

## PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The case-crossover design for studying sudden events: methods primer
<b>AUTHORS</b>	Lewer, Dan; Petersen, Irene; Maclure, Malcolm

### VERSION 1 - REVIEW

<b>REVIEWER</b>	<b>Riley, Richard</b> Keele University, School of Medicine. <b>Competing Interest: None</b>
<b>REVIEW RETURNED</b>	02-Apr-2022

<b>GENERAL COMMENTS</b>	<p>Thanks for the opportunity to read this methods primer for potential publication in BMJ Medicine, which I very much enjoyed. It's very well written and fits the 'primer' format expertly. The examples are excellent, and I learnt something new from reading the paper. I have the following minor comments for improvement.</p> <ol style="list-style-type: none"><li>1) Box 2 should be Box 1?</li><li>2) "In contrast, standard observational studies make comparisons between individuals, such differences in MI rates ..." – I think 'as' is missing, so that it should read '..., such as differences in ...'?</li><li>3) "Figure 1 is an illustrative study looking the association" – should read "Figure 1 is an illustrative study looking AT the association ..."</li><li>4) "The probability of exertion shortly before MI is compared to the probability 24hr before in the same individuals" – I think we need more clarity here. Is this at exactly 24 hours before? For example, if someone played football 25 before, but not 24 before, then does it count? I cannot understand from the text how the 'probability of exertion' is derived and what assumptions this calculation is making. We need more practical details. Also, if an individual died, then how do we know what they were doing 24 hours earlier? I know the window is considered in a later section, but some clarity early on, for this example, would help.</li><li>5) Figure 1 legend – are the 'open circles' the green circles?</li><li>6) "case crossover design compares the probability of exertion in the hour before MI" – why one hour? Why not two hours, or 90 minutes? Can this window impact upon the conclusions?</li><li>7) Box 2 – I would make the left hand column to be bold, to make it clear the items are essentially row headings. I would add a row about whether (at selection) non-cases are included for each method, to make their distinction better.</li><li>8) Box 2 - "Ratios or differences in outcomes" – do the authors mean</li></ol>
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	<p>“Ratios or differences in risk of outcomes”?</p> <p>9) In Box 2 – is the statistical model shown the typical one, or is it always used? E.g. could a Cox model be used instead of Poisson?</p> <p>10) Box 2 – I’m not sure the non-specialist reviewer will understand the “Outcome fixed, random exposure ... Exposure fixed, random outcome” statements. Can this be written more explanatory?</p> <p>11) Can the authors point, at the end of the piece, to further reading on the design and analysis of case-crossover studies, for those readers wanting more? Is there anything on sample size calculations too and dedicated statistical software that can be pointed to? I think this would be helpful.</p> <p>12) Figure 1 – I wonder if having the green circles in both plots is confusing? In the first plot, the green circles relate to different people than the cases, but in the case-crossover they relate to the same person. So, in the second plot, perhaps we should have white open circles instead of green circles?</p> <p>13) Figure 2 does not have any open circles, unlike Figure 1. Also, unlike Figure 1, the time window is not clear on the x axis.</p> <p>In summary, I think it will be an excellent addition to the journal, and I hope the authors can address my minor comments in their revision.</p>
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### VERSION 1 – AUTHOR RESPONSE

Comment #1: Box 2 should be Box 1?

Response: Box 1 is currently the ‘key messages’, on the first page. We were not sure of the correct numbering but we are happy to change it if needed.

Comment #2: “In contrast, standard observational studies make comparisons between individuals, such differences in MI rates ...” – I think ‘as’ is missing, so that it should read ‘..., such as differences in ...’?

Response: Thank you for picking up this typo, which we have corrected.

Comment #3: “Figure 1 is an illustrative study looking the association” – should read “Figure 1 is an illustrative study looking AT the association ...”

Response: Thank you for picking up this typo, which we have corrected.

Comment #4: “The probability of exertion shortly before MI is compared to the probability 24hr before in the same individuals” – I think we need more clarity here. Is this at exactly 24 hours before? For example, if someone played football 25 before, but not 24 before, then does it count? I cannot understand from the text how the ‘probability of exertion’ is derived and what assumptions this calculation is making. We need more practical details. Also, if an individual died, then how do we know what they were doing 24 hours earlier? I know the window is considered in a later section, but some clarity early on, for this example, would help.

