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Methods primers article template

February 2022

Sophie Cook

The case-crossover design for studying sudden events: methods primer

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Box 1: Key messages

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

Conflicts of Interest
We have read and understood BMJ policy on declaration of interests and have no interests to declare.

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Standfirst

Case-crossover studies measure the triggering effect of transient exposures on sudden events. This article outlines key design features, applications, and limitations.

Introduction

The case-crossover method is an epidemiological design for studying potential causes of sudden events,[1] such as whether vigorous exertion or drinking alcohol triggers a myocardial infraction (MI).[2] Case-crossover studies are one of a family of 'self-controlled' study designs,[3] including cross-over experiments and the self-controlled case series[4] (Box 2). Each subject serves as their own control. These designs address the question 'why now?', by studying whether exposure times are associated with outcome times within individuals. In contrast, standard observational studies make comparisons between individuals, such differences in MI rates between alcohol drinkers and non-drinkers (a cohort study) or whether sedentary lifestyles are more common among MI cases than other people who have not had an MI (a case-control study).

A case-crossover study only includes individuals who experience an event ('cases'). Figure 1 is an illustrative study looking the association between vigorous exertion and MI. In the case-crossover approach, non-cases are excluded. The probability of exertion shortly before MI is compared to the probability 24hr before in the same individuals. In contrast to the case-crossover approach, a case-control study might match cases who had an MI with controls who had not had an MI by that point in time, and compare the probability of recent exercise.

Figure 1: Illustrative case-crossover study of the association between vigorous exertion and myocardial infarction

Figure 1 caption: The relation between case-crossover and case-control designs is illustrated with timelines for six individuals (A to F) in a case-control study (left). A, B and C had myocardial infarctions (encircled X). D, E and F were controls selected at the same times (open circles). The exposure of interest was vigorous exertion (rectangles). A case-crossover design (right) compares the probability of exertion in the hour before MI to the same time the previous day in the same individual. Non-cases (D to F) do not contribute to the case-crossover analysis.

Box 2: Comparison of features of the case-crossover and self-controlled case series designs

	Case-crossover	Self-controlled case series
Analogous to	Case-control study	Cohort study
Developed to study	Multiple causes of an outcome	Multiple effects of an exposure
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 exposure period
Potential bias	Exposure trend or persistence	Reverse causality
Comparisons	Ratios of odds of exposure	Ratios or differences in outcomes
Statistical model	Conditional logistic regression	Poisson conditioned on person and time
Model assumes	Outcome fixed, random exposure	Exposure fixed, random outcome

Example applications

The case-crossover design was developed for an interview study of triggers of MI such as exertion, alcohol, anger, and cannabis.[1] It has since been used with databases in many contexts,[8] and here we give four brief examples.

(i) Air pollution and cardiovascular events. Case-crossover studies have found elevated concentrations of pollutants on the day of a stroke or heart attack compared to 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. (ii) 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 to similar a time-of-day earlier in the week.[6,7] (iii) Adverse medication effects. A study of falls among hospital inpatients found that new prescriptions of various drugs such as antihypertensives and hypnotics were more common in the three days before the fall than during earlier referent windows.[8] (iv) Triggers of drug overdoses. A study of deaths in England found that decedents were four times more likely to have been recently discharged after inpatient medical treatment compared with the two years before death.[9] Common features of these research questions include the focus on sudden events and the 'triggering' effect of transient exposures.

Selection of control (or 'referent') windows

The choice of referent windows is a key design decision. It is dependent on the definition of 'at-risk' time, or the 'study base'.[2] In the study of car crashes in Australia,[7] the 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]: the period after exposure when we hypothesise that the event might be triggered. This may not be known precisely and may vary between individuals. When attempting to set referent windows that match effect periods, researchers often need to make informed judgements and simplifying assumptions. Referent windows that are too short will reduce power by excluding relevant events, while windows that are too long will dilute the estimated effect.

The time between the event and referent window is also important. The referent windows should be sufficiently distant 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 five 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 if it was during a COVID-19 lockdown.

