Use of self-controlled designs in pharmacoepidemiology

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Self-controlled observational study designs, such as the case–crossover design and the self-controlled case series, are reviewed, and their respective rationale, strengths and limitations are compared. Although no single design is generally superior to the others, they share the trait of being robust towards confounders that are stable over time. The self-controlled designs can be particularly useful when using secondary healthcare data for pharmacoepidemiological research and might be useful in screening for adverse drug effects. The main limitations of self-controlled designs are that they are amenable only to transient effects; some may be inefficient with long-term exposure; and they may be sensitive towards trends in exposure.

Keywords: adverse drug effects, design, epidemiology, methods.

Introduction

The clinical trial is widely considered the pinnacle of design for studying intentional drug effects [1]. However, there are situations where the trial design cannot be applied, typically because of ethical issues or resource constraints. For example, it would be considered unethical to conduct a placebo-controlled trial with the sole purpose of demonstrating safety. Also, it has been argued that most trials are conducted in highly artificial settings and that they therefore often lack external validity. Observational or nonrandomized studies may overcome some of these limitations. Most observational designs compare outcomes in subjects who take the drug in question with those who do not. The obvious limitation is that drug users and nonusers are not readily comparable, leading to biased results. Although the armamentarium for confounder adjustment is extensive, the possibility of residual confounding is always a concern.

Since the early 1990s, several designs have been proposed, where the comparison is not between drug users and nonusers but between time spent as a drug user and time spent as a nonuser, within the same subjects. Because the comparison is between different experiences in the same subjects, potential confounders that are stable over time, such as genetic disposition, cancel out. This even extends to confounders that cannot be measured or are unknown. These designs pose the question 'why now?' instead of 'why me?' that is posed in a design based on other control subjects [2].

In this review, we describe the properties of the case–crossover design and variants, case–time–control design, symmetry design, and self-controlled case series and discuss their rationale and respective strengths and limitations.

Case–crossover design

Maclure proposed the case–crossover design in 1991 [3]. The design was illustrated by the research question of whether there is an acutely elevated risk of myocardial infarction (MI) in connection with sexual activity. A conventional cohort or case–control approach to this question would entail a Gordian knot of confounder problems. Atherosclerosis, a history of atherosclerotic conditions, autonomic neuropathy, mental depression, poor physical shape, diabetes and obesity are all risk factors for MI and are all inversely related to sexual activity. A conventional epidemiological study of the association between sexual activity and MI should therefore account fully for all of these factors. Some of them are difficult to measure or require more- or less-invasive measurements on cases and controls. In addition, there could be problems with selective recruitment of cases and controls who are willing to answer questions about their sexual behaviour.

In the application of the case–crossover design, only cases are included. They are asked two questions: Were you sexually active when you had your MI and what is your usual frequency of sexual activity? From these questions, it can be determined whether there was a relative excess of subjects who were sexually active at the time when had their MI, given their usual frequency of sexual activity.

As case–crossover studies are usually performed today, the usual frequency approach originally described by Maclure is rarely used. Instead, a set of reference dates or periods in the past is used, and exposure is assessed at these reference dates. This is best understood as a match-pair analysis with a particularly tight matching. In a simple example of the case–crossover design, a number of case subjects are asked about their drug exposure on the date of disease and a reference date in the past. We then count the number of subjects who report being exposed on the case date, but not on the reference date, as well as the number of subjects who report the opposite pattern. The odds ratio (OR) can then be calculated simply as the ratio between the number of subjects with the first pattern and the number with the second. Subjects whose exposure is similar on the case and reference dates do not contribute to the analysis and are taken out. The comparison is performed within each individual; therefore, all potentially confounding characteristics that are stable over the time frame are effectively controlled. A hypothetical application of the case–crossover design, using three controls samplings, is illustrated in Fig. 1.

There has been extensive methodological work on the properties of the design. The original simple version can be modified to accommodate other scenarios; multiple control samplings can be used to improve statistical precision, exposure periods rather than exposure dates can be used, timing of drug intake can be modified to accommodate assumptions about induction time and effect periods, and known time-variant confounders can be adjusted by conventional techniques in match-pair design, for example, by conditional logistic regression. The case–crossover design was applied in actual studies of sexual activity, anger or physical exertion as triggers of MI [4–6].

