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Interpretation and Bias in Case-Crossover Studies

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ABSTRACT. The case-crossover design is an innovative epidemiologic technique with distinct strengths and limitations. We review the fundamental logic of this self-matching non-randomized design and direct attention to 15 concerns related to the available data, unavailable data, analytic technique, quantitative statistics, and etiologic model. Implications for each concern are discussed in the context of a recent report on whether cellular telephone calls are associated with an increased risk of a motor vehicle collision. We suggest that an understanding of the case-crossover design may help investigators explore selected questions in behavioral medical research. J CLIN EPIDEMIOL 50;11:1281–1287, 1997. © 1997 Elsevier Science Inc.

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INTRODUCTION

The case-crossover design was introduced in 1991 as a new epidemiologic technique for examining the transient effects of a brief exposure on the onset of an acute outcome [1]. Such analyses can be completed quickly, at low cost, and with minimal ethical worries. Common and rare outcomes can be examined, hazardous and protective exposures tested, and both statistical significance and clinical significance determined. Given that behavior contributes to many diseases and that behavior keeps changing, the development of the case-crossover design marks a distinct advance in behavioral medical research. Coupled with the advent of new statistical tests for repeated measures designs and novel methods for collecting huge amounts of real-time data, the case-crossover design may enable and encourage new efforts to analyze rapidly fluctuating processes (such as activity, emotion, or pain) [2]. A review of the design's strengths and weaknesses is, therefore, timely.

DEFINITION AND EXAMPLE

The case-crossover design compares exposures during intervals when an event occurs to exposures during intervals when an event does not occur. A study on the association between cellular telephone calls and motor vehicle collisions illustrates the essentials (Fig. 1) [3]. In this example, drivers were selected after each was in a collision. Telephone records were obtained to assess each driver's use of a cellular telephone during the day of the collision and during the preceding week. The time of the collision was established to determine whether a call occurred during the brief interval immediately before the collision (hazard interval). A comparison day was identified for each person to determine whether a call occurred during a similar interval on a day when the individual was driving but was not in a collision (control interval). Case-crossover analysis identified a significant increase in risk by finding more calls immediately before the collision than would be expected solely due to chance (Table 1).

More generally, the case-crossover design is an epidemiologic technique for assessing the change in the risk of an acute event during a brief interval after exposure to a transient risk factor [1]. The logic follows peoples' natural inclination to wonder, in the aftermath of a vivid change, whether something special triggered the event. Thus, a woman who goes into labor may be convinced that weather is important if contractions started immediately after a snowstorm began—particularly if no snow occurred earlier in the pregnancy. Similarly, a man may be convinced that weather is important in heart disease if the first snow of the year was the first day he had angina. Such coincidences are unforgettable [4]. The main task of the case-crossover design is to collect data from many people and test for consistent relationships. This scientific approach is similar to classic matching studies investigating exposures to radiation, chemicals, and other interventions [5–7].

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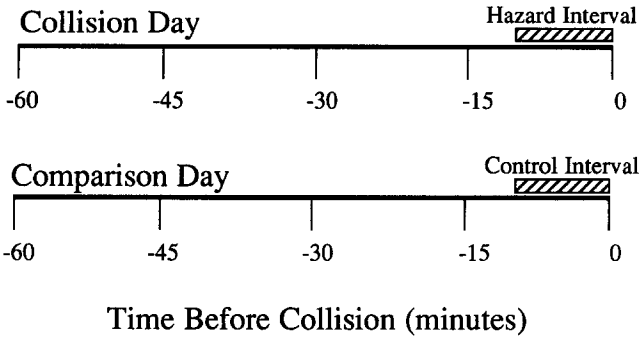

FIGURE 1. Case-crossover design. Comparison of exposures immediately prior to a collision with exposures at a similar time on a comparison day when no collision occurred. In this example, the hazard interval has a width of about 10 minutes and no delay. The control interval is defined to have the same width and clock-time but is identified from a different day. Statistical analysis compares the frequency of exposures for each individual during the hazard interval and during the control interval.

