108 cases	108 controls	odds ratio
Smoking status			
One or more cigarettes/day	63.0% (a)	45.4% (b)	2.0
Non-smoking	37.0% (c)	54.6% (d)	1.0
	$a+c$	$b+d$	

Non-smokers are considered as the reference category (odds ratio 1.0). The data are derived from a case-control study on smoking and lung cancer published by Doll and Hill in 1952 [6].

Odds ratio = exposure odds ratio = odds of exposure in cases/odds of exposure in controls = $[(a/(a+c))/(c/(a+c))]/[(b/(b+d))/(d/(b+d))] = (a/c)/(b/d) = ad/bc$

Odds ratio of lung cancer of smoking compared to non-smoking men = ad/bc = (99.5%.4.5%)/(95.5%.0.5%) = 0.045/0.005 = 9.0

Odds ratio of lung cancer in smoking compared to non-smoking women = ad/bc = (99.5%.4.5%)/(95.5%.0.5%) = 0.045/0.005 = 9.0

3. The history of case-control studies

The case-control study as an option in study design was developed by sociologists at the beginning of the eighteenth century [7]. In the first case-control study in medicine published in 1920 [5], smoking habits of 537 patients with epithelioma of the lip were compared to 500 patients "without" epithelioma. Although the percentage of smokers among cases and controls was similar (79% and 80%), a higher proportion of tobacco-consuming cases smoked a pipe (78%) compared to smoking controls (38%). 1950 heralded an important period in clinical epidemiology in general and in the development of the case-control method in particular. In that year, 4 case-control studies assessing the association between tobacco consumption and the risk of cancer of the lung were published [8–11]. These early studies, although with methodological problems in several aspects, clearly illustrate the potential of this study design. In 1951, Cornfield gave a strong impulse to the application of the case-control method, by proving that, under the assumption that the outcome at interest is rare, the odds ratio equals the ratio of the incidences in exposed and the unexposed [12]. Another influential paper was published in 1959 when Mantel and Haenszel described a procedure to derive odds ratios from stratified data and thus enabled adjustment for potential confounding variables [13]. During the last decades, case-control studies have been applied throughout the field of clinical medicine far beyond research on cancer aetiology for which it was first developed: e.g., in diagnostic research or in the evaluation of treatment efficacy or adverse effect. Especially in the latter field, the case-control method has proven its potential. Examples include studies on aspirin use and Reye's syndrome [14], and, recently, beta-agonists and fatal asthma [15].

4. The choice of a control group

A crucial issue in the conduct of a case-control study is the choice of a proper control group. Using the case-base approach [3,16], controls should be sampled randomly from the study base, i.e. the whole population whose disease experience is captured in a particular study (Fig. 1). Thus, valid sampling of controls involves a clear understanding of the definition of the study base. In practice, controls are usually sampled from the non-cases (i.e., patients who do not develop the outcome during the study period), rather than from the entire study base. In theory, this results in a biased estimate of the relative risk in that the odds ratio provides an overestimate of the disease incidence ratio. This, however, does not lead to appreciable bias when the disease under study is rare ("rare disease assumption"). Alternative methods by which the odds ratio per definition provides an unbiased estimate of the incidence ratio include sampling of controls each time a case occurs in a dynamic population (when controls are, in principle, non-cases but may become cases later in the study period) or the case-cohort design [17]. In view of the specific characteristics of an empirical study general guidelines for valid sampling of the controls leading to preferential use of, e.g., neighbourhood, population, or hospital controls, cannot be given. However, a useful rule of thumb is that subjects included in the control group should have been recognized as a case, and had this control experienced the outcome under study during the study period? When, for example, in a study on the relationship between alcohol consumption and duodenal ulcer, the cases are derived from an outpatient clinic, the use of a random sample of the population at large as a control group seems inappropriate. Controls developing duodenal ulcer are unlikely to always have become a case in this study; e.g., because the general practitioner may decide to treat the patient without referral to a specialist. This could lead to an overestimation of the risk associated with alcohol intake, because patients attending an outpatient clinic may, irrespective of the presence of dyspepsia, have a higher level of alcohol consumption than the (relatively healthy) general population. This example also illustrates that the way in which both cases and controls come to the attention of the investigator should be independent of the exposure to the determinant. Dyspepsia patients with a history of alcohol consumption may be more likely to be referred, and thus become cases, than abstinent dyspepsia patients.

The choice of the number of referents sampled per case differs among case-control studies. The ratio has no impact on the validity of the study but reflects a trade-off between the increase in precision of the estimate of the odds ratio (narrowing of the 95% confidence interval) and the cost in terms of time and money required to collect the information in more controls. It is generally accepted that a case/control ratio beyond 1 to 5 does not appreciably add to the statistical power of a case-control study. A more controversial issue is the inclusion of several control groups in a case-control comparison. In a study on aspirin and Reye's syndrome, for example, 4 control groups were chosen [14]. In general, a clear understanding of the essentials of the study base will lead to sampling of one control group only. The inclusion of more control groups seems a waste of resources, and could, in case the odds ratios differ, hamper the interpretation of the results. Other authors argue that similar results in several case-control comparisons within one study could increase the validity of the study. This, however, is more likely to be achieved by comparing the results of several case-control studies with valid sampling of one control group than by multiple case-control comparisons within one study.

