bmjmedicine

The case-crossover design for studying sudden events

Dan Lewer ,[1] Irene Petersen,[2] Malcolm Maclure[3]

Dan Lewer and colleagues explain how case-crossover studies can help understand triggers of sudden events

[1]Epidemiology and Public Health, UCL, London, UK
[2]Department of Primary Care and Population Health, UCL, London, UK
[3]Department of Anaesthesiology, Pharmacology, and Therapeutics, University of British Columbia, Vancouver, BC, Canada
Correspondence to: Dr Dan Lewer, Epidemiology and Public Health, University College London, London WC1E 6BT, UK; d.lewer@ucl.ac.uk

Cite this as: *BMJMED* 2022;1:e000214. doi:10.1136/bmjmed-2022-000214

Received: 31 March 2022
Accepted: 25 May 2022

Introduction

The case-crossover method is an epidemiological design used for studying potential causes of sudden events,[1] such as whether vigorous exertion or drinking alcohol triggers a myocardial infarction.[2] Case-crossover studies are one of a family of self-controlled study designs,[3] including crossover experiments and the self-controlled case series[4] (table 1). Each participant serves as their own control, and the analysis tests whether exposure times are associated with outcome times within individuals. By contrast, standard observational studies make comparisons between individuals, such as differences in myocardial rates between alcohol drinkers and non-drinkers (a cohort study) or whether sedentary lifestyles are more common among people who have had a myocardial infarction than among those who have not (a case-control study).

A case-crossover study only includes individuals who experience an event (known as cases). Figure 1 shows an illustrative study looking at the association between vigorous exertion and myocardial infarction. In the case-crossover approach, non-cases are excluded. In this example, the probability of exertion in the time window before myocardial infarction is compared with the probability of exertion in that window 24 hours earlier in the same individuals. If someone had a myocardial infarction at 6 pm on Friday and we are interested in the risk up to 1 hour after physical exertion, we would take their history of exertion between 5 pm and 6 pm on that day, and compare it with their physical exertion between 5 pm and 6 pm on Thursday. If the participant died, this information could be ascertained by interviewing family members or other informants. By contrast with the case-crossover approach, a case-control study might match people who had a myocardial infarction with controls who had not had an myocardial infarction by that point in time, and compare the probability of recent exercise.

KEY MESSAGES

- ⇒ Case-crossover studies focus on the triggers of sudden events such as heart attacks, car crashes, adverse reactions to medicines, and drug overdoses
- ⇒ In this design, comparisons are made within individuals by comparing exposures (potential causes of the sudden event) just before an event to exposures at another control time, eliminating many confounding problems that affect traditional epidemiological studies
- ⇒ Researchers should consider the role of time-varying confounding, and make decisions about the timing of control time windows
- ⇒ Databases and technologies that record health exposures over time will allow many new applications of the case-crossover study

Case-crossover studies in practice

The case-crossover design was developed for an interview study of triggers of myocardial such as exertion, alcohol, anger, and cannabis.[1] It has since been used with databases in many contexts, and we give four brief examples below. Common features of these research questions include the focus on sudden events and the triggering effect of transient exposures.

- Air pollution and cardiovascular events: case-crossover studies have found that concentrations of pollutants are elevated on the day of a stroke or heart attack compared with the concentration on earlier or later days.[5] These studies are often statistically powerful because researchers can include large numbers of cases and determine pollution from routine weather records.
- Car crashes and mobile phone use: case-crossover studies have found that drivers have several times the odds of using a mobile phone in the minutes before the crash when compared with a similar time of day earlier in the week.[6 7]
- Adverse medicine effects: a study of falls among hospital inpatients found that new medicine prescriptions such as antihypertensive and hypnotic agents were more common in the three days before the fall than during earlier referent windows.[8]
- Triggers of illicit opioid overdoses: a study of deaths in England found that deceased individuals were four times more likely to have been recently discharged after inpatient medical treatment than during the two years before death.[9]

Choosing the right control

The duration and timing of referent windows is a key design decision. It depends on the definition of at-risk time, or the study base.[2] In a study of car crashes in Australia,[7] researchers compared mobile phone use at the time of the crash to earlier car trips at similar times of day; not just the same time on previous days when the participant might not have been driving.