RELATION TO PAST WORK

The case-crossover design has advantages over parallel group designs by allowing each person to serve as their own control. Fixed characteristics (both measured and unmeasured) thereby cancel out. This procedure removes confounding from many uncontrollable determinants of patient outcomes (such as age, intelligence, genetics, and socioeconomic status). Imbalances are still possible in transient individual and environmental factors (such as anger and daylight), although the importance of such short-term exposures on patient outcomes is generally unknown. As there is no need to find a separate cohort to serve as a control group, self-matching designs are particularly appealing in situations with rare or reluctant populations. Moreover, these analyses offer further savings in the sample size because pair-matching, in contrast to group-matching (as in a randomized trial), is extremely powerful from a statistical perspective.

The case-crossover design has been formalized only recently and few analyses have been published in the medical literature [8–13]. Why? First, the time lag between exposure and outcome must be brief, thereby excluding most studies on the progression of a chronic disease. Second, exposures must have little carry-over effect; thus, an intervention which is anticipated to cause cumulative changes in the patient cannot be evaluated using these techniques. Third, the effects of the exposure on the likelihood of an outcome must be fairly consistent (so that initial and repeat applications yield similar results) if the analysis is to provide a meaningful estimate of the magnitude—not just the presence—of an association. Finally, the design is awkward when attempting to detect potential effect modulators, so that comparisons between individuals with different characteristics typically follow conventional subgroup analyses.

TABLE 1. Basic results of one study

		Exposure during control interval?	
		Yes	No
Exposure during hazard interval?	Yes	13	157
	No	24	505

Results from one case-crossover analysis on the association between cellular telephone calls and motor vehicle collisions. Numbers represent counts of individuals with corresponding exposures. For example, 157 individuals had a call during the hazard interval but not during the control interval, thereby suggesting a potential harmful association. Relative risk indicates the odds of a collision when using a telephone compared to the odds of a collision when not using a telephone. Relative risk = 6.5; 95% confidence interval (4.5–10.0).

BIAS AND INTERPRETATION

The case-crossover design is both novel and limited. In the following section we discuss concerns related to bias and interpretation of potential results. Fifteen items are presented (Table 2), and then illustrated using the study on the association between cellular telephone calls and motor vehicle collisions. The comments direct particular attention to biases which might alter the main finding of the study; namely, that using a cellular telephone was associated with an increased risk of a motor vehicle collision. Our goal is to provide a framework relevant to any case-crossover analysis, even though many of the items could also be relevant to other epidemiology designs. We focus all criticisms on our own work, and we concentrate on biases which we consider especially serious or worthy of further research. The sequence is organized for clarity of presentation, rather than order of importance, and identifies each item under a separate heading.

Incomplete Data on Exposures

The main task of a case-crossover analysis is to compare the frequency of exposure in the hazard interval to the frequency of exposure in the control interval. One problem to avoid, therefore, is error in measuring the two frequencies. Consistent errors in ascertaining these frequencies can alter the magnitude of an observed association, but not its direction. Differential errors can be even more worrisome. For example, the positive risk found in the cellular telephone study could be misleading if exposure was overestimated prior to the collision or underestimated on the comparison day. The reliance on objective telephone records does not completely eliminate this worry if people own multiple telephones (which are used differentially on different days) or if activity occurs which is not recorded (due to intermittent failures in the billing system). Of course, a case-crossover

TABLE 2. Summary of potential biases and interpretation issues

Category	Item
Available data	Incomplete data on exposures
	Overestimating exposures during hazard interval
	Underestimating exposures during control interval
Unavailable data	Distortions from sample selection
	Extrapolation to different outcome severities
	Retrospective identification of outcomes
Analytic technique	Quantitative estimates from statistical models
	Dose–response gradients
	Inferring individual risks from aggregate statistics
Quantitative statistics	Presentation of results
	Subgroup analyses
	Checking multiple control intervals
Etiologic model	Inferring causality from association
	Distinguishing between triggering and etiologic agents
	Framing differences as positive or negative

analysis based on self-report statements rather than objective records of exposures could be distorted by recall bias, presentation bias, and other problems [14].

Overestimating Exposures Immediately Prior to the Outcome

Even with perfect records, the intensity of activity immediately prior to the event could still be miscalculated in a case-crossover analysis due to imprecision in the onset time. For example, people are likely to use a cellular telephone immediately following a collision; hence, errors in determining the collision time generally lead to overestimates rather than underestimates of the intensity of activity prior to the collision. An onset time which is incorrectly late will lead to substantial errors in assessing the association if the event causes a sudden increase (or termination) in exposure. Conversely, an onset time which is incorrectly early will tend to bias the analysis toward finding no association. It is not always possible to establish that exposure preceded outcome: one way to check the extent of such residual error in a case-crossover study is to assess the results for individuals with especially precise or imprecise onset times.

