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Assessment of the "Case-Chaos" Design as an Adjunct to the Case-Control Design

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In 2012, a novel case series method dubbed the "case-chaos" design was proposed as an alternative to case-control studies, whereby controls are artificially created by permutating the exposure information of the cases. Our aim in the current work was to further evaluate the case-chaos method. Using a theoretical example of 2 risk factors, we demonstrated that the case-chaos design yields risk estimations for which the odds ratios obtained for every risk factor are in the same ascending order as the risk factors' exposure prevalences in the case group. Applying the method to data from the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR; 1997–2001), we were not able to obtain sensible results but instead produced results as predicted by our theoretical assessment. We therefore claim that the method is equivalent to declaring risk solely on the basis of prevalences obtained in cases. While the proposers of the case-chaos method view it as a useful adjunct, we show that it cannot produce sensible estimates.

case-control studies; research design; Stevens-Johnson syndrome; toxic epidermal necrolysis

Abbreviations: EuroSCAR, European Study of Severe Cutaneous Adverse Reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Assessment of the impact of risk factors on events such as disease occurrence and their risk quantification is a major topic in epidemiology for which different study designs can be applied (1). If the event of interest is relatively frequent, the usual choice is that of a cohort design; otherwise a case-control design is commonly utilized (2). However, there are situations where the application of a case-control design is limited. The selection of suitable controls is a constant challenge that may be even more demanding in certain settings (3, 4). Problems may also be due to the rareness (or commonness) of the exposure of interest (4). For these reasons, but also to save time and costs, various approaches for the analysis of case series methods have been developed (5–8). Though not without their problems, some of them have proven very useful in different areas and have been increasingly applied (9, 10).

Recently, a new method for the analysis of a case series, the "case-chaos" method of Gillespie et al. (11), has been suggested. The method follows quite a different approach in comparison with the previous ones. It was developed in the context of infectious disease outbreaks, where a quick identification of risk factors is needed. The case-chaos method is viewed by its proponents as a useful adjunct to help identify risk factors for further investigation. The motivation for the case-chaos method stems from an outbreak of an infectious disease among visitors to a petting farm in England. The goal was to identify the animals which may have been the carriers of the disease. Gillespie et al. noticed that "cases appeared to act randomly in terms of the attractions they visited" (11, p. 503). They hypothesized that artificial controls could be simulated that would exhibit similar random behavior. The basic idea is that controls can be generated artificially by using the exposure information from the cases. With these matched artificial controls—we will call them chaos-controls—risks can then be assessed in the same way as in a conventional matched case-control study.

Since this method seems appealing at first glance, we aimed to evaluate it in more detail and guide readers with regard to its applicability, especially because 2 recent comments on this method had brought up some general concerns (12, 13). We use case data from a case-control study on patients with

Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) to illustrate our findings.

METHODS

The case-chaos procedure

The procedure proposed by Gillespie et al. (11) for generation of artificial chaos-controls is shown in Table 1. Each chaos-control is then matched with the case from which it was generated. Within every matched pair, the case and the chaos-control will have the same number of exposures; only the patterns of exposure will differ. The resulting data set of cases and chaos-controls is treated the same way as in any conventional matched case-control study. Risks can then be assessed using conditional logistic regression. The second and third steps in Table 1 may also be repeated m times to generate a matched set of m chaos-controls per case.

Data example: EuroSCAR

To apply the case-chaos method to actual data, we used data on SJS/TEN (representing severe cutaneous adverse reactions) from the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR), a multinational case-control study conducted in Europe and Israel between 1997 and 2001. The main aim of EuroSCAR was to assess the risk of SJS/TEN associated with use of specific medications. A future follow-up study to EuroSCAR will include cases only; therefore, we evaluated the case-chaos design in this context to test it as a potential analysis method. EuroSCAR is described in detail elsewhere (14), and a brief description is provided in the Web Appendix (available at http://aje.oxfordjournals.org/).