Variants of the case–crossover design

Bias generated by trend in exposure

One of the limitations of the case–crossover design is that it is sensitive towards trends in exposure. If there is a dramatic overall increase in the use of a particular drug, this alone will render a subject more likely to use the drug at the time of the end-point than at an earlier reference point. This will elevate the OR and may create a spurious, non-causal association. It is particularly a problem with use of reference points long before the end-point. Exposure trends can be strong, for example, for drugs that are relatively new on the market.

Case–time–control

Suissa suggested that the trend problem could be removed by measuring the trend effect in a control group without the end-point and using that as a reference for the OR observed in the case–crossover analysis, an approach that was termed the case–time–control design [7]. A nondiseased control group should be selected by standard techniques,
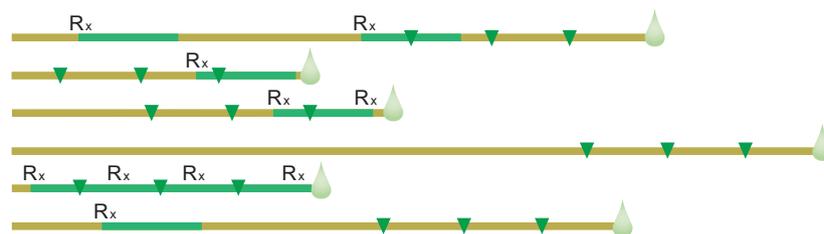
Fig. 1 *Schematic presentation of a case–crossover analysis. Each horizontal line represents a timeline illustrating the experience of one individual. The case-defining event is a bleeding episode, illustrated by a stylized droplet, and the prescription is a nonsteroidal anti-inflammatory drug. For each individual, three reference points in time are selected (illustrated by dark triangles). Three of the subjects are exposed at the time of their bleeding, illustrated by the black bar. Between zero and three of the reference points are exposed. A Mantel–Haenszel estimate of the association treating each individual as a separate stratum yields an OR of 4. The fourth and sixth individuals are unexposed on all occasions, and the fifth is exposed on all occasions. Neither of these individuals contribute to the analysis.*

such as risk-set sampling, and the contrast between current exposure on the index date and past exposure can be determined in exactly the same fashion as for the cases. Any contrast between current and past exposure for the controls can only be explained by nonspecific trend effects. The observed OR for cases should be divided by the observed OR in controls to provide a trend-adjusted estimate.

The case–time–control approach was illustrated by an analysis of the link between high use of long-acting β-agonists and asthma deaths. An OR of 3.2 was found in a conventional case–crossover analysis by use of a reference point 1 year prior to the asthma deaths. However, the use of long-acting β-agonists had increased dramatically during the study period. A control group, not experiencing asthma mortality, showed a similar OR, when comparing exposure on a random index date with exposure 1 year prior to this index date. The resulting OR, adjusted for the trend effect, was 1.2 (3.2/2.6) with a confidence interval of 0.5–3.0 [7].

It should be noted that trend should not be understood too narrowly as a trend by calendar time. The case–time–control design may also adjust for trend by age, which may occur completely independent of a temporal trend. In a case–crossover study of the link between use of an ephedrine–caffeine-based dieting product and adverse cardiovascular outcomes, Hallas et al. [8] found a strong age dependency in utilization of the products, that is, elderly subjects were considerably less likely to be users than younger subjects. Because a reference point 1 year in the past was used (because of a strong seasonality in use), this would have created a spurious protective effect. Subjects would have been less likely to use the products at their end-point than at their reference time, simply because they had aged by 1 year. However, this trend effect by age also applied to the nondiseased controls and was thus eliminated using the case–time–control approach. After adjustment for trend by age, a null effect was observed.

