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The Self-Controlled Case Series Design as a Viable Alternative to Studying Clinically-Relevant Drug Interactions

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To the Editor,

We congratulate Bykov et al¹ on their use of the case-crossover design to screen electronic healthcare data for clinically important drug-drug interactions (DDIs). We believe though that their discussion may overstate the benefits of the case-crossover design over the self-controlled case series (SCCS) design for DDI screening.² Two case-only designs, SCCS and case-crossover, have been suggested as viable approaches for DDI screening.^{1,2} Both designs are self-controlled and therefore eliminate confounding by stable patient factors (See Table 1 for a simplified comparison of the two designs). The SCCS is analogous to a cohort study, and its standard implementation is bi-directional, resulting in the assumption that exposure and censoring are independent of the outcome. The case-crossover design is analogous to a case-control study, and its standard implementation is uni-directional, resulting in the assumption that there are no secular or within-person trends in exposure. These differences are mitigated in that 1) either design can be implemented uni- and/or bi-directionally, and 2) approaches exist to examine the impact of violations of these assumptions on study results.^{3,4} The major inherent difference is that the case-crossover design requires identification of specific control periods (analogous to selection of control subjects in a case-control study), and therefore may be sensitive to this selection,⁴ although the impact of specific choices can be examined. In contrast, the SCCS design, like a cohort study, requires no such sampling. Therefore, we believe that the choice of case-crossover vs. SCCS is not as important as that of uni- vs. bi-directionality (although the impact of

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None related to this work.

directionality depends on the design choice⁴), and that trade-offs in potential biases resulting from the choice of directionality are likely to be context-specific.

Additionally, despite the potential limitations of using a negative control object drug that are described by Bykov et al,¹ we wish to note that a potentially important advantage is that such a control population may be more similar to that receiving the study object drug than the general population. This would reduce the potential that the association with the precipitant drug measured in the control population is not generalizable to those receiving the object drug, thus reducing the potential for a biased association measure for the potential DDI.

Despite these minor differences, we greatly appreciate the significant advancements provided by the work of Bykov et al and look forward to future developments in using healthcare data to screen for clinically important DDIs.⁵

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Table 1.

Comparison of self-controlled case series and case-crossover designs.

Self-controlled case series		Case-crossover
Similarities	Case-only	
	<ul style="list-style-type: none"> Only individuals who experienced one or more outcomes are included 	
	Self-controlled	
Differences	<ul style="list-style-type: none"> Each individual serves as his/her own control Controls for fixed covariates by design 	
	Design	<ul style="list-style-type: none"> Follows individuals longitudinally over observation time Compares outcome rates in exposed vs. unexposed time
		<ul style="list-style-type: none"> Follows individuals backward through time beginning with their outcome Compares exposure frequencies in hazard window and referent window (i.e. control period) retrospectively Requires sampling of control periods
	Example	<p>Ratio of the incidence rate of hypoglycemia among glimepiride+acetaminophen-exposed time to glimepiride-exposed (i.e., acetaminophen-unexposed) time</p> <p>Odds ratio comparing the ratio of individuals on both glimepiride+acetaminophen in the hazard window and on glimepiride alone (i.e. acetaminophen unexposed) in the referent window to the number of individuals on glimepiride alone in the hazard window but on both glimepiride +acetaminophen in the referent window</p>
	Assumption	<ul style="list-style-type: none"> Events are rare or arise in non-homogenous Poisson process The occurrence of an outcome does not influence the length of the observation period The occurrence of an outcome does not influence subsequent exposures Exposures do not influence outcome ascertainment
		<ul style="list-style-type: none"> Exposure is transient and exposure prevalence is stable over time (i.e. no secular or within-person trends in exposure) The time between exposure and event onset (length of the exposure effect) is specified by the length of the hazard and referent windows There is no or little carryover effect
	Standard design	<p><i>Bi-directional</i>, including unexposed time before and after exposure</p> <p><i>Uni-directional</i>, examining observation time prior to, but not after, outcome occurrence</p>
		<ul style="list-style-type: none"> Susceptible to reverse causality bias Susceptible to exposure-trend bias because the referent window always precedes the hazard window
		<ul style="list-style-type: none"> Example: the occurrence of an outcome serves as a contraindication to exposure and results in its discontinuation Example: Utilization of a newly marketed drug increases substantially over time. By nature of their temporality, exposure odds may be lower in referent vs. hazard windows as a result of this trend.