Referent windows can be before the event, after the event, or both. In the example in Figure 1, MI is likely to reduce vigorous exercise, at least temporarily, so we would only select historical referent windows. Referent windows after a non-fatal MI would overstate the risks of exercise ('reverse causality bias' in Box 2). If the event does not affect subsequent exposure, such as in studies of air pollution, then referent windows both before and after the event reduces the risk of bias due to time trends in the exposure.

Strengths and limitations

In common with other self-controlled designs, a strength of the case-crossover design is that it eliminates time-invariant confounders, even when unmeasured. This includes personality traits, genetics, country of birth, and many other constant characteristics of patients not recorded in medical charts. For example, in Figure 1, the underlying severity of atherosclerosis is constant over the two days of observation.

Another reason for using the case-crossover design is if suitable controls are difficult to find in case-control studies. For example, in the 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.

Three key limitations of the case-crossover design are time-varying confounding, the limitation to the short-term effects of transient exposures, and selection biases.

Co-occurring acute exposures are especially challenging in 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 relationship between exposures and potential confounders must be interpreted by the researcher based on 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: Example of time-varying confounding in a case-crossover study of injuries: co-occurrence of cannabis and alcohol consumption would result in the association between cannabis use and injury being confounded by alcohol use.

Case-crossover only capture the short-term effects of transient exposures, such as an adverse event soon after starting a medication. However, cumulative harms or benefits from long-term medication 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 MI, 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. This also helps understand different forms of bias and contribute to 'triangulation' of causal associations.[11]

Case-crossover studies use information from cases only if their exposure status varies over time. These individuals may be unrepresentative of the whole population. In 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 will be the same at the time of the MI and 24 hours earlier. Multiple referent windows may increase the number of cases who have varying exposure status.

Conclusion

The case-crossover design is a widely used tool for studying triggers of sudden health events. As databases following individuals over time increase in number and richness, many new opportunities to use this design will be found.[12]

Competing interests

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

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 and 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;: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, et al. 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 Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol 2017;:dyw314. doi:10.1093/ije/dyw314

12 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

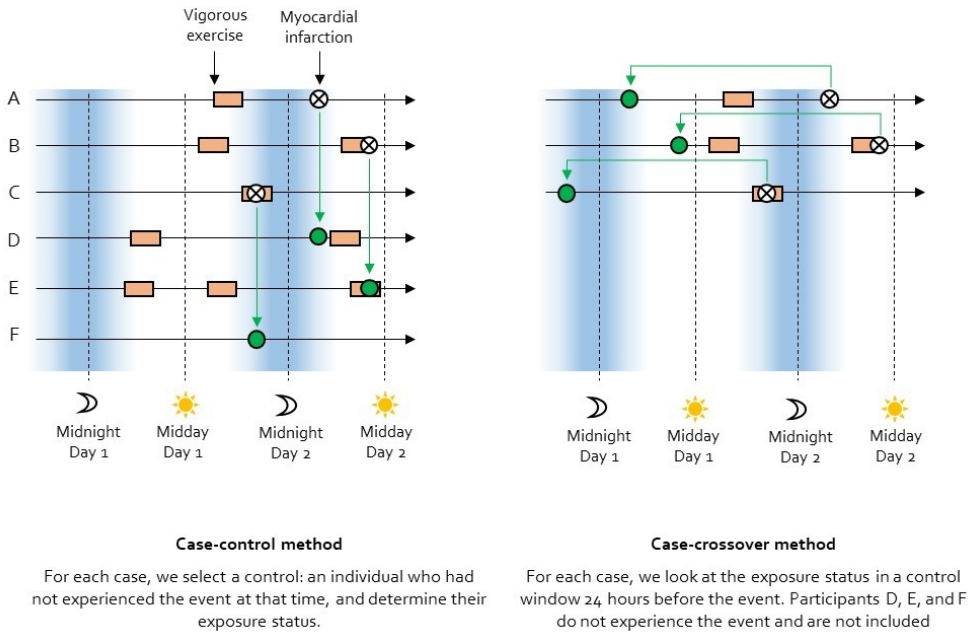

Figure 1: Illustrative case-crossover study of the association between vigorous exertion and myocardial infarction