Finally, it can be argued that the case–time–control design also corrects the bias conferred by including subgroups of indefinite drug users. The case–crossover design is only amenable to intermittent exposure, and applying it to indefinite use should be considered a violation of its conditions. If we consider a hypothetical case–crossover study of

statin-induced retinal detachment (an assumed null association), we would enquire about current and past use of statins in a group of patients with newly diagnosed retinal detachment. Statins are most often prescribed as secondary prevention after an ischaemic event, and it is recommended that such patients take statins for the rest of their lives. Therefore, these patients would rarely report that they were statin nonusers at the time of their retinal detachment, but were users at a prior point in time. Exceptions may occur, but they would be driven by poor compliance, by adverse experience with the drug or by terminal illness. The opposite pattern, being users at the index time and nonusers in the past would occur occasionally, if the patient happens to have started the drug between the reference and case dates, and the resultant OR would be high. If a drug may be used both indefinitely and intermittently (as most drugs may, even antibiotics), the subgroup of indefinite users would bias the OR of a conventional case–crossover analysis upward, with the degree of bias depending on what proportion of users were indefinite. This can be viewed as a third type of trend effect that may occur independently of a trend by calendar time or age. Provided that the control group would have a similar proportion of indefinite users, this trend bias would also be adjusted using the case–time–control design.

The advantages of the case–time–control approach do not come without a cost. Obviously, the use of a control group introduces more variation in the estimates. This would hardly be a problem in a registry-based study, where the solution would be to recruit more controls, but it could be problematic in field studies. Furthermore, Greenland has pointed out that the trend adjustment might also introduce bias that was not present in the case–crossover approach if the trends were different in cases and controls. Such a pattern might be seen if the indication for treatment with the drug or the threshold for prescribing the drug changed over time [9].

Using future cases as controls

An interesting new variant of the case–crossover paradigm is the case–case-time design [10]. The approach is similar to the case–time–control design, except that the controls are not sampled from the source population, but from subjects that become cases in the future. It is argued that it could correct some variants of reverse causation

(protopathic) bias, which would neither be handled by the case–crossover or the case–time–control design. Or, it could be viewed as solving the problem of differential trends between cases and controls that we have in the case–time–control approach. In an example analysing the link between vitamin intake and stroke [10], an assumed null association, it was observed that cases had an increasing use of vitamins in the year prior to the event. A conventional case–crossover analysis yielded an OR of 1.5, whilst a case–case-time analysis gave an OR of 1.1.

The case–case-time design may be criticized for violating the principle of not conditioning on future events. Subjects cannot become future cases, unless they survive until they have a case-defining event, which may introduce selection bias. Also, it can be argued that if the purpose of using the case–case-time control design is to eliminate reverse causation bias, future cases should not be too distant in time. Although the case–case-time design is an interesting new addition to the armamentarium, further studies are needed to clarify its properties and its relation to other self-controlled designs.
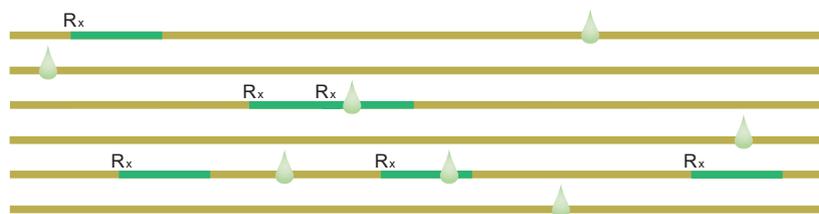
Self-controlled case series

The self-controlled case series, proposed by Farrington [11], can best be understood as a cohort logic applied to a case-only design. Again, only cases are included, but in contrast to the case–crossover design, the entire exposure history inside a given time window is retrieved, not just exposure attributes of selected dates or periods. Other important features of standard self-controlled case series are that the exposure history occurring after the case-defining event is included in the estimates and (by consequence) that more than one

occurrence of the end-point is allowed. By including follow-up after the outcome, the self-controlled case series can be viewed as a bidirectional design [12]. As in a conventional cohort study, all follow-up inside the time window is stratified according to main exposure and other variables that would be included as potential effect modifiers or confounders. The incidence rate ratio associating the exposure and the outcome can then be estimated by a Poisson regression model conditional on the individual person. The analysis is confined to subjects who become cases; therefore, risk factors that are stable, such as a genetic susceptibility towards the outcome, do not affect the estimate. The application of a self-controlled case series is illustrated in Fig. 2.