5. Advantages and disadvantages of case-control studies

The main advantage of a case-control study is its efficiency. Information on exposure to a particular determinant needs to be obtained in all cases and a sample of the reference population only. Thus, the costs of case-control studies are relatively low. Especially when the disease studied is rare, the case-control approach offers obvi-

ous advantages compared to a follow-up study or RCT, and may even be the only feasible option in design. The important association between diethylstilbestrol during pregnancy and the risk of vaginal carcinoma in daughters would never have received the attention it deserved without the publication of a case-control study on the putative relation [18]. Another advantage of case-control studies, although not often recognized, is the possibility of studying the influence of a wide variety of exposure levels (e.g., different dosages or duration of use of a particular drug) on the occurrence of an outcome. In contrast, there are several disadvantages inherent in case-control studies. In analogy to the efficiency of case-control studies when the incidence of the outcome is low, the approach is less feasible when exposure to the determinant is rare. As indicated above, the choice of a proper control group is crucial to the validity of the study, but may pose important problems in practice. As a consequence, the method of sampling of the controls is often heavily criticized, although one sometimes gets the impression that this criticism is based on prejudice concerning the invalidity of case-control studies in general than on the actual methodology of a particular study. Case-control studies are often considered to be more liable to bias, notably selection bias and recall bias, than alternative designs [19]. Indeed, selection bias in case-control studies may occur when the selection of cases or controls is associated with the presence, or absence, of the determinant of interest. An example frequently cited is a case-control study assessing the relationship between the use of oral contraceptives and thromboembolism [20]. Physicians may be more prone to include thrombosis in the differential diagnosis and consequently perform adequate diagnostic tests in women with prior use of contraceptives than in unexposed women. It should be stressed, however, that selection bias is a threat to validity in all types of (non-experimental) studies. A bias more particular to case-control studies is recall bias. This type of information bias refers to the tendency of patients with a disease to recall an exposure to a particular determinant more often than subjects without the disorder, especially when an association between the determinant and the disease seems plausible. In a study on the relationship between head trauma and the occurrence of Alzheimer's disease, relatives of patients with dementia are more likely to recall any head trauma than relatives of non-demented patients. A way to limit this type of bias would be to choose a control group of patients with a disease believed to be associated with head trauma by laymen but which is known to be unrelated to it (e.g., patients with brain tumours).

A final disadvantage of case-control studies, but also of other non-experimental studies, is the difficulty of ensuring validity when the objective is to assess treatment efficacy. Especially in comparing the beneficial effect of treatment versus non-treatment, the lack of randomisation in these studies will almost certainly lead to baseline differences in prognosis between cases and controls. This will result in an underestimation of the beneficial effect of treatment. This phenomenon, which is caused by the natural tendency of physicians to treat those with a less favourable prognosis (e.g., those who need treatment), is known as confounding by indication. Under these circumstances, case-control studies could be of more value in the evaluation of the relative efficacy of different treatment regimes for a given indication [21].

6. Conclusion

In conclusion, case-control studies have proven to be an important tool in clinical epidemiological research, although their validity has been, and will be, criticized. The qualification of this type of study as a poor alternative to RCT's and follow-up studies seems to be the result of an overemphasis of the disadvantages of the case-control method, without recognition of its important merits. A better understanding of the essentials of the case-control study, and its pitfalls as well as potentials, may lead to more appropriate application and an even more prominent role of the case-control approach in clinical research.

Appendix: Case control summary

The object of a follow-up study, or case-control study, is to document the occurrence relation: the occurrence of disease as a function of a certain determinant.

The measure of association is the relative or absolute rate of disease in the presence or absence of the determinant. In a follow-up study or RCT, in which information on the determinant is available on all participants, the basic results can be summarized in a two by two table.

	Disease	No disease	
Determinant +	a	$(N-a)$	N
Determinant −	b	$(N'-b)$	N'
			$(N+N')$

The disease rates can easily be calculated as a/N in the exposed versus b/N' in the unexposed. In a case-control study, interest is similarly in the disease rates. For these rates, as in follow-up studies or RCTs, the numerators are provided by the cases.

	Disease
Determinant +	a
Determinant −	b
	$a+b$
	cases

However, in order to obtain denominators of the rates, a sample from the population is taken rather than the whole population. This control group, as it is representative of the population, has a distribution of the determinant that is similar to the whole population.

Determinant +	n	N
Determinant −	n'	N'
	controls	total population

n is proportional to N, and n' is proportional to N'. From these estimates of the whole population determinant distribution, estimates of the disease rates can be obtained (quasi-rates). Moreover, if the sampling fraction n or n' is known, the true rates N, N' can be obtained.

In essence, contrary to common belief, in a case-control study cases are not compared to controls with respect to exposure, but cases provide numerators and control denominators to estimate disease rates in an efficient manner. The approach, however, is similar to that in follow-up studies and RCTs.

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