Researchers must consider the duration of effect, or effect period.[3] This is the plausible duration of induction times between the trigger (eg, physical exertion) and its outcome (eg, myocardial infarction). This period might not be known precisely and could vary between individuals. When attempting to set referent windows that match effect periods, researchers often need to make informed judgments

Table 1 | Comparison of design features: case-crossover study versus self-controlled case series

Feature	Case-crossover design	Self-controlled case series design
Analogous to	Case-control study	Cohort study
Developed to study	Multiple potential causes of an outcome	Multiple effects of an exposure (the potential cause of sudden events)
Example	Triggers of myocardial infarction	Adverse effects of vaccines
Anchor point (time zero)	Onset of the outcome	Exposure time, birth, or calendar date
Timing of referent windows	Usually before the outcome	Before and after the outcome
Potential bias	Exposure trend or persistence	Reverse causality
Comparisons	Ratios of odds of exposure	Ratios in risk of outcomes
Statistical model	Conditional logistic or conditional Poisson regression	Conditional logistic or conditional Poisson regression, offset by person time

based on previous research and simplifying assumptions. These decisions are likely to affect the results. Referent windows that are too short will reduce power by excluding events, while windows that are too long are likely to bias results towards the null.

The time between the event and referent window is also important. The referent windows should be far enough from the event so that exposure is not affected by the event. Simultaneously, referent windows should be sufficiently recent that the underlying rate of exposure is comparable, or exchangeable.[10] In a study of mobile phone use and car crashes, the probability of mobile phone use during a referent window 5 minutes before the crash would be correlated with mobile phone use at the time of the crash because some phone calls are longer than this. A control window one year before the crash might be inappropriate, for example if a covid-19 lockdown meant different patterns of mobile phone use.

Referent windows can be before the event, after the event, or both. In the example in figure 1, myocardial infarction is likely to reduce vigorous exercise, at least temporarily, so we would only select historical referent windows. Referent windows after a non-fatal myocardial infarction would overstate the risks of exercise (reverse causality bias in table 1). If the event does not affect subsequent exposure, such as in studies of air pollution, then referent windows both before and after the event can reduce the risk of bias owing to time trends in the exposure.

Positives and pitfalls

In common with other self-controlled designs, a strength of the case-crossover design is that it eliminates time invariant confounders, even when unmeasured. Such confounders include personality traits, genetics, country of birth, and many other characteristics of patients not recorded in medical