For the case-chaos analysis, only data on the 379 cases were extracted. The risk factors consisted of 30 distinct drugs (see Web Table 1 for a full list of the drugs). Medications were classified on the basis of the EuroSCAR study results (14) as "highly suspected," "suspected," or not suspected ("other") of causing SJS/TEN. Chaos-controls were created by permutating the information on the drug exposure of cases. We considered 3 separate scenarios with different numbers of chaos-controls per case (1:1, 1:3, and 1:10) and created 100 sets of chaos-controls for each scenario. As was done by Gillespie et al. (11), we used univariate conditional logistic regression to obtain risk estimates in terms of odds ratios.

Table 1. Illustration of How to Generate Chaos-Controls for the "Case-Chaos" Study Design[a,b]

Data Set	Outcome	x_1	x_2	x_3
Cases[c]				
1	1	0	0	1
2	1	1	1	0
3	1	0	1	0
Chaos-controls[d]				
1	0	1	0	0
2	0	1	0	1
3	0	0	0	1
Combined[e]				
1	1	0	0	1
1	0	1	0	0
2	1	1	1	0
2	0	1	0	1
3	1	0	1	0
3	0	0	0	1

[a] Procedure proposed by Gillespie et al. (11).
[b] The outcome and risk factors, x_1, x_2, x_3, are coded as 1 (case or exposure) or 0 (control or nonexposure).
[c] A given data set of cases.
[d] Copy the case data set and recode the outcome variable from case to control; next, randomly permutate the exposure information within every such chaos-control.
[e] The chaos-controls are merged together with the original data.

RESULTS

Theoretical assessment: monotonicity of estimators

As Höhle (12) and Pulliam and Dushoff (13) have pointed out, the odds ratios for risk factors obtained from case-chaos analysis are ordered the same way as the risk factors' exposure prevalences in cases. While Höhle (12) analytically demonstrated this for an unmatched setting, we show here that the same holds true in a matched setting, which requires a different approach since the likelihood functions of a matched setting and an unmatched setting are different.

Consider a 1-1 matched study of K pairs. The likelihood function for conditional logistic regression is written as

$$\ell(\boldsymbol{\beta}) = \prod_{k=1}^{K} \ell_k(\boldsymbol{\beta}) = \prod_{k=1}^{K} \frac{e^{\boldsymbol{\beta}' \boldsymbol{x}_{1k}}}{e^{\boldsymbol{\beta}' \boldsymbol{x}_{1k}} + e^{\boldsymbol{\beta}' \boldsymbol{x}_{0k}}}, \qquad (1)$$

where $\boldsymbol{\beta}$ is the vector of regression coefficients, $\boldsymbol{x}_{1k}$ denotes the data vector for the case in the kth pair, and $\boldsymbol{x}_{0k}$ denotes the data vector for the control in the kth pair (15). The goal is to estimate $\boldsymbol{\beta}$, which represents the vector of log odds ratios of the risk factors. For simplicity, we assume that there are only 2 risk factors, so that $\boldsymbol{\beta} = (\beta_1, \beta_2)$, $\boldsymbol{x}_{1k} = (x_{1k1}, x_{1k2})$, and $\boldsymbol{x}_{0k} = (x_{0k1}, x_{0k2})$. Since case-chaos is restricted to binary risk factors, data vectors are coded so that 1 denotes exposure and 0 denotes nonexposure. As usual, only pairs with discordant exposures contribute to the maximum conditional likelihood. This is where the case-chaos method is special: Within each pair, cases and controls have the same number of exposures, since the control is generated by permutating the exposure information of the case. In the simple situation of 2 risk factors, there are only 2 possible discordant pairs that contribute to the maximum conditional likelihood; thus, the data can be summarized by

$$\begin{aligned} n_1 &:= \text{number of pairs where } (x_{1k1}, x_{1k2}) \\ &= (1,0) \text{ and } (x_{0k1}, x_{0k2}) = (0,1), \\ n_2 &:= \text{number of pairs where } (x_{1k1}, x_{1k2}) \\ &= (0,1) \text{ and } (x_{0k1}, x_{0k2}) = (1,0). \end{aligned}$$