The self-controlled case series approach was first applied in studies of vaccine safety. It was confirmed that the Urabe mumps strain was strongly associated with aseptic meningitis in the 15–25 days postvaccination [13], and an association was established between mumps–measles–rubella vaccine and idiopathic thrombocytopenic purpura and febrile convulsion [11]. In an elaborate tutorial, Whitaker *et al.* has provided a worked example using actual individual-level data from the vaccine study. Raw data and software that are available online are also referenced [13].

The fact that self-controlled case series make use of exposure history after the occurrence of a case-defining event has several advantages. First, it is less sensitive to exposure trends than the case–crossover design. If we study a drug that is increasingly used by the source population, the case–crossover design estimates would be biased towards higher values. However, as periods both before and after the outcome are used as references in the self-controlled case series, these exposure

Fig. 2 *Schematic representation of the self-controlled case series, using the same symbols as in the illustration of the case–crossover design. A cohort is followed within a predefined time window. All subjects have at least one case-defining event, and follow-up continues after each event. Follow-up is characterized by its exposure and confounder attributes, and all follow-up is analysed according to conventional methods for cohort studies, comparing event rates in exposed and nonexposed periods [13].*

trends tend to cancel out [12]. Secondly, the self-controlled case series does not require that the exposure is intermittent, as in the case–crossover design and variants. By including exposure history after the occurrence of an outcome, it is possible to study the effect of indefinite drug exposure by simply following the standard template for self-controlled case series. An important caveat, however, is that the occurrence of the end-point should not affect the likelihood of being prescribed the drug in question. This could be a particular problem when studying associations that are already known or suspected; clinicians would often consider the occurrence of the outcome as a relative contraindication for prescribing the drug afterwards, which would bias the self-controlled case series estimate towards higher values. Under some conditions, however, the occurrence of event-dependent exposure can be handled by minor modifications of the standard technique [13].

Symmetry design

The symmetry design was proposed by Hallas in 1996 as a screening tool for adverse drug reactions [14]. The underlying premise is that if treatment with drug A causes a disease, that is, a side effect, treated with drug B, there should be a relative excess of subjects who start treatment with drug B, whilst being treated with A. However, a simple comparison of users and nonusers of drug A with respect to the initiation of drug B would most likely be severely confounded by clustering of disease, frequency of physician contact and overzealous prescribers.

The design was first applied to study the association between β-blockers and depression. New use of antidepressants was used as a surrogate for depression. All persons initiating both β-blockers and antidepressants during a predefined period were identified. If β-blockers do not cause depression, this particular population should show equal numbers of persons starting either drug first. None of the potential confounders mentioned above would generate a nonsymmetrical distribution of orders. However, if β-blockers caused depression, it would generate a relative excess of persons starting β-blockers first, that is, a nonsymmetrical distribution of prescription orders in this selected group. It can be shown that the ratio of sequence orders is an estimate of the incidence rate ratio associating β-blocker and antidepressant therapy and that confounders that are stable over time are effectively controlled [14]. The application of the symmetry analysis is illustrated in Fig. 3.

It can be argued that the symmetry design is not really self-controlled, because it does not use the experience of the cases themselves as a reference, but the experience of other cases. Unlike the crossover design and its variants, there is no requirement that subjects cross back and forth between exposed and unexposed periods. Another important advantage is that the symmetry analysis is easy to process and may be a useful screening tool. The example above is based on two pharmacological treatments, but the principle may also be applied to diseases or combinations of diseases and treatments [15, 16].