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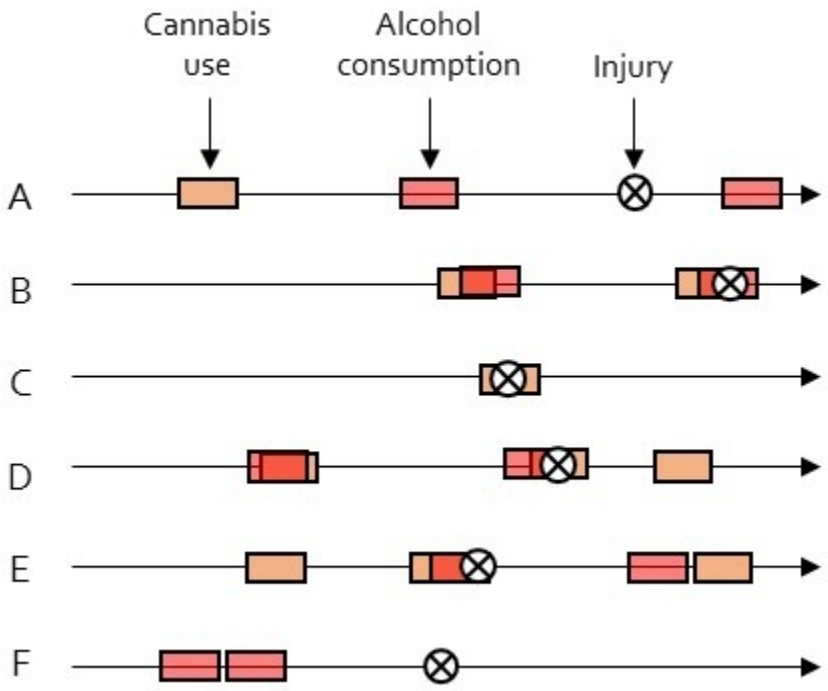

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A case-crossover study only includes individuals who experience an event ('cases'). Figure 1 is an illustrative study looking at the association between vigorous exertion and MI. In the case-crossover approach, non-cases are excluded. In this example,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

Figure 1: Illustrative case-crossover study of the association between vigorous exertion and myocardial infarction

Figure 1 caption: The relation between case-crossover and case-control designs is illustrated with timelines for six individuals (A to F) in a case-control study (left). A, B, and C had myocardial infarctions (encircled X). D, E, and F are controls selected at the same times (green circles). The exposure of interest was vigorous exertion (rectangles). A case-crossover design (right) compares the probability of exertion in the hour before MI to the same time the previous day in the same individual. Non-cases (D, E, and F) do not contribute to the case-crossover analysis.

Box 2: Comparison of features of the case-crossover and self-controlled case series designs

	Case-crossover	Self-controlled case series
Analogous to	Case-control study	Cohort study
Developed to study	Multiple causes of an outcome	Multiple effects of an exposure
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

Example applications

The case-crossover design was developed for an interview study of triggers of MI such as exertion, alcohol, anger, and cannabis.[1] It has since been used with databases in many contexts,[8] and here we give four brief examples.

(i) Air pollution and cardiovascular events. Case-crossover studies have found elevated concentrations of pollutants on the day of a stroke or heart attack compared to 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. (ii) 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 to similar a time-of-day earlier in the week.[6,7] (iii) Adverse medication effects. A study of falls among hospital inpatients found that new prescriptions of drugs such as antihypertensives and hypnotics were more common in the three days before the fall than during earlier referent windows.[8] (iv) Triggers of drug overdoses. A study of deaths in England found that decedents were four times more likely to have been recently discharged after inpatient medical treatment compared with the two years before death.[9] Common features of these research questions include the focus on sudden events and the 'triggering' effect of transient exposures.

