Use of the self-controlled case series method beyond vaccine safety: a review and discussion

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Abstract

The self-controlled case series (SCCS) method is an epidemiological study design that was developed during the mid 1990s for use in vaccine safety studies. It is a case-only design suitable for testing temporal hypotheses, with the advantage of eliminating time-invariant confounding. Use of SCCS for vaccine safety studies is now well established. The aim of this paper is to review and discuss use of SCCS beyond vaccine safety, in other areas of pharmacoepidemiology and wider use in epidemiology.

We selected publications from Scopus and ISI web of knowledge in a systematic way. Data were extracted using a standardized form. The review includes 79 articles. Results are presented and discussed on the exposures and outcomes identified, data description and accuracy, software, observation periods, risk periods, confounders, methodological assumptions and sensitivity analyses.

Where more than one study design was used within an article, one or two results were extracted for direct comparison with SCCS results, selected for best comparability in design choices. Pairs of results are compared and discussed.

Our review largely found appropriate and growing use of SCCS methods beyond vaccine safety.

Introduction

The self-controlled case series (SCCS) method is an observational study design that may be used to study the association between time varying exposures and an outcome with a defined onset using information only on cases, individuals who have experienced the outcome of interest at least once [1, 2]. It may be used to study a hypothesis about when events arise in relation to exposures, rather than about who those events arise in, as in a cohort or case-control design. A major advantage is that SCCS automatically controls for all measured and unmeasured time-invariant confounding variables that act multiplicatively to modify the association between exposure and outcome event. However, use of the SCCS method is limited by some strong assumptions. Namely, that occurrence of the outcome event does not affect subsequent exposures; that occurrence of the outcome event does not affect an individual's time observed; and that events must be independent and either recurrent or rare and unique.

The self-controlled case series method has now been in use for over 20 years [2]. Since its publication in 1995, several papers that popularise and extend the method have been published including [1, 3-14]. It was originally developed to investigate potential associations between vaccines and adverse outcomes. Its use for this original purpose is now commonplace; in 2011, we published a review of 40 vaccine safety studies that used SCCS and provided recommendations for best practice [3]. In general, we found that the method was being used appropriately. Moreover, because vaccines are not generally expected to perturb usual routines, have clear dates of vaccination followed by a limited period in which the immune response occurs, vaccines often make particularly suitable exposures for use in SCCS studies. Therefore, in this paper we examine SCCS studies beyond vaccine safety, in applications that may be more challenging in practice. This includes applications to the safety of prescription medications, outcome events post infection and surgery, during pregnancy or coinciding with environmental exposures.

Aside from our review of vaccine safety SCCS studies two other reviews on the use of case-only methods in pharmacoepidemiology have been published [15, 16]. These systematic reviews include in addition applications of the case-crossover method, an alternative case-only design that shares with SCCS the advantage of automatic control of time-invariant confounders. Both reviews considered whether use of a case-only method was appropriate for the particular application; reporting on whether events had an abrupt onset, whether events were rare or recurrent and whether exposure was intermittent, and for SCCS whether events were independent, whether events affected subsequent exposures and whether the event affects short-term mortality probability. It should be noted that exposures need not be intermittent for the SCCS design; indefinite or long-term exposures can be handled using SCCS under certain circumstances. Also, while outcomes with an abrupt onset are more ideal, events with an insidious onset have been studied using SCCS, using a defined marker day for onset (e.g. age at diagnosis) with longer or indefinite windows of exposure to allow for the uncertainty in timing. Both reviews considered the quality of reporting. Nordmann et al [16] additionally reported in more detail on the characteristics of data sources, risk and reference periods. These reviews are, however, limited to applications in pharmacoepidemiology (including vaccine exposures), thus this is the first review to include SCCS applications beyond pharmacoepidemiology. The earlier reviews [3, 16] showed growing use of the SCCS design. However, Gault et al [15] searched for articles that met validity assumptions for case only designs and showed that opportunities for using a case-only design in pharmacoepidemiology are often missed.

A further growing use of SCCS in pharmacoepidemiology is in risk identification studies [17]. Researchers apply a number of common, standardized models (often including an SCCS model) to a large number of prescription medications and potential risks within large databases. Interest does not lie primarily in quantifying risks, rather in identifying them. While we acknowledge this as a growing area of application for SCCS models, we have not included such papers in our review; here we review papers that use SCCS to quantify risks for more focused hypotheses.