Underestimating Exposures During Control Intervals

A spurious association may also occur if the intensity of exposure is poorly estimated on normal days. For example, one issue in the cellular telephone study relates to fluctuations in driving behavior. If individuals rarely drive, a given number of calls should be distributed over a small number of intervals. Overestimating the amount of driving on days prior to the collision would dilute the apparent intensity of cellular activity during the control interval and inflate the measure of relative risk. However, this bias is unlikely to account for the reported association for two reasons. First, analyses adjusted for sporadic driving patterns still showed a substantial relative risk. Second, estimates from different hazard windows demonstrated that the association was not found in calls not close to the time of collision. More generally, one method for evaluating any case-crossover analysis is to check both the association for exposures close to the outcome and the lack of association for exposures remote from the outcome.

Distortions from Sample Selection

Concerns about external generalizability are common in epidemiology. For the cellular telephone study, individuals were recruited from one region over a few months. The estimates of relative risk, therefore, may not apply to other settings to the extent that driving conditions vary elsewhere or proficiency with cellular telephone technology changes with time. Further research should be encouraged. One noteworthy aspect of selection bias in the cellular telephone study reflects the exclusion of individuals who refused to participate. The estimates of increased risk may be too small if some individuals who were using the telephone at the time of collision declined to participate for fear of liability. Adjusting for this bias is difficult and avoiding this bias would require circumventing the ethics of informed consent. This form of selection bias serves to lower the apparent association between telephone calls and vehicle collisions. In other case-crossover analyses, however, distortions due to sample selection could lead to positive or negative biases.

Extrapolation to Different Outcome Severities

Another issue in epidemiology is spectrum bias [15]. For example, the cellular telephone study analyzed moderate

collisions whereas clinical outcomes are most important in severe collisions. The estimated relative risk, therefore, may be misleading if factors contributing to a collision differ substantially across the range of injury severity. This is unlikely to be a serious issue in the cellular telephone study for two reasons. First, the classification of collisions as either "minor," "moderate," or "severe" is somewhat arbitrary given data from multi-occupant events showing that one person may walk away from a collision with no signs of trauma while another person may be fatally injured even though both were in the same vehicle [16]. Second, "moderate" collisions, in their own right, are still important given that they can be associated with significant costs [17]. Despite these arguments, further research is warranted. Case-crossover analyses that focus on a consistent clinical disorder would encounter less trouble related to spectrum bias.

Retrospective Identification of Outcomes

Similar to the case-control design, the case-crossover design involves identifying individuals who have experienced an outcome and analyzing their preceding exposures. The exclusion of individuals with extreme outcomes (Neyman bias) is a problem because individuals are sampled only if they can be identified after the fact [18–20]. In the cellular telephone study, individuals were recruited following a moderately severe collision. The estimate of relative risk, for example, may be too high if cellular telephones were protective for particularly minor events and prevented multiple small collisions from occurring at all. The paradox, however, would not explain why heavy telephone users were more common in the study sample than in the general population. Yet this paradox is not impossible if heavy users also drove much more than average. Prospective case-crossover analyses are theoretically possible in some settings and may merit consideration as a method for eliminating Neyman bias.

Quantitative Estimates from Statistical Models

Several different statistical models have been developed for measuring the magnitude of the relative risk in a case-crossover analysis. Distortions found in different models are unlikely to change the direction of an observed association but can make it difficult to interpret the degree of statistical significance or the size of the estimated risk. For example, data from the cellular telephone study showed that a random effects analysis can yield systematically different estimates compared to a conditional effects analysis [21]. In this case, but not in others, the conditional effects analysis provided much more conservative estimates of both statistical significance and clinical significance (and the presentation of results was restricted to the more conventional approach). One drawback of conditional analysis is to disregard information from concordant cases in a case-crossover analysis. More research is needed to better understand the complex statistical techniques now available through high-intensity computer simulations [22].