The conditional likelihood then becomes proportional to

$$\ell(\boldsymbol{\beta}) \propto \left(\frac{e^{\beta_1}}{e^{\beta_1}+e^{\beta_2}}\right)^{n_1}\left(\frac{e^{\beta_2}}{e^{\beta_2}+e^{\beta_1}}\right)^{n_2}. \quad (2)$$

Through factorization, this can be rewritten as

$$\ell(\boldsymbol{\beta}) \propto \underbrace{\frac{(e^{\beta_1+\beta_2})^{n_2}}{(e^{\beta_1}+e^{\beta_2})^{n_1+n_2}}}_{(*)}\underbrace{e^{\beta_1(n_1-n_2)}}_{(**)}. \quad (3)$$

Note that the term $(*)$ is symmetric in β_1 and β_2; that is, the regression coefficients can be switched interchangeably and the term $(*)$ does not change. Therefore, when maximizing the conditional likelihood over $\boldsymbol{\beta}$, only $(**)$ will lead to a difference between β_1 and β_2.

Let

$N_1 :=$ number of cases where $(x_{1k1}, x_{1k2}) = (1, 0)$ and

$N_2 :=$ number of cases where $(x_{1k1}, x_{1k2}) = (0, 1)$.

Then n_1 and n_2 follow a binomial distribution of N_1 and N_2 trials, respectively, both with a success probability of 0.5. The success probability is 0.5 because permutating the exposures of 2 risk factors has only 2 possible patterns, each with equal probability. Correspondingly, the expected values of n_1 and n_2 are $N_1/2$ and $N_2/2$, respectively. As a consequence, when risk factor 1 is more prevalent in cases than risk factor 2 (i.e., $N_1 > N_2$), it follows that $n_1 > n_2$ in expectation. The term $(**)$ therefore increases in β_1 independently of β_2. When maximizing the conditional likelihood function over $\boldsymbol{\beta}$, it follows that $\beta_1 > \beta_2$ in expectation. Likewise, if risk factor 2 is more prevalent in cases than risk factor 1, then $(**)$ is decreasing in β_1, and it follows that $\beta_2 > \beta_1$ in expectation.

Thus, the case-chaos method will lead to risk estimates that have the same ordering as the risk factors' exposure prevalences in the cases. Put another way, this means that the only inference that can be made is one about the prevalences of the exposures. Proving this for more than 2 risk factors would be more complicated; however, this result can also be observed in practice in our data example where more than 2 risk factors are considered.

Theoretical assessment: unbiased estimation

As we showed above, the case-chaos method yields odds ratio estimates that have a predictable order, which leads one