For this paper, we firstly systematically identified published SCCS hypothesis-testing studies and reviewed them against a standard form. Secondly, we use this review to show how the SCCS method has been used and to identify good, poor or unusual practice for further discussion. Our ultimate aim was to broaden insight into the use of the SCCS design and encourage good practice in design, application and reporting. Prior basic knowledge of the self-controlled case series method is assumed, for a simple introduction see [11].

We also aim to compare selected headline results between SCCS and other designs, where more than one study designs have been used. Powels et al [18] found moderate concordance between case-only (including both SCCS and case-crossover) and parallel group designs in a systematic comparison. Instead, we display and focus on similarities and differences in pairs of one or two extracted study results per article.

Materials and Methods

A review of self-controlled case series studies was conducted in a systematic manor. SCCS studies with non-vaccine exposures were identified. These studies were published (in print or electronically) between 1995, when the SCCS method was first introduced, and May 2016, when the papers were extracted. We searched for those papers citing references [1-10] in the Scopus and the ISI Web of Knowledge databases. No review protocol exists.

All articles were initially screened on title and abstract by one author. Excluded articles were later re-screened by another author to ensure none had been missed. Among the identified SCCS studies, papers that included vaccines as exposures were excluded from the review. SCCS studies on vaccine safety were reviewed by [3]. We also excluded all methodological papers and commentaries. We only included studies in which study authors specifically identified the design as self-controlled case series. Note that other study designs are special cases of SCCS, such as the self-controlled risk interval design [19] and the time stratified case-crossover design [20], but these were not included as authors would not necessarily be aware of the similarities.

We reviewed each paper against a standard form that included details on: exposures and adverse events studied, whether multiple or single exposure was studied, case ascertainment, whether repeated events were used in the analysis, data collection and description, sample size, observation period, age groups, the allowance for any other temporal confounders, risk periods and their rationale, sensitivity analyses undertaken, statistical features, whether key SCCS assumptions were met, any good, poor or unusual practice, and comparison with other study methods used in addition to SCCS. See S1 Table for a full list of elements included in the review form.

Where another study was used in addition to SCCS, we extracted one or two 'headline' results for a specific exposure-outcome pair for each study design. We identified the headline exposure-outcome pair by (1) identifying the main analysis within the article, (2) where there was exactly two main analyses we extracted results for both, (3) where there were multiple exposure-outcome pairs studied we simply took that of the first reported result within the article abstract. For comparisons with cohort and case-control designs, we identified and extracted only pairs of results with the most similar design choices, the minimum requirement for which was that the definition of exposure in the cohort or case-control study matched the exposure risk window in the SCCS study. We noted the sample sizes, whether the same population of cases was used, and for cohort studies we additionally noted whether the study/observation periods differed. Where the other study design was case-crossover, we noted risk and reference periods for SCCS, and case and referent windows for case-crossover. When results using several choices of referent windows were reported for the case-crossover analysis, we identified a primary case-crossover analysis result or if no primary analysis was identified in the article, we took the first listed. Results are reported as a relative risk for cohort, odds ratio for case-crossover and case-control and relative incidence for SCCS.

Results and Discussion

A flowchart of the selection of articles is included in Figure 1. 461 records were identified in SCOPUS and 401 in Web of Science. After excluding 374 duplicates, 488 records were screened on title and abstract for inclusion eligibility. 97 full text papers were screened, from which we identified 79 studies that met our selection criteria and were included in the final study. Note that two of the 97 full text papers were excluded because we were unable to fill in our standard form; one was excluded because the SCCS analyses were secondary to other analyses and there was no detail on the SCCS analyses in the paper, and the other was excluded because a large number of analyses were carried out on multiple outcomes that could not be generalised sufficiently on one form.

Figure 1. Flowchart of articles searched and reviewed.