Amongst the limitations are a sensitivity towards trends in both the exposure drug and the outcome drug, sensitivity to reverse causation, and that for drugs that have mutual indications, first-line drugs would systematically precede second-line drugs. There are also other limitations [14], particularly if wide time windows are allowed. The bias conferred by trends in exposure or outcome can be adjusted by a statistical model based on the source population's trends in drug use or occurrence of end-point [14, 17].
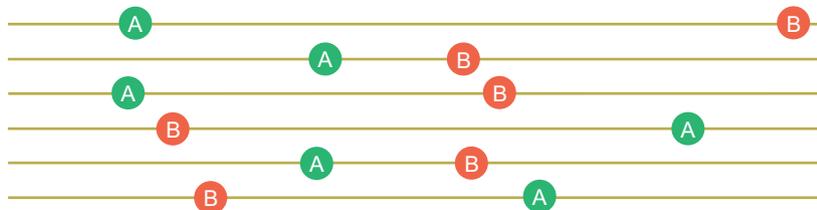
Fig. 3 *Schematic presentation of the symmetry analysis. Drug A represents the exposure, and drug B is a proxy for an adverse event. All subjects who start drugs A and B within a predefined time window are identified. Under the null assumption, there should be an equal number of persons starting either drug first. In this example, four persons have A prescribed before B, whilst the opposite order is followed for two persons. The crude sequence ratio is thus 4/2 = 2.*

Strengths

The characteristics, advantages and limitation of each of the designs is summarized in Table 1. The all-dominant advantage of using self-controlled designs is that they effectively control for confounders that are stable over time. This even extends to confounders that are unmeasured or unknown. As such, the utility of the self-controlled designs in pharmacoepidemiology is obvious; we are often in a situation with potentially strong unmeasured confounders, and drug exposure is often intermittent. A common scenario is a large database of secondary health data based on records of prescriptions and other healthcare activities, but without data on potentially confounding lifestyle factors.

As an example, the study on the ephedrine–caffeine combination and cardiovascular outcomes was based on the Danish National Prescription Registry, which was linked to the Danish National Patient Registry [8]. Ephedrine–caffeine were prescribed as a supportive measure in attempting weight loss. An obvious confounder was overweight, which was linked to the exposure and was a risk factor for the outcome. However, the subjects' body mass index was not recorded, nor were other lifestyle habits, such as smoking. In using a crossover technique, it was assumed that these factors were constant over the time window used in the study (1 year). There is good evidence that both body mass index and smoking can be viewed as stable [18, 19], but even if these factors did change over the course of the time window, their detrimental effect on the subjects' health would have changed very little.

Another strength of self-controlled designs is that they may overcome some of the difficulties and pitfalls of control selection. If the study on sexual activity and risk of MI had been conducted as a conventional case–control study, it is likely that there would have been differences in the willingness of cases and controls to respond when queried about their recent sexual experience, or in their ability to recall previous sexual activity. In the case–crossover design, cases and controls are the same people, and recruitment, recall and willingness to respond are therefore similar in the two groups.

Finally, it has been argued that the number of subjects required for a self-controlled study tends to be smaller than for a conventional approach [13]. This is hardly important for a registry-based study, but could be an important advantage in a field study.

Limitations and pitfalls

The major limitation of the self-controlled designs is that the effect of exposure has to be transient. For research questions in which the key is cumulative rather than current exposure, conventional case–control or cohort approaches are better suited. For example, it would make little sense to use a crossover design in the study of drug-induced cancer.

Another limitation is that the case–crossover design and its variants become statistically inefficient, if crossover is rare, that is, if exposure tends to be chronic as opposed to transient. This is not a bias, that is, it does not by itself systematically affect the OR estimates, but confidence intervals become wide. If we consider the most extreme example; male sex as a risk factor for a disease. In a crossover analysis, those who have the same sex at the index and reference date are taken out of the analysis, and only subjects who change sex during the time window contribute to the estimate. Not only does a crossover approach dramatically reduce the number of subjects that contribute to the analysis, it also subtly, yet profoundly redefines the exposure from 'being male' to 'having changed your sex to male' [12].

Also, the exposure should not be indefinite in a crossover design. This is a different problem than long-term use, which renders the crossover designs inefficient. Indefinite use is a true source of bias, which results in higher OR estimates, at least for the case–crossover design. Most drugs can be used both intermittently and indefinitely; therefore, nearly all case–crossover studies of drugs have some potential for this bias. If this is thought to be a potentially serious problem in a given analysis, one solution could be to use a case–time–control approach.