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Researchers must consider the duration of effect, or 'effect period'[3]: the plausible duration of induction times between the trigger (e.g. physical exertion) and its outcome (e.g. MI). This may not be known precisely and may vary between individuals. When attempting to set referent windows that match effect periods, researchers often need to make informed judgements 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 sufficiently distant 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 five 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 if it was during a COVID-19 lockdown.

Referent windows can be before the event, after the event, or both. In the example in Figure 1, MI is likely to reduce vigorous exercise, at least temporarily, so we would only select historical referent windows. Referent windows after a non-fatal MI would overstate the risks of exercise ('reverse causality bias' in Box 2). If the event does not affect subsequent exposure, such as in studies of air pollution, then referent windows both before and after the event reduces the risk of bias due to time trends in the exposure.

Strengths and limitations

In common with other self-controlled designs, a strength of the case-crossover design is that it eliminates time-invariant confounders, even when unmeasured. This includes personality traits, genetics, country of birth, and many other constant characteristics of patients not recorded in medical charts. For example, in Figure 1, the underlying severity of atherosclerosis is constant over the two days of observation.

Another reason for using the case-crossover design is that suitable controls can be difficult to find in case-control studies. In the 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 (i.e. they produce precise estimates) because they allow sampling of a large proportion of cases. Traditional cohort or case-control studies may include more person-time, but capture fewer events and yield less precise estimates. Power calculations for case-crossover studies must account for the within-individual comparisons and the likelihood of correlated exposures. This may be done through simulation or formulas designed to account for these factors.[11]

Three key limitations of the case-crossover design are time-varying confounding, the limitation to the short-term effects of transient exposures, and selection biases.

Co-occurring acute exposures are especially challenging in 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 relationship between exposures and potential confounders must be interpreted by the researcher based on existing evidence and common sense. Where time-varying confounders are measured, they can be controlled in multivariable analysis as in traditional epidemiological studies.

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Conclusion

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]

Competing interests

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

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Contributorship statement

DL, IP, and MM wrote the article together.

References

1 Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. *American Journal of Epidemiology* 1991;**133**:144–53. doi:10.1093/oxfordjournals.aje.a115853

2 Maclure M, Mittleman and MA. Should We Use a Case-Crossover Design? *Annual Review of 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;: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, *et al.* 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. *British Journal of Clinical Pharmacology* 2010;**69**:535–42. doi:10.1111/j.1365-2125.2010.03613.x

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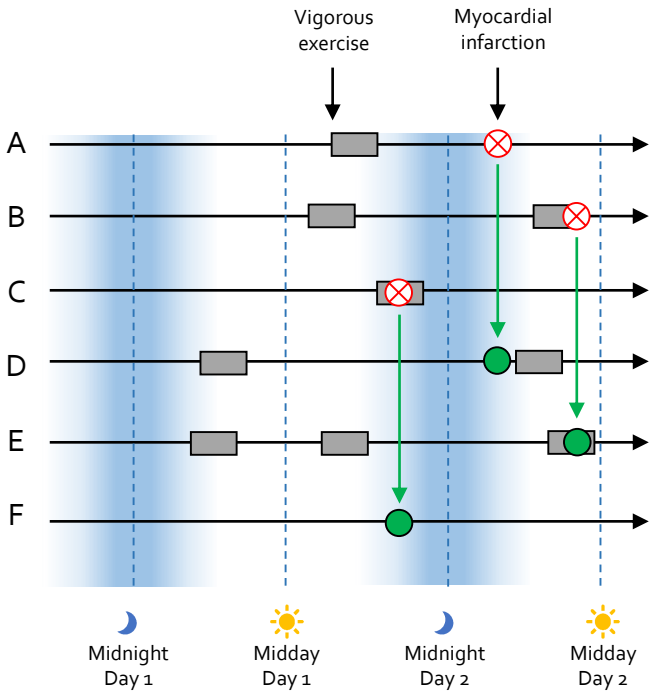
10 Mittleman MA, Mostofsky E. Exchangeability in the case-crossover design. *International Journal of Epidemiology* 2014;**43**:1645–55. doi:10.1093/ije/dyu081

