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The Case-Population Study Design
An Analysis of its Application in Pharmacovigilance

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Abstract

Background: The case-population approach or population-based case-cohort approach is derived from the case-control design and consists of comparing past exposure to a given risk factor in subjects presenting a given disease or symptom (cases) with the exposure rate to this factor in the whole cohort or in the source population of cases. In the same way as the case-control approach, the case-population approach measures the disproportionality of exposure between cases of a given disease and their source population expressed in the form of an odds ratio approximating the ratio of the risks in exposed and not-exposed populations (relative risk).

Objective: The aim of this study was to (i) present the case-population principle design in a way understandable for non-statisticians; (ii) propose the easiest way of using it for pharmacovigilance purposes (mainly alerting and hypothesis testing); (iii) propose simple formulae for computing an odds ratio and its confidence interval; (iv) apply the approach to several practical and published examples; and (v) discuss its pros and cons in the context of real life.

Methods: The approach used is derived from that comparing two rates expressed as person-time denominators. It allows easy computation of an odds ratio and its confidence interval under several hypotheses. Results obtained with the case-population approach were compared with those of case-control studies published in the literature.

Results: Relevance and limits of the proposed approach are illustrated by examples taken from published pharmacoepidemiological studies. The odds ratio (OR) reported in a European case-control study on centrally acting appetite suppressants and primary pulmonary hypertension was 23.1 (95% CI 6.9, 77.7) versus 31 (95% CI 16.2, 59.2) using the case-population approach. In the European case-control studies SCAR (Severe Cutaneous Adverse

Reactions) and EuroSCAR on the risk of toxic epidermal necrolysis associated with the use of medicines, the OR for cotrimoxazole was 160 and 102, respectively, versus 44.4 using the case-population approach. Similarly, these two case-control studies found ORs of 12 and 72 for carbamazepine versus 24.4 using the case-population approach, 8.7 and 16 for phenobarbital versus 21.9, 12 for piroxicam (analysed in the SCAR study only) versus 14.5, and 5.5 and 18 for allopurinol versus 3.4 using the case-population approach.

Conclusions: Being based on the estimate derived from sales statistics of the total exposure time in the source population of cases, the method can be used even when there is no information about the actual number of exposed subjects in this population. Although the case-population approach suffers from limitations stemming from its main advantage, i.e. impossibility to control possible confounders and to quantify the strength of associations due to the absence of an *ad hoc* control group, it is particularly useful to use in routine practice, mainly for purposes of signal generation and hypothesis testing in drug surveillance.

Background

Most statistical comparisons made in epidemiology and pharmacoepidemiology refer to the inevitable contingency table, of which the simplest form (one exposure variable and one binary outcome) is the two-by-two table (see figure 1).

Apart from the particular situation of equivalence testing, the null hypothesis generally posits that exposure and outcome (e.g. occurrence of the disease) are two independent phenomena. Under this hypothesis, (i) the proportion of diseased patients is expected to be similar in exposed and not-exposed groups (cohort design); or (ii) the odds of exposure is expected not to differ across diseased and not-diseased groups (case-control design).

As the study and reference groups are sampled from the same source population, it is tempting to use this whole population as the reference.

In this case, the control group is not a set of individuals specifically selected for the purpose of the study but an aggregated comparator consisting of global population data. This can apply to a prospective or to a retrospective analysis, the latter being termed population-based case-cohort study,[1,2] case-population study[3,4] or case-only study (figure 2).[5]

The case-population approach described here has been developed as a simplified design, i.e. without an *ad hoc* control group, mainly for pharmacovigilance purposes.[2,6-11]

In the follow-up of these pioneering contributions, we propose to calculate an odds ratio (OR) as a raw estimate of the relative risk associated with exposure in measuring the degree of disproportionality of exposure odds between the source population and the subgroup having presented the event (the cases). In the absence of bias, a value differing significantly from 1 indicates an association, causal or not, between exposure and disease.

More accurately, the five main contributions of the present paper were (i) to present the case-population principle design in a way understandable for non-statisticians; (ii) to propose the easiest way of using it for pharmacovigilance purposes (mainly alerting and hypothesis testing); (iii) to propose simple formulae for computing an OR and its confidence interval; (iv) to apply the approach to

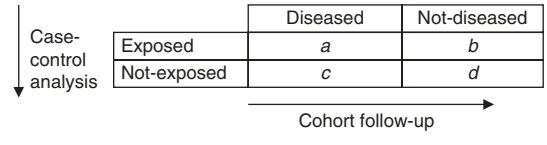

Fig. 1. Patient distribution according to disease and exposure.