In general, the self-controlled designs do not correct for confounding by indication. None of the self-controlled designs is inherently robust towards confounders that vary over time. Most indications do vary over time; antihypertensives are prescribed after the patient has developed hypertension, and antibiotics are prescribed when the patient is infected. Thus, if the indication is a confounder for the association in question, it is not inherently controlled for by these designs.

Finally, it has been shown that both the case–crossover and the case–time–control design are

Table 1 *Overview of self-controlled designs available in pharmacoepidemiology*

Design	Description	Strengths[a]	Limitations[b]
Case–crossover (Maclure 1991, [3])	Only cases are included. Their exposure at the index date is compared with exposure in their past. Analysed by match-pair technique.	Small sample required. Control selection less problematic than with conventional approach.	Sensitive to trends in exposure. Inefficient if crossover is rare. Biased if there are indefinite users.
Case–time–control (Suissa 1995, [7])	Same as for case–crossover design. Additionally, a nondiseased control group is used to measure nonspecific trends in exposure that would otherwise bias the case–crossover estimate. The OR for the control group is used as a reference for the case group.	Adjusts for different trends in exposure; temporal trends, trends by age and for bias caused by indefinite drug use.	Complicated processing. May introduce bias if trends are different for cases and controls, as may be seen with changing indications or thresholds for prescribing.
Case–case–time (Wang 2011, [10])	Same as case–time–control design, except that the controls are not sampled from the source population but from persons who become cases in the future.	Same as case–time–control. Adjusts for reverse causation bias.	Limited experience.
Self-controlled case series (Farrington 1995, [11])	Only cases are included. Their entire exposure history inside a predefined time window is included. Standard self-controlled case series allow multiple occurrences of the end-point and also incorporate follow-up after an end-point has occurred. Analysed with a conditional likelihood technique. A number of variants exist.	Small sample required. May be used with indefinite drug use. Adjusts for trends in exposure.	Complicated data processing and analysis.
Symmetry design (Hallas 1996, [14])	All subjects who start drugs A and B within a predefined time window are identified. Under the null hypothesis, there should be equal numbers of persons starting either drug first. If use of A causes use of B, there will be an excess of the A→B sequence over the B→A sequence. The ratio between sequence orders is an estimate of the incidence rate ratio associating drug A with drug B.	Simple processing. May be used with indefinite exposure. May be useful for screening.	Sensitive to trends in use for either drug. Sensitive to reverse causation.

[a]All designs have the strength of adjusting for confounders that are stable over time.
[b]All designs have the limitation of being more sensitive to misclassification than standard approaches.

more vulnerable to misclassification bias than the conventional case–control approach [9]. If a subject is a chronic user of the drug but his/her exposure is misclassified on one occasion – either the case-defining date or one of the reference dates – the exposure pattern will appear to be discordant. If we are in a situation where genuine crossover is rare, even a small degree of misclassification may easily become the main source of apparently discordant exposure. A conventional approach, such as a case–control or a cohort study, is less affected by small degrees of misclassification.

The future

The advantage of self-controlled designs, namely, that confounders that are stable over time are effectively controlled, has led some researchers to suggest that they can be used to screen large databases for evidence of unknown adverse drug reactions. Using conventional approaches such as the case–control or cohort design for screening purposes is problematic. The set of confounders that are relevant for a given drug–disease association are specific for that association, and it is difficult to develop an approach for confounder selection that has general applicability in case–control or cohort screening.

Owing to its simplicity in processing, the symmetry approach has been used to screen broadly, for example, for drug-related dyspepsia [20, 21] and unknown adverse effects of anti-epileptic drugs [17]. It is, however, our experience that even though time-independent confounders are eliminated, there is still a large output of noncausal association, explained by, for example, time-dependent confounders, by reverse causation or by clinical practices in the management of diseases.

The Observational Medical Outcomes Partnership (OMOP) [22] and the Sentinel Project in the USA [23] are two large database networks that have been developed with the primary purpose of safety surveillance for drugs. Both systems have case–crossover and self-controlled case series as part of their screening armamentarium. There is currently a lot of ongoing work on establishing the sensitivity and specificity of these tools in capturing true adverse drug reactions [24].

Conflict of interest statement

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