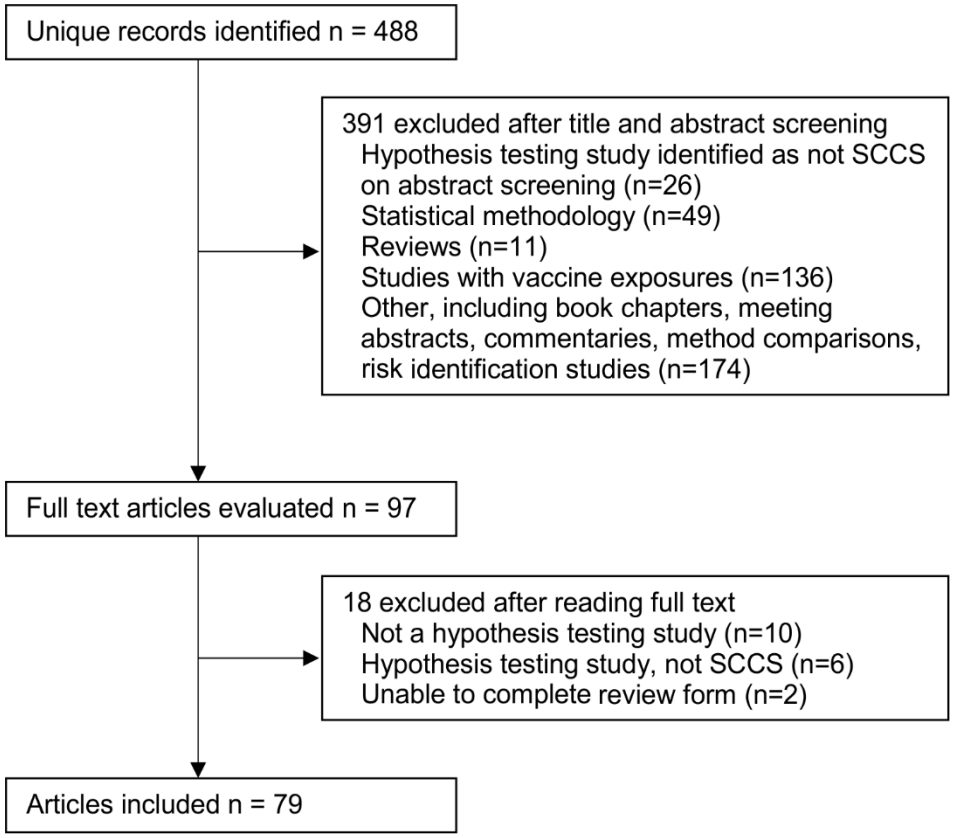
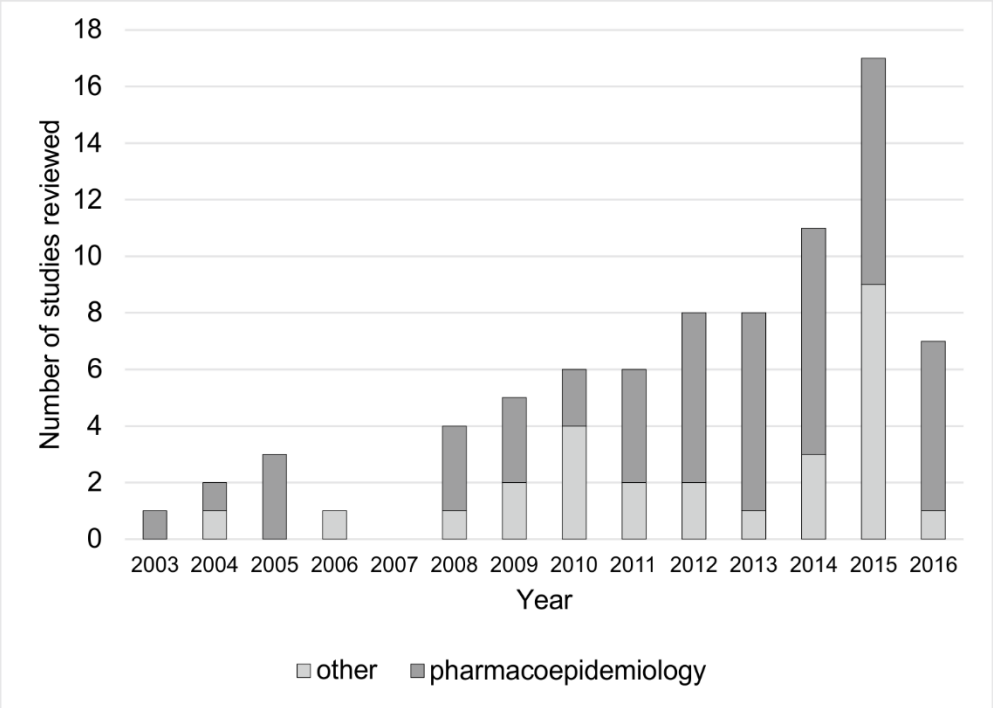


Figure 2 shows that the number of studies included in this review has increased by year. Researchers should have found SCCS more accessible to apply after publication of a tutorial [1] and example scripts were made available online in 2006 (http://statistics.open.ac.uk/sccs). Note that the databases were searched in May 2016, hence the low number included in the review that were published in 2016.