11 Dharmarajan S, Lee J, Izem R. Sample size estimation for case-crossover studies. *Statistics in Medicine* 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;:dyw314. doi:10.1093/ije/dyw314

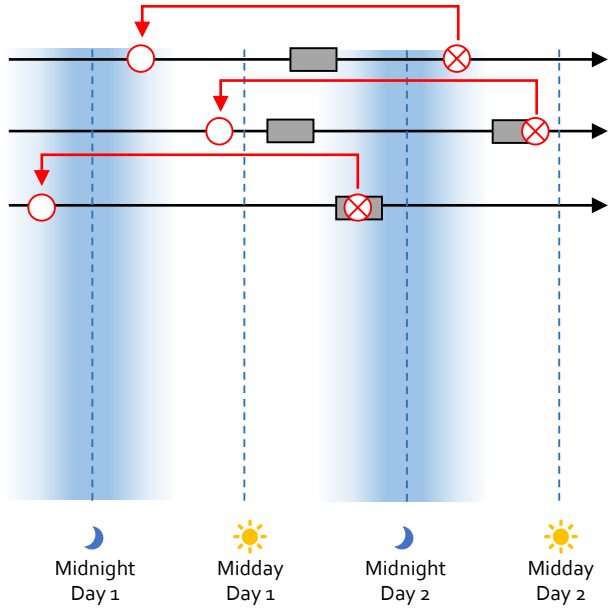
13 Dixon WG, Beukenhorst AL, Yimer BB, *et al.* How the weather affects the pain of citizen scientists using a smartphone app. *npj Digit Med* 2019;**2**:105. doi:10.1038/s41746-019-0180-3

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. *Spatial and Spatio-temporal Epidemiology* 2022;**40**:100458. doi:10.1016/j.sste.2021.100458



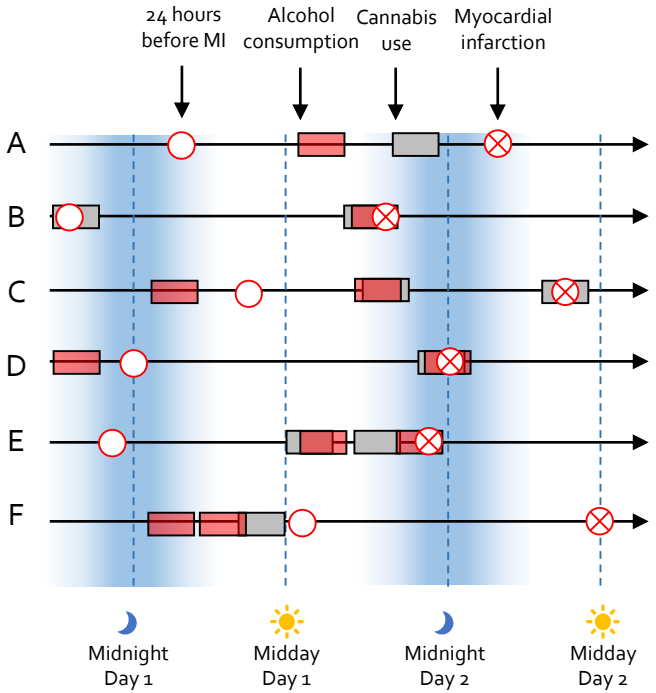
Case-control method

For each case, we select a control: an individual who had not experienced the event at that time, and determine their exposure status.



Case-crossover method

For each case, we look at the exposure status in a control window 24 hours before the event. Participants D, E, and F do not experience the event and are not included


24 hours before MI
Alcohol consumption
Cannabis use
Myocardial infarction
A
B
C
D
E
F
Midnight Day 1
Midday Day 1
Midnight Day 2
Midday Day 2

Methods primers article template

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Sophie Cook

The case-crossover design for studying sudden events: methods primer

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References: ~~12~~14

Box 1: Key messages

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

Conflicts of Interest
We have read and understood BMJ policy on declaration of interests and have no interests to declare.