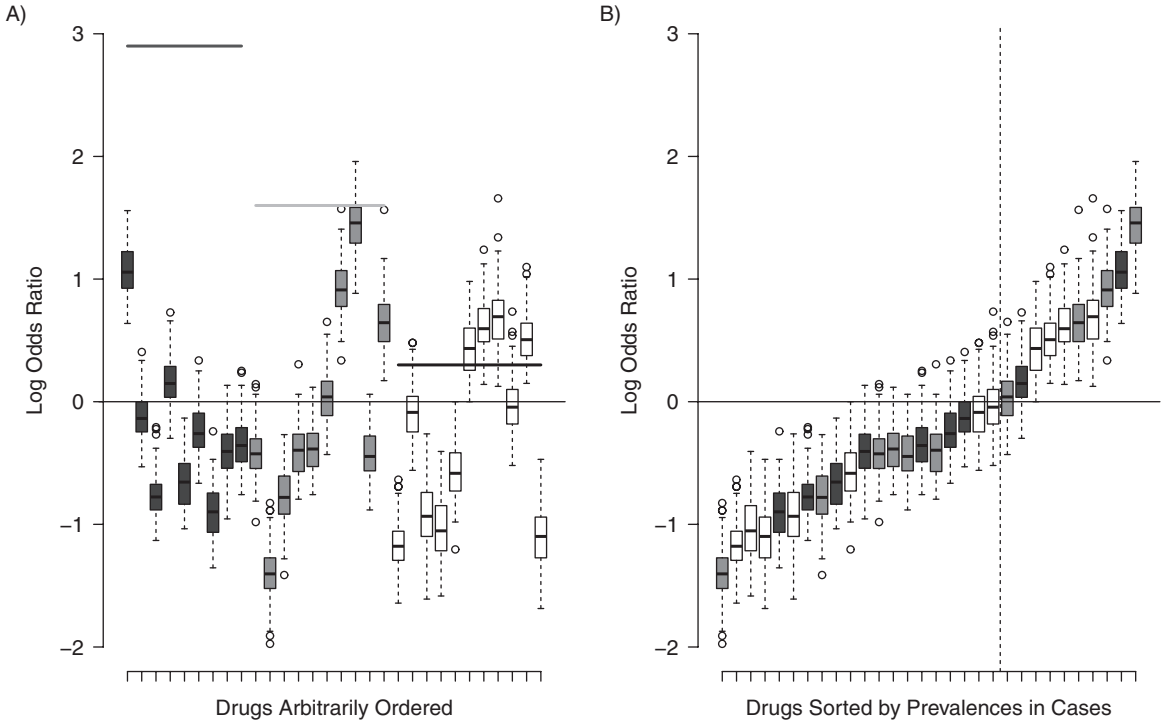

Figure 1. Results from case-chaos analysis of data from the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR; 1997–2001) in the first scenario with 1 chaos-control per case (100 studies). The filling of the boxes denotes their class in terms of suspicion of causing Stevens-Johnson syndrome/toxic epidermal necrolysis, as determined by the EuroSCAR results (14): ■, highly suspected drugs; ▒, suspected drugs; □, nonsuspected (other) drugs. In part A, the horizontal bars denote the median β per class of EuroSCAR results: ——, highly suspected drugs (median, 2.9); ——, suspected drugs (median, 1.6); ——, other drugs (median, 0.3). Parts A and B show the same results, except that in part B the drugs are reordered by their prevalences, making the ascending order of log odds ratios apparent. The dashed line in part B marks the dividing line between drugs which have an exposure prevalence in cases below the mean exposure prevalence in cases and drugs which have an exposure prevalence in cases above the mean exposure prevalence in cases.

to question their usefulness. Can these estimates be unbiased under certain assumptions?

One issue regarding unbiased estimation is that any correlation between risk factors that may have been present will be lost in the chaos-controls due to the random permutation. It is therefore necessary to assume that these risk factors are uncorrelated in order for the chaos-controls to model the true underlying population well.

Another necessary requirement concerns the prevalences of the exposures in the true underlying population. For $j = 1, \ldots, J$ risk factors, the probability of a chaos-control in the kth pair being exposed to one particular risk factor j, $P(x_{0kj} = 1)$, follows the same distribution as a Bernoulli trial. With a sample of size J, of which $\sum_{j=1}^{J} x_{1kj}$ are considered successes, it follows that $P(x_{0kj} = 1) = \frac{1}{J}\sum_{j=1}^{J} x_{1kj}$, which is the same for all x_{0kj}, $j = 1, \ldots, J$. In other words, all risk factors have an equal probability of receiving exposure status in the chaos-controls, regardless of prevalences in the true underlying population. This can be more easily understood if one keeps in mind that the exposure information of the chaos-controls is merely the result of random permutation. If this implied exposure prevalence were valid in the true underlying population, then the chaos-control group might be a substitute for real controls. Unfortunately, the assumption is very restrictive and is unlikely to hold in many settings, as was already noted by Gillespie et al., who stated that "studies assessing a range of rare and common exposures are problematic" (11, p. 503).