Software for SCCS analyses

13 studies did not state which statistical software package was used for analysis, 66 did and of these, 9 used more than one software package. 4 studies reported use of GLIM, 5 use of R, 26 use of SAS, 37 use of STATA, and 1 use of SPSS.

Figure 2. Number of studies reviewed against year. Separated by articles in pharmacoepidemiology (typically with prescription medication exposures) and those with other exposures.



Exposures and outcomes identified

The exposures and outcomes of studies included are summarised in two separate tables. Table 1 includes only (non-vaccine) pharmacoepidemiology studies, concerned with the safety of prescription medications, of which there were 52. The most common outcomes studied were broadly accidents and injuries, and cardiovascular outcomes. Table 2 includes all other studies, of which there were 27. 10 studies were on the association between infections and cardiovascular outcomes, 4 studies had surgical exposures, 2 environmental and 2 pregnancy.

Table 1. Exposures and outcomes in 52 pharmacoepidemiology studies (non-vaccine), grouped by broad drug class.

Broad drug class	Exposure(s)	Outcome(s)	Reference
antibiotics / anti-infectives	fluoroquinolones	retinal detachment	[21]
	palivizumab	diarrhoea, bronchitis, eczema	[22]
	antibiotics	liver injury	[23]
	clarithromycin	MI, stroke, arrhythmia	[24]
cardiovascular	statins	RF, VTE, PD, dementia, RA, cataract, fractures	[25]
	antihypertensive	falls	[26]
	beta blockers	heart failure	[27]
	antihypertensive	hip fracture	[28]
	antihypertensive	falls	[29]
	Tamsulosin	hypotension	[30]
	Antihypertensives (generic vs brand name)	treatment discontinuation	[31]
	α-adrenoceptor blocker therapy	hip, femur fractures	[32]
	beta blockers	MI	[33]
	α-blocker therapy	stroke	[34]

gastrointestinal / metabolism	thiazolidinediones	fracture	[35]
	orlistat	liver injury	[36]
	PPIs	MI, HF	[37]
	PPIs	pneumonia	[38]
	sitagliptin and exenatide	pancreatitis	[39]
	PPIs, HS2RAs	clostridium difficile infections	[40]
psychotropic	TCAs, SSRIs	hip fracture	[41]
	TCAs, SSRIs	MI	[42]
	bupropion	sudden death, seizures	[43]
	antipsychotics	stroke	[44]
	antipsychotics	stroke	[45]
	SNRIs	falls	[46]
	antipsychotics	hip fracture, pneumonia	[47]
	overdose on psychotropic drugs	RTAs	[48]
	antipsychotics	MI	[49]
	TCAs, SSRIs	suicide related events and self harm	[50]
	stimulant treatment	injury	[51]
	benzodiazepine	fracture	[52]
	antipsychotics	MI	[53]
	methylphenidate	trauma	[54]
	methylphenidate	injuries	[55]
	antidepressants	hip, femur fracture	[56]
	antidepressants	work-related injuries	[57]
addictive disorders	nicotine replacement therapy	MI, stroke, death	[58]
anti gout	colchicine	clostridium difficile Infection	[59]
glucocorticoids	discontinuation of glucocorticoid therapy	psychiatric outcomes	[60]
ophthalmological	ranibizumab	stroke, TIA, MI	[61]
	ophthalmic timolol	bradycardia	[62]
osteoporosis	strontium ranelate	VTE, GI disturbance, skin complaints, memory loss	[63]
	bisphosphonates	AF and flutter	[64]
opioid	opioid analgesics	serious infections	[65]
reproduction	ART	MS exacerbations	[66]
respiratory	tiotropium bromide	stroke	[67]
multiple drug classes	SSRI, NSAID	GI bleed	[68]
	prescription medications	RTAs	[69]
combinations	clopidogrel and PPIs	MI	[70]
	concomitant tramadol and VKA	high INR	[71]
	drug combinations	GI bleed	[72]

PPIs: proton pump inhibitors, H2RAs: histamine-2 receptor antagonists , SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants, SNRIs: serotonin-norepinephrine reuptake inhibitor antidepressants, ART: assisted reproduction technology (gonadotropin-releasing hormone agonists and recombinant follicle-stimulating hormone), VKA: vitamin K antagonist, MI: myocardial infarction, RF: renal failure, VTE: venous thromboembolism, PD: Parkinson's disease, RA: rheumatoid arthritis, HF: heart failure, AS: attempted suicide, TIA: transient ischaemic attack, GI: gastrointestinal,

RTA: road traffic accident, AF: atrial fibrillation, MS: multiple sclerosis, INR: international normalized ratio measurement.