Dose–Response Gradients

Studies of causation gain credibility by establishing multiple lines of evidence. The criteria proposed by Hill include: findings from true experiments, a strong observed association, consistency between different analyses, a clear temporal relationship, a dose–response gradient, epidemiologic plausibility, biologic plausibility, specificity between exposure and outcome, and analogy to other phenomena [23,24]. One weakness in some case-crossover analyses, including the cellular telephone study, is the failure to explore detailed dose–response gradients. Yet such explorations could be performed by distinguishing different frequencies, intensities, or other features of the exposures occurring during the hazard and control intervals. A case-crossover analysis, in principle, could evaluate how multiple brief exposures compare to one prolonged exposure. And how the first moments compare to subsequent and final moments. Clear answers might help when interpreting associations found in a case-crossover analysis.

Inferring Individual Risks from Aggregate Statistics

A fundamental quandary in statistics is to estimate individual risk from group frequencies [25]. This inference demands that group members be similarly prone to the expected outcome and becomes problematic if the exposure is hazardous for some and protective for others. For example, a protective effect has been postulated in the "peace-of-mind" hypothesis, which asserts that telephones allow drivers to call ahead when late, to feel less of a need to rush, and consequently to drive less dangerously. In the cellular telephone study, heterogeneity of individual sensitivities is unlikely to be large because the results were consistent across different subgroups and because the hypothesized mechanism (psychological distraction) is a basic feature of human reasoning [26]. However, the peace-of-mind hypothesis cannot be rejected if it acts in a uniform manner for all individuals and serves to attenuate what would otherwise be a much larger risk. Heterogeneity of individual risks may be a larger problem in case-crossover analyses conducted in other settings.

Presentation of Results

It is important to emphasize that the results of a case-crossover analysis are short-term risks rather than cumulative risks (and relative risks rather than absolute risks). Estimating total danger requires integrating the short-term risk over the duration of exposure. Consider, for example, an individual with a one in fifty (2.0%) annual probability of

being in a collision who spends about 1 hour daily driving of which 1 minute involves using a cellular telephone. Given an instantaneous relative risk estimate of 4, the cumulative daily relative risk is 1.05 ($1/60 \times 4 + 59/60 \times 1$). Over a 1-year interval, the absolute risk of a collision would increase from 2.0% to 2.1% (1.05×2.0). One extra collision would require 1000 such individuals (1/0.1%) and reflect about 365,000 calls (365×1000). With other assumptions the risk could be smaller or larger than one crash per 365,000 calls. Finally, it is important to emphasize that these risks would be above and beyond the driver's usual level of danger and usual driving habits.

Subgroup Analyses

Case-crossover analyses tend to collect massive amounts of observations and may be prone to errors related to data dredging [27]. The cellular telephone study, in particular, presented several subgroup analyses examining how the relative risk of a collision might vary according to calling times or individual characteristics. Such multiple comparisons may capitalize on chance and detect spurious p-values. Conditional logistic regression provides one safeguard against errors related to data dredging. Limiting the number of subgroups is also helpful; for example, in the cellular telephone study only one subgroup analysis was prespecified (the comparison of hand-held to hands-free telephones) and the presentation emphasized only this single test of significance. Finally, a Bayesian approach might also be worthwhile by motivating the investigator to make *a priori* predictions on where differences were and were not likely to be found [28].

Checking Multiple Control Intervals

The Achilles' heel of all non-experimental designs is in the selection of an appropriate comparison standard. In recognition of this difficulty, one strategy is to examine multiple standards and check the robustness of all results. The cellular telephone study, for example, checked five different standards and found that the estimates of relative risk were reasonably similar. An additional strategy available in case-crossover analyses is to select an extended control interval (or to combine multiple small control intervals) to increase statistical power and minimize random error. However, enlarging or aggregating the control window can lead to biases if temporal trends alter either the exposure or the outcome in an unpredictable manner [29]. The conservative approach is to collect and include data from multiple alternative control intervals only as a method for checking the robustness of final results.