Response: In the case-crossover design, we compare the probability of exposure shortly before the event with the probability in a referent/control window. In this example, the period-of-interest is set at 1 hour before the event. If someone died at 6pm on Friday, we would look at whether they exercised between 5pm and 6pm on Friday, and compare this to 5pm-6pm on Thursday.

We have edited the text and added this example, which we hopes improves the clarity, but please let us know if it can be improved further.

We also agree that the history of physical exercise may be difficult to ascertain, particularly if the individual died. In the example of MI and physical exertion, the exposure data is likely to be based on interviews and for cases who died the interview would be with a family member or other informant. We have also noted this in our example. Many case-crossover studies now use databases with precise exposure timings, such as phone billing records in studies of mobile phone use and car crashes.

Comment #5: Figure 1 legend – are the ‘open circles’ the green circles?

Response: Yes, we have edited the figure caption to clarify this.

Comment #6: “case crossover design compares the probability of exertion in the hour before MI” – why one hour? Why not two hours, or 90 minutes? Can this window impact upon the conclusions?

Response: One hour is an example, and researchers need to set this duration based on plausible durations of induction times between the trigger (exertion) and its outcome (MI). It could equally be two hours, or 90 minutes. This decision can impact on results. In general, windows that are too long will bias the association towards the null while windows that are too short will reduce power. We have edited the section “selection of control (or ‘referent’) windows” to try and ensure that the importance of this decision is clear.

Comment #7: Box 2 – I would make the left hand column to be bold, to make it clear the items are essentially row headings. I would add a row about whether (at selection) non-cases are included for each method, to make their distinction better.

Response: We agree that bolding the left hand column helps and have made this change. We did not add the extra row showing whether non-cases are included, as non-cases would be excluded for both designs in this table.

Comment #8: Box 2 - “Ratios or differences in outcomes” – do the authors mean “Ratios or differences in risk of outcomes”?

Response: Thank you for picking up this typo, which we have corrected.

Comment #9: In Box 2 – is the statistical model shown the typical one, or is it always used? E.g. could a Cox model be used instead of Poisson?

Response: Both case-crossover and self-controlled case series data can be analysed using conditional logistic or conditional Poisson regression. Observation windows in self-controlled case series vary in duration and therefore the exposures are offset by the logged duration of these windows. We have edited Box 2 to show that either model can be used. We have never seen a Cox model used for the self-controlled case series. We believe this is because the method assumes the outcome has a constant probability of occurring over time (i.e. it is a Poisson variable), while a shared frailty Cox model would allow the hazard to vary over time but assume proportionality between exposure windows within individuals (not a meaningful assumption!). We felt this discussion is too detailed for our primer and have limited our edits to the ‘statistical model’ row of Box 2.

Comment #10: Box 2 – I’m not sure the non-specialist reviewer will understand the “Outcome fixed, random exposure ... Exposure fixed, random outcome” statements. Can this be written more explanatory?

Response: We agree that this wording may be confusing to some readers. As it is not crucial to the article, we decided to delete this row.

Comment #11: Can the authors point, at the end of the piece, to further reading on the design and analysis of case-crossover studies, for those readers wanting more? Is there anything on sample size calculations too and dedicated statistical software that can be pointed to? I think this would be helpful.

Response: We have added a sentence pointing readers to two key texts on the case crossover design.

In terms of sample size / power, case-crossover studies are often statistically powerful because they allow researchers to include more events than traditional case-control or cohort studies. We have added this to the section on the strengths of the design, and also included a summary of considerations when doing power calculations.

We have not added any discussion of software, because specialised software is typically not needed. The most specialist aspect of the analysis is conditional regression, which is commonly available in packages such as R and Stata.

Comment #12: Figure 1 – I wonder if having the green circles in both plots is confusing? In the first plot, the green circles relate to different people than the cases, but in the case-crossover they relate to the same person. So, in the second plot, perhaps we should have white open circles instead of green circles?

Response: We agree, and have made this edit.

Comment #13: Figure 2 does not have any open circles, unlike Figure 1. Also, unlike Figure 1, the time window is not clear on the x axis.

Response: We agree and have made these changes to the figure.