Evaluation of EuroSCAR data

Figure 1A shows the results derived from our analysis in the first scenario with 1 chaos-control per case. We added the results of the original EuroSCAR study for each class of medications, and it can be seen that risk estimates from our case-chaos analysis do not resemble the median log odds ratios of the EuroSCAR study (14). Figure 1B displays the exact same results as part A, except that the drugs are reordered on the x-axis by their corresponding exposure prevalences in cases, from least prevalent to most prevalent. This way the monotonic increase of the log odds ratios becomes apparent.

Figure 2 displays the results from the second and third scenarios. It can be seen that the interquartile ranges of the log odds ratios decrease with the number of chaos-controls used. Since any number of chaos-controls can be used, the estimation can reach any desired level of "precision." The dashed lines in Figures 1 and 2 mark the dividing line between drugs that have an exposure prevalence in cases below the mean exposure prevalence in cases (left of line) and drugs that have an exposure prevalence in cases above the mean exposure prevalence in cases (right). It can be seen that drugs

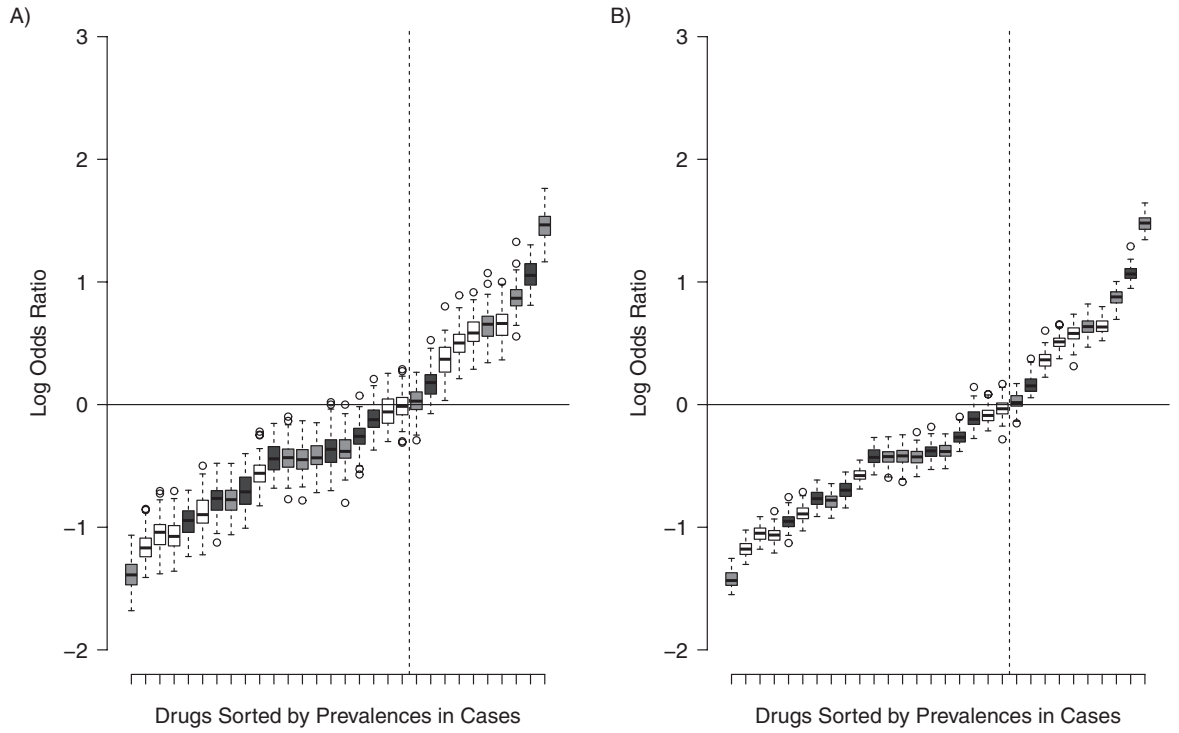

Figure 2. Results from case-chaos analysis of data from the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR; 1997–2001) for the second (A) and third (B) scenarios with 3 and 10 chaos-controls per case (100 studies), respectively. The filling of the boxes denotes their class in terms of suspicion of causing Stevens-Johnson syndrome/toxic epidermal necrolysis, as determined by the EuroSCAR results (14): ■, highly suspected drugs; ■, suspected drugs; □, nonsuspected (other) drugs. The dashed lines mark the dividing line between drugs which have an exposure prevalence in cases below the mean exposure prevalence in cases and drugs which have an exposure prevalence in cases above the mean exposure prevalence in cases.

with a case exposure prevalence above the mean also have an increased estimated risk, while those with a prevalence below the mean have a decreased risk.

Conditional logistic regression could only be performed by univariate assessment. Since the chaos-controls' exposure information is a permutation of their matched cases' exposure information, within every pair the risk factors will be linearly dependent.

DISCUSSION

The case-chaos method of Gillespie et al. (11) is proposed to be a novel approach to assessing risk factors in epidemiology. By randomizing patients' exposure information, controls can be artificially generated. This case series method would allow for a much quicker, cheaper, and easier study and is therefore proposed by Gillespie et al. as an adjunct to regular case-control studies. The method seems very appealing on first glance, and Gillespie et al. support its usefulness by finding some agreement between the case-chaos method and the results of 3 case-control studies (11). However, by closer inspection, we revealed that the case-chaos method did not yield very sensible results: The odds ratios obtained for every risk factor had the same ascending order as the risk factors' exposure prevalences in the case group. In other words, the case-chaos method is simply another way of presenting the exposure prevalences. The applicability of the method is therefore very questionable.