The case-crossover design for studying sudden events: methods primer

Standfirst

Case-crossover studies measure the triggering effect of transient exposures on sudden events. This article outlines key design features, applications, and limitations.

Introduction

~~The case-crossover method is an epidemiological design for studying potential causes of sudden events,[1] such as whether vigorous exertion or drinking alcohol triggers a myocardial infraction (MI).[2] Case-crossover studies are one of a family of 'self-controlled' study designs,[3] including cross-over experiments and the self-controlled case series[4] (Box 2). Each subject serves as their own control. These designs address the question 'why now?', by studying whether exposure times are associated with outcome times within individuals. In contrast, standard observational studies make comparisons between individuals, such differences in MI rates between alcohol drinkers and non-drinkers (a cohort study) or whether sedentary lifestyles are more common among MI cases than other people who have not had an MI (a case-control study).~~

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

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

Figure 1: Illustrative case-crossover study of the association between vigorous exertion and myocardial infarction

Figure 1 caption: The relation between case-crossover and case-control designs is illustrated with timelines for six individuals (A to F) in a case-control study (left). A, B, and C had myocardial infarctions (encircled X). D, E, and F ~~were~~are controls selected at the same times (~~open~~green circles). The exposure of interest was vigorous exertion (rectangles). A case-crossover design (right) compares the probability of exertion in the hour before MI to the same time the previous day in the same individual. Non-cases (D ~~to~~, E, and F) do not contribute to the case-crossover analysis.

Box 2: Comparison of features of the case-crossover and self-controlled case series designs

	Case-crossover	Self-controlled case series
Analogous to	Case-control study	Cohort study
Developed to study	Multiple causes of an outcome	Multiple effects of an exposure
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 ~~exposure period~~outcome
Potential bias	Exposure trend or persistence	Reverse causality
Comparisons	Ratios of odds of exposure	Ratios ~~or differences~~ in risk of outcomes
Statistical model	Conditional logistic or conditional Poisson regression	Conditional logistic or conditional Poisson ~~conditioned on~~regression, offset by person ~~and~~ time
~~Model assumes~~	~~Outcome fixed, random exposure~~	~~Exposure fixed, random outcome~~

Example applications

The case-crossover design was developed for an interview study of triggers of MI such as exertion, alcohol, anger, and cannabis.~~[1]~~[1] It has since been used with databases in many contexts,[8] and here we give four brief examples.

(i) Air pollution and cardiovascular events. Case-crossover studies have found elevated concentrations of pollutants on the day of a stroke or heart attack compared to 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. (ii) 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 to similar a time-of-day earlier in the week.[6,7] (iii) Adverse medication effects. A study of falls among hospital inpatients found that new prescriptions of various drugs such as antihypertensives and hypnotics were more common in the three days before the fall than during earlier referent windows.[8] (iv) Triggers of drug overdoses. A study of deaths in England found that decedents were four times more likely to have been recently discharged after inpatient medical treatment compared with the two years before death.[9]~~[5] These studies are often statistically powerful because researchers can include large numbers of cases and determine pollution from routine weather records. (ii) 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 to similar a time-of-day earlier in the week.[6,7] (iii) Adverse medication effects. A study of falls among hospital inpatients found that new prescriptions of drugs such as antihypertensives and hypnotics were more common in the three days before the fall than during earlier referent windows.[8] (iv) Triggers of drug overdoses. A study of deaths in England found that decedents were four times more likely to have been recently discharged after inpatient medical treatment compared with the two years before death.[9] Common features of these research questions include the focus on sudden events and the 'triggering' effect of transient exposures.