	Diseased	Population
Exposed	*a*	*b*
Not-exposed	*c*	*d*
Total	*n*	N

Fig. 2. Comparison of previous exposure in diseased patients with global populational data

several practical and published examples; and (v) to discuss its pros and cons in the context of real life.

Methods

The Case-Population Design

As mentioned in the previous section, in the case-population design the study population encompasses the whole population of a given territory (e.g. a state, a country).

In order to minimize selection bias, efforts should be made to identify and collect all cases of the considered event occurring in this territory during the study period, or, at least, to obtain a sample that is actually representative of the whole case population, i.e. without any selection bias.

For the control group, the cells *b* and *d* of the contingency table are expressed not in number of individuals but in person-time units (e.g. person-months), the latter representing the sum of the durations of exposure (PT_E) and not-exposed time (PT_{NE}) in the source population (figure 3):

Among the *n* collected cases, some are expected to be exposed to the factor studied and others not. Under the null hypothesis (i.e. no association between exposure and event), and in the absence of selection bias, the ratio of exposed to not-exposed cases $\frac{a}{c}$ is not expected to differ from the ratio of exposed person-time to not-exposed person-time $\frac{PT_E}{PT_{NE}}$ in the source-population. In other words, one should test whether their ratio or estimated OR (denoted as $\hat{OR}$) significantly differs from equation 1:[12]

$$\hat{OR} = \frac{a/c}{PT_E/PT_{NE}} = \frac{a}{c} \times \frac{PT_{NE}}{PT_E} \qquad \text{(Eq. 1)}$$

If so, the test hypothesis is rejected and one accepts the alternative hypothesis that an association, causal or not, exists between exposure and the disease.

As mentioned above, an OR could be considered as a satisfactory estimate of the actual value of the relative risk, if, and only if:

1. The diseased, i.e. cases, and not-diseased subjects belong to, or are unbiased samples of, the same source population. In other words, diseased subjects should have had the same probability of exposure as the not-diseased had they not been diseased. In a classical case-control design, this can in part be achieved by different methods such as matching and/or controlling for the main putative confounding variables. This is obviously almost impossible to attempt when the control group consists of aggregated statistics not allowing access to individual data.
2. The ratio of exposed and not exposed person-times is a satisfactory estimate of the ratio of exposed and not exposed subjects in the source population. This cannot be the case when exposure and risk periods are not superimposed, e.g. if a risk persists after cessation of the treatment, or in the case of multiple exposures. This limitation is discussed below.

Calculation of Key Variables

Cases

In equation 1, given the total number (*n*) of cases of the considered disease (e.g. agranulocytosis) identified exhaustively in the catchment population, *a* is the number of cases exposed to the studied factor, i.e. treated with a given medicine, according to an appropriate definition, and *c* is the number of cases not exposed to the considered factor under the same conditions.

It is crucial that *a* constitutes an exhaustive, or at least representative, sample of the cases having

	Diseased (cases)	Population (person-time)
Exposed	*a*	PT_E
Not-exposed	*c*	PT_{NE}
Total	*n*	PT_{POP}

Fig. 3. Comparison of previous exposure in diseased patients with global exposure data from the entire population from which the cases were identified. $\mathbf{PT_E}$ = sum of the durations of exposure; $\mathbf{PT_{NE}}$ = sum of the durations of not-exposed time; $\mathbf{PT_{POP}}$ = total person-time.

occurred in the catchment population during the period considered.

Moreover, on account of the nature of the controls used in case-population studies, i.e. aggregated exposed and non-exposed times, it is safer to restrict this approach to situations in which the risk induced by the drug is assumed to be encompassed within the treatment period. Therefore, a case will be considered as exposed if treated when the disease or its first symptoms occurred.

Exposed and Not-Exposed Person-Time

One should first compute the total person-time (PT_{POP}) in the source population. For example, if a survey has been conducted over a 14-month period and the catchment population is 2.7 million inhabitants, then PT_{POP} is $14 \times 2.7 = 37.8$ million person-months.

PT_E in equation 1 is the exposed person-time in the source population for the considered period of time. It can be roughly estimated from the number of drug packages sold during this period and from the average or defined daily dose (DDD) for this drug, two parameters readily available in most countries.