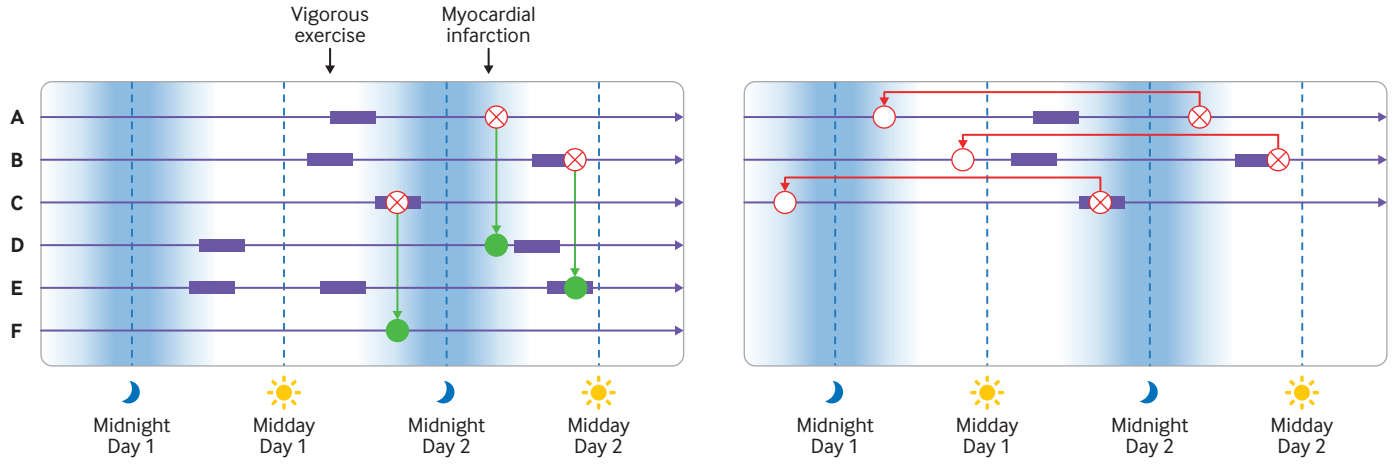

Figure 1 | Illustrative study of the association between vigorous exercise and myocardial infarction, using case-crossover and case-control study designs. Figure shows timelines for six individuals (A to F). In a case-control study (left), individuals A, B, and C had myocardial infarctions (crossed red circles); individuals D, E, and F are controls selected at the same times (green circles); and the exposure of interest was vigorous exertion (occurring at the left edge of rectangles). A case-crossover design (right) compares the probability of exertion in the hour before myocardial infarction to the same time the previous day in the same individual (empty red circles); non-cases (individuals D, E, and F) do not contribute to the case-crossover analysis

charts. For example, in figure 1, the underlying severity of atherosclerosis would be constant over the two days of observation (not shown).

Another reason for using the case-crossover design is that suitable controls can be difficult to find in case-control studies. In a study of hospital discharges and opioid overdoses,[9] a traditional case-control study would be challenging because it would need to recruit a representative sample of controls who were at risk of opioid overdose at the time the cases died.

Case-crossover designs are often statistically powerful (that is, they produce precise estimates) because they allow sampling of a large proportion of cases. Traditional cohort or case-control studies might include more person time, but they capture fewer events and yield less precise estimates. Power calculations for case-crossover studies must account for the comparisons within individuals and the likelihood of correlated exposures, which can be done through simulation or formulas designed to account for these factors.[11]

However, the case-crossover design has some key limitations: time-varying confounding, the limitation to the short term effects of transient exposures, and selection biases. Co-occurring acute exposures are especially challenging in the case-crossover design. For example, if we want to study the effect of cannabis use on injury, the association might be confounded by co-occurring alcohol consumption (figure 2). As in any observational study, the causal relation between exposures and potential confounders must be interpreted by researchers on the basis of existing evidence and common sense. Where time-varying confounders are measured, they can be controlled in multivariable analysis as in traditional epidemiological studies.

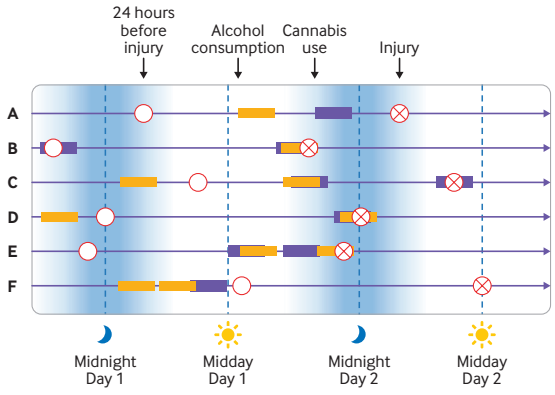

Figure 2 | Illustrative case-crossover study of the effect of cannabis use on injury, demonstrating time-varying confounding. Figure shows timelines for six individuals (A to F); different to those individuals A to F in figure 1. All individuals had an injury (crossed red circles). Cannabis use (occurring at the left edge of the purple rectangles) and alcohol consumption (left edge of orange rectangles) in the hour before death are compared with the same period 24 hours before death (empty red circles). In this example, co-occurrence of cannabis and alcohol consumption would result in the association between cannabis use and injury being confounded by alcohol use