Selection of control (or 'referent') windows

~~The choice of referent windows is a key design decision. It is dependent on the definition of 'at-risk' time, or the 'study base'.[2] In the study of car crashes in Australia,[7] the 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]: the period after exposure when we hypothesise that the event might be triggered. This may not be known precisely and may vary between individuals. When attempting to set referent windows that match effect periods, researchers often need to make informed judgements and simplifying~~

~~assumptions. Referent windows that are too short will reduce power by excluding relevant events, while windows that are too long will dilute the estimated effect.~~

The duration and timing of referent windows is a key design decision. It is dependent on the definition of 'at-risk' time, or the 'study base'.[2] In a study of car crashes in Australia,[7] the 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]: the plausible duration of induction times between the trigger (e.g. physical exertion) and its outcome (e.g. MI). This may not be known precisely and may vary between individuals. When attempting to set referent windows that match effect periods, researchers often need to make informed judgements 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 sufficiently distant 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]~~[10] In a study of mobile phone use and car crashes, the probability of mobile phone use during a referent window five 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 if it was during a COVID-19 lockdown.

Referent windows can be before the event, after the event, or both. In the example in Figure 1, MI is likely to reduce vigorous exercise, at least temporarily, so we would only select historical referent windows. Referent windows after a non-fatal MI would overstate the risks of exercise ('reverse causality bias' in Box 2). If the event does not affect subsequent exposure, such as in studies of air pollution, then referent windows both before and after the event reduces the risk of bias due to time trends in the exposure.

Strengths and limitations

In common with other self-controlled designs, a strength of the case-crossover design is that it eliminates time-invariant confounders, even when unmeasured. This includes personality traits, genetics, country of birth, and many other constant characteristics of patients not recorded in medical charts. For example, in Figure 1, the underlying severity of atherosclerosis is constant over the two days of observation.

Another reason for using the case-crossover design is ~~if~~that suitable controls ~~are~~can be difficult to find in case-control studies. ~~For example, in~~In the study of hospital discharges and opioid overdoses,~~[9]~~[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 (i.e. they produce precise estimates) because they allow sampling of a large proportion of cases. Traditional cohort or case-control studies may include more person-time, but capture fewer events and yield less precise estimates. Power calculations for case-crossover studies must account for the within-individual comparisons and the likelihood of correlated exposures. This may be done through simulation or formulas designed to account for these factors.[11]

Three key limitations of the case-crossover design are time-varying confounding, the limitation to the short-term effects of transient exposures, and selection biases.

Co-occurring acute exposures are especially challenging in 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 relationship between exposures and potential confounders must be interpreted by the researcher based on 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: Example of time-varying confounding in a case-crossover study of injuries: 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 medication. However, cumulative harms or benefits from long-term medication 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 MI, 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. This also helps understand different forms of bias and contribute to 'triangulation' of causal associations.[~~11~~12]

Case-crossover studies use information from cases only if their exposure status varies over time. These individuals may be unrepresentative of 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 will be the same at the time of the MI and 24 hours earlier. Multiple referent windows may increase the number of cases who have varying exposure status.

Conclusion

The case-crossover design is a widely used tool for studying triggers of sudden health events. ~~As databases following individuals over time increase~~The fundamental points of the design have not changed since it was developed in ~~number~~the 1990s, and ~~richness, many new~~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 ~~this design will be found~~, and retail purchases.[~~12~~][13,14]

Competing interests

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

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 and 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;: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, et al. 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 Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol 2017;:dyw314. doi:10.1093/ije/dyw314~~

~~12 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~~

1 Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. *American Journal of Epidemiology* 1991;**133**:144–53. doi:10.1093/oxfordjournals.aje.a115853

2 Maclure M, Mittleman and MA. Should We Use a Case-Crossover Design? *Annual Review of 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;: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, *et al.* 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. *British Journal of Clinical Pharmacology* 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. *International Journal of Epidemiology* 2014;**43**:1645–55. doi:10.1093/ije/dyu081

11 Dharmarajan S, Lee J, Izem R. Sample size estimation for case-crossover studies. *Statistics in Medicine* 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;: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. *Spatial and Spatio-temporal Epidemiology* 2022;**40**:100458. doi:10.1016/j.sste.2021.100458