Table 2. Exposures and outcomes in 27 studies (with non-drug and non-vaccine exposures), grouped by type of exposure.

Exposure type	Exposure(s)	Outcome(s)	Reference
acute infections	acute infection or vaccination	MI, stroke	[73]
	acute respiratory or urinary tract infections	DVT, PE	[74]
	staphylococcus aureus bacteremia	MI	[75]
	acute bacterial pneumonia	ACS	[76]
	infection-related hospitalization	MI, unstable angina, stroke, TIA	[77]
	influenza	MI	[78]
	herpes zoster	stroke	[79]
	hemorrhagic fever with renal syndrome	MI, stroke	[80]
	chickenpox	stroke	[81]
	herpes zoster	MI, stroke	[82]
environmental	heat waves	renal disease/failure	[83]
	extreme heatwaves	ambulance call out, ED visits, hospitalization, death	[84]
pregnancy	pregnancy	antibiotic prescribing	[85]
	pregnancy	tuberculosis	[86]
surgical	invasive dental treatment	MI, stroke	[87]
	bariatric surgery	asthma exacerbation	[88]
	carotid angioplasty and stent placement	stroke, death	[52]
	bariatric surgery	heart failure	[89]
other	exacerbation of COPD	MI, stroke	[90]
	inflammatory bowel disease	VTE	[91]
	screening for depression in patients	depression	[92]
	psychological stress	herpes zoster	[93]
	possible trigger events (diary-recorded)	seizures	[94]
	web search of specific categories	pregnancy, allergy, HIV, HSV, MI, PTSD, eating disorder	[95]
	hospital discharge after microbiome perturbation	severe sepsis	[96]
	retinal vein occlusion	MI, stroke	[97]
	central retinal artery occlusion	MI, stroke	[98]

MI: myocardial infarction, DVT: deep vein thrombosis, PE: pulmonary embolism, ACS: acute coronary syndromes (includes MI), VTE: venous thromboembolism, HIV: human immunodeficiency virus, HSV: herpes simplex virus, PTSD: post-traumatic stress disorder, ED: emergency department visits, TIA: transient ischaemic attack, GBS: Guillain-Barre syndrome

Ideal outcomes for a SCCS study are acute with a clear, abrupt date of onset. This will, in general, be true for cardiovascular outcomes, accidents, injuries and acute infections which covers the majority

of outcomes studied in Tables 1 and 2. Although a precise outcome date was available for all 79 studies, there was occasionally potential for delay in diagnosis or treatment date used. For example, in a study of retinal detachment, only treatment or surgery date was available [21], or for diagnosis of depression or psychiatric outcomes, there may be some delay in diagnosis [60, 92]. Such limitations were made clear in the articles.

Data description and data accuracy

As for any epidemiological study design, ascertainment of outcomes and exposures should be independent. For a SCCS design, this also applies to the timing of outcomes and exposures. A clear description of how the data were obtained is needed in order to ascertain whether this is met. All 79 studies reviewed gave a clear explanation of how the data were obtained.

Almost all studies obtained data retrospectively from healthcare databases. There were a couple of exceptions. The data used in [95] were web searches. In a paper that was exploratory in nature, possible triggers for multiple epileptic seizures within single individuals were studied; carers recorded in diaries both timings of the exposures, possible trigger events, and outcomes, epileptic seizures [94].

For one study we had concerns that the exposure and outcome timings were not independent [31]. The association between prescription medication discontinuation (outcome) and prescription medication type (generic or brand name) was studied. Risk periods included time whilst taking generic drugs and reference periods included time whilst taking brand name drugs. The outcome was defined as the date of the final prescription before discontinuation of the drug. In this study, the event date will always be timed to fall one prescription before the end of a course of medication, thus end of exposure and outcome timing are not independent. SCCS methodology was not appropriate here.