Inferring Causality from Association

The non-randomized nature of the case-crossover design raises unsolvable problems related to inferring causality from association [30]. Confounding can arise from many sources and would be only partially mitigated by assessing all characteristics of the situation. First, many confounders are impossible to measure accurately. Second, a diligent search for confounders would inevitably detect other correlations, thereby necessitating a huge sample size to determine the independent contribution of each component. Third, a statistically significant association attributable to an identified component would not distinguish between elements that initiated the chain of events and elements that were epiphenomena occurring in the cascade of reactions. Investigators using a case-crossover design, therefore, the authors should caution readers against interpreting an observed association as necessarily indicative of a causal link between exposure and outcome.

Distinguishing between Triggering and Etiologic Agents

A troubling question in the case-crossover design relates to the brief follow-up interval. Namely, does a positive effect indicate that an exposure hastened an outcome that was inevitable or that an exposure induced an outcome that would not have occurred otherwise? This question cannot be answered by further data collection or statistical manipulation. Instead, one must appeal to theory. For some situations, such as the association between heavy exercise and the onset of a heart attack, a positive effect most likely represents triggering an event which would probably have had its onset at some later date (albeit, not necessarily to the same severity). For other situations, such as the association between using a cellular telephone and the incidence of a motor vehicle collision, a positive effect most likely relates to an event which was not necessarily destined to happen at some time in the future. The distinction between triggering and etiology is inherent to the case-crossover design and can have practical implications.

Framing Differences as Positive or Negative

The final results of a case-crossover analysis yield an estimate of relative risk comparing exposed to unexposed conditions. A relative risk greater than 1 might indicate either that the exposure was harmful or that withdrawal from the exposure was beneficial. These two explanations are indistinguishable from a statistical perspective yet can have different implications for decision makers. In the cellular telephone study, the first interpretation would lead to recommendations to avoid calls at all times as a method for improving driving safety. In contrast, the second interpretation would lead to recommendations to maximize the number of calls during otherwise safe circumstances and deliberately abstain from calls during particularly treacherous times (thereby exploiting the protective effects of the withdrawal condition). In our opinion, this ambiguity between positive risk with negative protection is not a serious problem in the

cellular telephone study but might be important for case-crossover analyses in other situations.

SUMMARY

In this article we have reviewed the case-crossover design with particular attention to bias and interpretation of a study about cellular telephone calls and motor vehicle collisions. Much of the material will be familiar to investigators skilled in other epidemiologic designs; however, the framework may help guide those who are either inexperienced or forgetful. The 15 concerns can be considered in groups of three according to whether the source involves the available data, the unavailable data, the analytic technique, the quantitative estimates, or the etiologic model. The most powerful research design for avoiding many of these concerns is a randomized trial; however, this approach is sometimes problematic because of costs, recruitment, enforcement, duration, and ethics [31]. In our opinion, the most important single strength of the case-crossover design is feasibility. The most important single weakness of the case-crossover design depends on the particular application.

The case-crossover design can be used in behavioral medical research to identify associations between an exposure and an outcome. However, the interpretation of an association is always problematic because of potential confounding. Consider a hypothetical possibility related to analyzing cellular telephone calls and motor vehicle collisions. Some people might deliberately avoid calls while driving in hazardous circumstances because of intuitive beliefs about potential dangers. Thus, they self-select times for using a cellular telephone to coincide with times of relatively safe driving. If so, a case-crossover analysis might detect a protective association between calls and collisions. We stress that this example is hypothetical but could apply to any case-crossover analysis that involves conscious participants. Subtle confounding is a fundamental concern when individuals can make strategic responses in anticipation of a perceived benefit or harm. Causal relationships are best established through multiple lines of converging evidence that use diverse study designs.

The case-crossover design is a powerful method applicable to a narrow range of scientific questions. Some appealing general applications for the case-crossover design could include studying falls in the elderly, seizures in epilepsy, and exacerbations of back pain. Cardiovascular events are also compelling, as already shown for myocardial infarction and perhaps possible for aneurysm ruptures, strokes, arrhythmias, and intermittent claudication. Other specialty issues could be considered such as retinal detachments, relapse after quitting cigarettes, and suicide attempts. Additional imaginative studies could focus on intriguing human behaviors. A common feature of the examples, and perhaps all applications of the case-crossover design, is in identifying a condition with a clear beginning. A troubling limitation of many of the examples, and many case-crossover analyses, will be in collecting accurate data on exposures. The most relevant studies are likely to be on acute-onset disorders with serious outcomes and modifiable exposures.

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