For example, if 224 000 packets of 30 tablets have been sold in the catchment area over the 14-month period, and the average prescribed (or used) daily dose was 2.1 tablets, the exposed population-time is (equation 2):

$$\frac{224\,000 \times 30}{2.1 \times 30.4} = 105\,263 \text{ person-months} \qquad \text{(Eq. 2)}$$

with 30.4 being the average number of days in a month (i.e. 365/12). Note that this computation, which is currently done in drug utilization studies, assumes that all tablets are actually used by patients.

In equation 1, PT_{NE} (not-exposed person-time) is the difference between PT_{POP} and PT_E. In the above example, $PT_{NE} = 37\,800\,000 - 105\,263 = 37\,694\,737$ person-months.

When PT_E is very small compared with PT_{POP}, the latter may be used instead of PT_{NE}.

As previously stated, *per se*, the case-population approach precludes any possibility of dealing with individual data in the source population and, therefore, of restricting the selection to the subjects exposed on the basis of a given time-window.

Estimation of Relative Risks

In the absence of bias, equation 1 makes it possible to derive an OR that could be considered as a rough estimate of the relative risk associated with exposure.

The validity of this estimate may be jeopardized if exposure and risk periods were not superimposed (see Discussion section), and by the fact that cases are compared, with respect to exposure, with a general population that may differ from an *ad hoc* reference group tailored to match characteristics of cases that could act as confounders. For example, if sex and age are known or suspected to be associated with the probability of exposure, cases should not be compared with the whole catchment population but with a subgroup of this population with the same sex ratio and age distribution. By using demographic statistics it is possible to restrict analyses to the subpopulation presenting such characteristics and to calculate the corresponding person-time (PT_{POP}). Furthermore, data from prescription panels may be used to derive the number or proportion of exposed in this population and thus the exposed person-time (PT_E and PT_{NE}).

The confidence interval for $\hat{OR}$ can be computed by using the formula used for the odds of exposure in cases a/b[13] and from the assumption that the ratio PT_E/PT_{NE} did not contribute to the variability because it is based on very large numbers.

As an odds is log-normally distributed and because $Var\left(\ln \frac{a}{c}\right) = \frac{1}{a} + \frac{1}{c}$, its confidence interval can be calculated as follows (equation 3):

$$CI_{a/c} = \frac{a}{c} \exp\left(\pm Z_{1-\alpha/2}\sqrt{\frac{1}{a} + \frac{1}{c}}\right) \qquad \text{(Eq. 3)}$$

Considering the values of person-time given above as an example, i.e. $PT_E = 105\,263$; $PT_{NE} = 37\,694\,737$ and a total number of 220 cases, 15 having been found exposed to the considered drug, the estimate of the OR is (equation 4):

$$\hat{OR} = \frac{15}{205} \times \frac{37\,694\,737}{105\,263} = 26.2 \qquad \text{(Eq. 4)}$$

The exposure odds in cases is (equation 5):

$$\frac{a}{c} = \frac{15}{205} = 0.0732 \qquad \text{(Eq. 5)}$$

According to equation 3, the lower and upper limits of the 95% two-sided confidence interval for the odds are 0.043 and 0.123, respectively.

The lower boundary of the 95% two-sided confidence interval for estimated OR is thus (equation 6):

$$0.043 \times \frac{37\,694\,737}{105\,263} = 15.51 \qquad \text{(Eq. 6)}$$

and the upper boundary (equation 7):

$$0.123 \times \frac{37\,694\,737}{105\,263} = 44.26 \qquad \text{(Eq. 7)}$$

Testing the Approach with Practical Examples

Let us consider the notorious relationship highlighted during the 1990s between centrally acting appetite suppressants and primary pulmonary hypertension (PPH).

The field case-control study conducted in Europe by Abenhaim et al.,[14] between 1 September 1992 and 30 September 1994, identified 64 cases of PPH in France. As Abenhaim et al.[14] did, a case can be considered as exposed if treated for at least 3 months before the index date. Therefore, 11 of 64 cases were exposed, and 53 were not exposed. According to sales statistics, the person-time exposure to appetite suppressants between 1992 and 1994 was 6 777 953 person-months.[15] For the same period (25 months), the total person-time was 1 017 432 752 person-months in the catchment population (aged over 19 years). Thus, the not-exposed person-time (PT_{NE}) was 1 010 654 799 person-months.

The OR estimated from equation 1 is (equation 8):

$$\hat{\mathrm{OR}} = \frac{11}{53} \times \frac{1\,010\,654\,799}{6\,777\,953} = 31. \qquad \text{(Eq. 8)}$$

The lower and upper limits of the 95% two-sided confidence interval for the odds 11/53 = 0.2075 are 0.1084 and 0.3973, respectively.