Case-crossover studies only capture the short term effects of transient exposures, such as an adverse event soon after starting a drug treatment. However, cumulative harms or benefits from long term drug treatment would not be picked up by a case-crossover study. Transient effects can be in the opposite direction of cumulative effects: while a single run increases your immediate risk of myocardial infarction, regular running reduces your risk. Transient and cumulative effects can be disentangled by combining a case-crossover design with a case-control study as in figure 1. Using different study designs to answer the same research question can also help researchers understand different forms of bias and contribute to triangulation of causal associations.[12]

Case-crossover studies use information from cases only if the exposure status varies over time. These individuals might not represent the whole population. In the example in figure 1, people who exercise at the same time each day, potentially an important part of the population, are excluded because their exposure status at the time of the myocardial infarction will be the same as that 24 hours earlier. Multiple referent windows might increase the number of cases who have varying exposure status.

The case-crossover design is a widely used tool for studying triggers of sudden health events. The fundamental points of the design have not changed since it was developed in the 1990s, and the original articles describing it remain a good starting point for researchers.[1 2] New opportunities to apply the method are arising with the availability of databases with time-stamped exposures, such as precise locations, mobile phone use, and retail purchases.[13 14]

Twitter Dan Lewer @danlewer

Contributors DL had the idea for the article. DL, IP, and MM together drafted and revised the article.

Funding DL is funded by the National Institute for Health Research (NIHR; Doctoral Research Fellowship DRF-2018-11-ST2-016). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD
Dan Lewer http://orcid.org/0000-0003-3698-7196

REFERENCES

1 Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133:144–53. doi:10.1093/oxfordjournals.aje.a115853
2 Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health* 2000;21:193–221. doi:10.1146/annurev.publhealth.21.1.193
3 Cadarette SM, Maclure M, Delaney JAC, *et al*. Control yourself: ISPE-endorsed guidance in the application of self-controlled study designs in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2021;30:671–84. doi:10.1002/pds.5227
4 Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ* 2016;354:i4515. doi:10.1136/bmj.i4515
5 Stieb DM, Zheng C, Salama D, *et al*. Systematic review and meta-analysis of case-crossover and time-series studies of short term outdoor nitrogen dioxide exposure and ischemic heart disease morbidity. *Environ Health* 2020;19:47. doi:10.1186/s12940-020-00601-1
6 Redelmeier DA, Tibshirani RJ. Association between cellular-telephone calls and motor vehicle collisions. *N Engl J Med* 1997;336:453–8. doi:10.1056/NEJM199702133360701
7 McEvoy SP, Stevenson MR, McCartt AT, *et al*. Role of mobile phones in motor vehicle crashes resulting in hospital attendance: a case-crossover study. *BMJ* 2005;331:428. doi:10.1136/bmj.38537.397512.55
8 Shuto H, Imakyure O, Matsumoto J. Medication use as a risk factor for inpatient falls in an acute care Hospital: a case-crossover study: case-crossover study on medication use and fall events. *Br J Clin Pharmacol* 2010;69:535–42. doi:10.1111/j.1365-2125.2010.03613.x
9 Lewer D, Eastwood B, White M, *et al*. Fatal opioid overdoses during and shortly after hospital admissions in England: a case-crossover study. *PLoS Med* 2021;18:e1003759. doi:10.1371/journal.pmed.1003759
10 Mittleman MA, Mostofsky E. Exchangeability in the case-crossover design. *Int J Epidemiol* 2014;43:1645–55. doi:10.1093/ije/dyu081
11 Dharmarajan S, Lee J-Y, Izem R. Sample size estimation for case-crossover studies. *Stat Med* 2019;38:956–68. doi:10.1002/sim.8030
12 Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol* 2017;22:dyw314. doi:10.1093/ije/dyw314
13 Dixon WG, Beukenhorst AL, Yimer BB, *et al*. How the weather affects the pain of citizen scientists using a smartphone APP. *NPJ Digit Med* 2019;2:105. doi:10.1038/s41746-019-0180-3
14 Eum Y, Yoo E-H. Using GPS-enabled mobile phones to evaluate the associations between human mobility changes and the onset of influenza illness. *Spat Spatiotemporal Epidemiol* 2022;40:100458. doi:10.1016/j.sste.2021.100458