Care must be taken to ensure that artefactual effects related to the idiosyncrasies of the ascertainment process are avoided. For example, Burton et al [92] studied the association between screening for depression in coronary heart disease patients and new treatment or diagnosis of depression. They were careful to exclude outcomes which occurred on the same day as exposure as a screening may only be recorded following diagnosis.

Observation periods

For an SCCS study, the observation periods and exposure risk periods should be defined rigorously and independently of outcome timings. Observation periods must be defined such that, if an event had occurred at any time in the period, that event would have been ascertained. In all 79 studies, observation periods were thoroughly defined. In the majority of studies observation periods were defined solely based on age and/or calendar time constraints, or time registered in a database (ending with death is also typical). Observation periods may also validly be determined based on the timing of exposures. For example, Hasegawa et al [88] defined observation periods to be two years before and two years after exposure. 9 studies in total determined observation periods in such a way. Such a study set up reduces efficiency over use of longer observation periods, however it may offer advantages in terms of data collection and in some specific situations, reference windows that are far (in time) from the exposure risk windows may be seen as unsuitable. Note that the self-controlled risk interval design [19] is a simplified SCCS design with reference periods defined in relation to exposure in a similar way (not included in this review), while the most common approach with SCCS is to account for changes over age and season by modelling them.

Some studies began observation periods with the start of exposures [30] [43]. In certain situations issues with event-dependent exposures can be avoided by beginning observation with exposure (see section on potential biases). Bird et al [30] used this approach because the disease for which the medication exposure is prescribed may also affect incidence of the adverse event, i.e. the disease is a time-varying confounder.

Some studies [35, 52, 60, 89, 93] chose a 'before and after' approach, with no reference window following exposure risk periods. This approach removes long-term post-exposure effects from the study. For example, Douglas et al [35] explicitly stated that this approach was chosen because the presence of a long-term washout effect could not be ruled out in a study on the association between thiazolidinedione antidiabetic agents and fractures.

Some situations require an alternative observation period definition. In a study of the effect of adherence to beta-blockers on *subsequent* myocardial infarction, observation periods were defined using time since hospital discharge after acute myocardial infarction [33]. In two drug interaction or combination safety studies [70] and [71], observation periods were defined for the duration that one drug was assumed to be in use, with risk periods defined in relation to prescription of the other drug. Note that another study that looked at drug combinations defined observation periods in a more usual way, but split exposure risk windows by time prescribed single drugs and combinations of drugs [72].

Risk periods

Risk periods must be rigorously and a priori specified based on information from other studies, a new hypothesis about the association between exposure and event of interest or an understanding of the biological mechanism. Risk periods were explicitly defined in all studies. 57 of the studies rigorously stated the rationale behind the choice of the risk periods, 15 of these defined risk periods based on prior studies, 8 studies based on general knowledge but not based on prior studies, 7 studies based on new hypothesis and 22 of the studies did not justify the rationale for the risk periods.

For point exposures, such as surgery, for example Bariatric surgery [89], a record of infection, for example acute bacterial pneumonia [76], heatwaves [83, 84] or initiation of a drug, for example initiation of antipsychotic agents [49], the exposure risk windows are defined from time since the point of exposure. In pharmacoepidemiology, exposure risk windows can also be the duration of time individuals are assumed to be taking a medication, based on prescription history. In 27 of the 52 pharmacoepidemiology studies, exposure risk windows were defined over all time prescribed a drug. To allow for the effect of therapy cessation, uncertainty in the time at which treatment ended, or uncertainty in the residual effect of the treatment, washout periods after the end of exposure risk periods can be added. Wash out periods were included in 23 of the pharmacoepidemiology studies. For the two studies with pregnancy exposures, the main exposure risk periods spanned pregnancy [85, 86] and either included an additional post-partum risk window [86] or removed this time [85].

Exposure risk periods are frequently subdivided into windows based on time since start of an exposure. Weise et al [65] used a different approach in a study with opioid analgesics exposures, here risk windows were divided into subgroups based on prescribed dose.

Three studies [35, 52, 88] used risk periods of indefinite length (i.e. to the end of observation). SCCS can handle indefinite exposures, but in order to model age, season or other time-varying confounder effects, it is necessary to have unexposed and exposed time in all confounder groups, and unexposed cases may be required to achieve this. However, use of such long or indefinite risk periods reduces efficiency [8], [99] (p.21). Examples of studies that include unexposed cases to help separate the effect of exposure from age effects are provided by Pratt et al [45] and Smeeth et al [74].