According to equation 2 the lower boundary of the 95% confidence interval for estimated OR is (equation 9):

$$0.1084 \times \frac{1\,010\,654\,799}{6\,777\,953} = 16.2 \qquad \text{(Eq. 9)}$$

and the upper boundary (equation 10):

$$0.3973 \times \frac{1\,010\,654\,799}{6\,777\,953} = 59.2 \qquad \text{(Eq. 10)}$$

Although not adjusted, this result is roughly of the same order of magnitude as that found by the International Primary Pulmonary Hypertension Study (IPPHS)[11] [OR = 23.1 (95% CI 6.9, 77.7)], and, in any case, would have corresponded to a clear signal for pharmacovigilance.

The second example concerns the risk of toxic epidermal necrolysis (TEN) related to the use of medicines investigated through a European case-control surveillance project from 1989 to 1993 (SCAR [Severe Cutaneous Adverse Reactions] study) and from 1997 to 2001 (EuroSCAR study). Cotrimoxazole appeared to be strongly associated with TEN, with a crude relative risk of 160 in the SCAR study[16] and 102 (95% CI 14, 754) in the EuroSCAR study.[17] Adjusted relative risks for other drugs were as follows:

- carbamazepine 12 (95% CI 3.5, 38) and 72 (95% CI 23, 225) in the SCAR and EuroSCAR studies, respectively[16,17]
- phenobarbital (phenobarbitone) 8.7 (95% CI 3.2, 23) and 16 (95% CI 5, 50)[16,17]
- piroxicam 12 (95% CI 3.1, 45)[16]
- allopurinol 5.5 (95% CI 2.0, 15) and 18 (95% CI 11, 32).[16,17]

In another study,[18] the same authors identified all cases of TEN occurring in France from 1981 to 1985 and reported the proportions of these cases exposed to drugs as well as the exposure to these drugs expressed as the number of defined daily doses (DDDs) for the same period of time. During the study period, a total of 253 cases of TEN were confirmed. The number of cases exposed to cotrimoxazole, carbamazepine, piroxicam, phenobarbital and allopurinol within the 2-month time period preceding the index date and possibly responsible for TEN, as well as the corresponding number of not-exposed cases, are

presented in table I. The catchment population surveyed over a 5-year period was estimated at 54.7 million inhabitants. The total person-time (PT_{POP}) was thus 99 827 500 000 person-days. For the same period of time, the sales data for each drug expressed in DDDs made it possible to estimate the number of exposed person-time (PT_E) in person-days. The ORs estimated according to equation 1, and their 95% lower and upper limits calculated by using equation 3, are presented in table I.

In all cases, the ORs computed by means of the case-population approach and sales data are roughly of the same order of magnitude as the corresponding relative risks estimated with an actual control group. For example, drugs such as cotrimoxazole and carbamazepine, which are strongly associated with the occurrence of TEN in the case-control design, also have the highest OR estimates in the case-population approach. For indometacin, a drug not classically associated with TEN[18-22] even though few case reports have been published to date,[23-25] the OR derived from the case-population approach was significant.

Discussion

The basic principle of the so-called case-population design is quite straightforward, consisting of comparing odds of exposure to a studied factor in a case-series to that of the source-population from where the cases were sampled. The method proposed in this article for computing ORs by estimating relative risks is straightforward to use and does not require previous knowledge of the actual number of exposed individuals in the catchment population. If an unbiased collection of cases of a given disease is available or feasible, e.g. registry or series, computations are simple and fast, required data generally being available from reimbursement databases and/or prescription panels. Such case series are common in most countries; for example, cases of classical case-control studies having explored other associations, data from registries, reference centres for certain diseases or prevalence studies.

However, because the selection process of 'controls', i.e. the whole source-population, does not take into account the individual characteristics and exposure patterns of the 'controls', this approach has four main limitations.[26-29]

The first limitation is that the comparison should involve the totality or a really representative sample of cases that have occurred in the considered territory during the study period. Equation 1 shows that the calculated value of the OR is correlated to the respective numbers of exposed and not-exposed cases. Thus, any bias in the selection process (e.g. the exposed cases have a higher probability of being referred to the study centre than not-exposed ones) would have a major impact on the estimate. This type of selection bias is also feared in classical case-control designs even though controlling for such a referral bias is generally easier.