By limiting the theoretical assessment to only 2 risk factors for simplicity, we demonstrated that the monotonic transformation from the exposure prevalences to the resulting odds ratios can be explained analytically. To illustrate our findings in a more complex setting, we used data obtained from 379 patients with SJS or TEN from EuroSCAR who were exposed to 1 or several of 30 different drugs. It could clearly be seen that when applying the case-chaos method, the order of risk estimates was a reflection of the order of the prevalences of drug exposure. These results did not reflect the previous findings of the original EuroSCAR case-control study (14). The case-chaos method was thus not suitable for the analysis of EuroSCAR data. Since the results of the case-chaos method are simply another way of conveying the exposure prevalences, we conclude that this elaborate design is superfluous. Höhle previously made this observation in a letter (12) to Gillespie et al. Pulliam and Dushoff reached the same conclusions using data from an outbreak of foodborne illness (13), in a fashion very similar to ours. In response to their letter, Gillespie et al. maintained that "comparing exposure distributions among cases in a formal and quantitative way appears to be useful" (16, p. 263) and were critical of Pulliam and Dushoff's use of mixed empirical and fictitious data (13).

Furthermore, in their reply to the letter by Höhle (12), Gillespie et al. pointed out that case-chaos "also provides a measure of statistical uncertainty, which remains an advantage" (17, p. 1022). However, it could be seen from the 3 separate scenarios used in our data example that increasing the number of chaos-controls led to lower statistical uncertainty. Since the number of chaos-controls can be chosen arbitrarily, we conclude that the measure of uncertainty is arbitrary as well.

The use of artificial controls is not new in epidemiology. For example, Zaffanella et al. (8) used artificial controls for the study of wire codes and childhood cancer. Along with their proposed method, they also discussed a list of strong assumptions that needed to be satisfied in order for their method to work. As such, their method has been accepted in the research community, but it is also limited to a very specific setting. The case-chaos method is also much too specific to work in general, and some of the necessary assumptions discussed may be too restrictive to ever be met. New information cannot be gained by permutating old information; thus, this use of artificial controls is not warranted.

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