The second limitation is the difficulty of controlling for potential confounders. As mentioned above, it is sometimes possible to compare the cases, not to the whole reference population, but to a subgroup selected with a view to having roughly the same distribution for one or several

Table I. Estimate of odds ratios for drug-associated toxic epidermal necrolysis from the case-population approach

Drug	Exposed cases[a] (n)	Not exposed cases (n)	PT_E (million person-days)	PT_{NE} (million person-days)	$\hat{OR}$ (95% CI)
Cotrimoxazole	21	232	203	99 624.5	44.4 (28.4, 69.4)
Carbamazepine	6	247	99	99 728.5	24.4 (10.9, 55.0)
Phenobarbital (phenobarbitone)	26	227	519	99 308.5	21.9 (14.6, 32.9)
Piroxicam	13	240	371	99 456.5	14.5 (8.3, 25.4)
Allopurinol	7	246	837	98 990.5	3.4 (1.6, 7.1)
Indometacin	3	250	272	99 555.5	4.4 (1.4, 13.7)

a Cases were considered as exposed if drug has been used within the 2 months before the occurrence of toxic epidermal necrolysis and that the delay between the last drug intake and the occurrence of the toxic epidermal necrolysis is of 3 weeks or less.

OR = odds ratio; $\hat{\mathbf{OR}}$ = estimated OR; $\mathbf{PT_E}$ = the sum of the durations of exposure; $\mathbf{PT_{NE}}$ = sum of the durations of not-exposed time.

potential confounders. However, in practice, the ecological nature of the reference data restricts this attempt to some basic sociodemographic variables such as sex and age and precludes more sophisticated analysis aiming to control for other major confounders encountered in pharmacoepidemiology (e.g. severity, therapeutic indication).

The third limitation, which is shared by many computations currently used in the framework of pharmacovigilance, concerns the possible inaccuracy of the estimates of the actual number of exposed subjects when using sales statistics. Two key parameters are needed here: (i) the number of units, e.g. tablets, capsules; and (ii) the average daily dose used in the source population during the study period. In numerous countries this information is directly available from electronic health record databases; however, they may not cover the whole population.[30-32] The accuracy of computations can be greatly improved by the knowledge of more precise usage patterns, including durations of treatment, continuous or intermittent exposure, variability of daily dose, indications, etc. As previously stated, the computation considers all the packets sold as being effectively used, and thus converted into exposed time. However, it is unlikely that all the parameters entering the computation process (e.g. daily dose, duration of treatment, compliance) would have variability acting in the same direction, which tends to minimize this effect.

The last and most serious limitation ensues from the basic principle of the case-population design, which compares two different entities: a number of subjects (the cases) and an amount of person-time assumed to represent the sum of exposure periods in the source population. Under the null hypothesis that exposure and disease are two independent phenomena, the number of cases occurring during the exposed and not-exposed periods is a linear function of the baseline incidence of the disease in the source population. Therefore, in the absence of selection bias, the odds of exposed time in this population should not differ from the odds of exposure in the sample of cases. In this sense, a significant difference between these odds means that the null hypothesis can be rejected. This disproportionality makes it possible to generate a signal concerning a possible association between exposure and the disease studied. That is the main value of this approach in pharmacovigilance. Even so, there may be a concern about quantifying the strength of this association, as would be the case in a classical epidemiological design, i.e. cohort or case-control, by comparing two samples of subjects with precise knowledge of their exposure characteristics. In the case of a single treatment period of whatever duration and encompassing the period at risk, the ORs derived from the case-population approach can satisfactorily estimate the actual values of the corresponding relative risks, as attested by the practical examples presented above. Conversely, when treatment and at-risk periods are not superimposed, as is the case for delayed effects (e.g. vaccines) or those persisting after cessation of the treatment, the computed value of the OR may constitute a biased estimate of the actual relative risk, the value of which is unknown. For example, in the case of a risk persisting 1 month after cessation of treatment, the PT_{NE}/PT_{E} ratio computed from sales statistics would be inflated as it would not account for this 1-month carryover effect and exposure is restricted to the treatment periods. This bias is particularly pronounced in the case of multiple exposure periods.

Conclusions

The case-population approach offers much interest in pharmacoepidemiology, mainly for signal generation or for exploratory purposes. The examples presented in the Results section show that the approach presented can produce coherent conclusions.

For other purposes, such as decision-making, considering the limitations of this approach, it would be good practice to validate conclusions and risk estimates obtained from the case-population approach with a more classical and validated epidemiological strategy such as *ad hoc* cohort or case-control studies.

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