In some studies exposure risk periods were imputed when information on the precise timing of exposure was unknown. For example, Douglas et al. [36] calculated the expected duration prescriptions using dosage and pack size information, but where this information was missing, it was imputed by the median pack duration. Markers for exposure dates are often used, for example date of hospitalization for an infection [80], or date of antidepressant prescription when date of a diagnosis of depression or delirium is not available [60]. Results might be sensitive to unavailability of accurate exposure dates and sensitivity analyses relating to imputation errors may be advisable.

Several studies conducted sensitivity analyses to check sensitivity to risk period choices [21, 23, 28, 31, 39, 54, 71]. Events that occur on the first day of exposure, or on the day of point exposure can be problematic in that it is unknown which came first, some studies ran sensitivity analyses that excluded this index exposure date from the risk period [32, 34, 79].

Confounders

The SCCS method automatically controls for both measured and unmeasured fixed multiplicative confounders. Unlike fixed covariates, time-varying confounders, such as age and season, are not automatically controlled for and must be included in the model. When using the standard SCCS method, where age and/or season effects are modelled using piecewise constant functions, the groups used should be rigorously specified.

37 studies specified age groups rigorously. 3 specified age groups only vaguely. 16 studies clearly stated that age was not adjusted for. This is reasonable when observation periods are short. 21 studies did not specify whether or not age was adjusted for. Since age adjustment is common practice, we encourage explicit reporting of the absence of age adjustment. 21 studies adjusted for either season or calendar years as appropriate.

In addition to applying the standard SCCS method, one study [30] used the semi-parametric SCCS where there is no need to specify age categories, and one study [24] used the spline-based SCCS method where age and exposure effects are smoothed [13].

In using the standard SCCS model, poorly specified age or season groups can sometimes lead to biased estimates of the exposure effect, hence sensitivity analysis in the presence of strong temporal effects is advised. 8 studies conducted sensitivity analysis of age classifications, see for example [74, 77, 79].

A small number of studies adjusted for time since a specific diagnosis, event or measurement, see for example [33, 34, 71]; and some studies further included adjustment for a comprehensive list of potential time-varying confounders, such as other prescription medications, move to a residential care home, see for example [27, 61, 65].

Rather than making an adjustment, some studies removed certain periods with especially low or high risk of event. For example, in a study on opioid analgesics and serious infections, hospitalization periods were removed [65].

Assumptions

We mainly concern ourselves with two assumptions of the SCCS method. The first is that occurrence of the outcome event does not affect subsequent exposures; we refer to this issue as ‘event dependent exposures’, others have used the term ‘reverse causality’ [100]. The second is that occurrence of the outcome event does not affect an individual’s time observed; we refer to this issue as ‘event-dependent observation periods’.

Event dependent exposures

The issue of event dependent exposures was mentioned in 34 of the 79 papers reviewed, although steps were sometimes taken to circumvent the issue by design without mention of why! This is the main limiting assumption of the SCCS method and warrants careful consideration. Substantial bias can result when exposure is more likely after the adverse event under study (bias toward 0), or if exposure cannot or rarely occurs following the event (bias upward).

When event dependence is temporary and short term, bias can sometimes be corrected by inclusion of a ‘pre-exposure risk period’ If there is an excess or dearth of exposures following an event, then equivalently there will be an excess or dearth of events prior to exposure. So a separate additional ‘risk’ period of length equal to the length of dependence just before the start of exposure is included [11]. It makes intuitive sense to remove this time from the baseline or reference period. 35 studies

included a pre-exposure risk period. A handful of studies equivalently completely removed a window of pre-exposure time from the study (see for example [60, 85]).

Long term event dependent exposures are more problematic, though there are solutions for some specific situations. These were formulated with death as the event in mind, as most exposures cannot take place after death (with the exception of exogenous exposures such as weather phenomena). When no exposure can occur after an event and exposures are (or are typically) unique and their associated risk periods are of a fixed duration, a simple solution is to begin the observation period with first exposure and end the observation at the planned end of study. Thus where death is the event, time after death is included, up until the planned study end. The full exposure history is always known after a unique exposure has been observed. Two studies took this approach [43, 58], both of which were analyses on the association between smoking cessation therapies and death. When there are multiple exposures with risk periods of a fixed duration, a more complicated extension to the SCCS method is available [7]. This was used in a study of antidepressants and suicide-related death in a wider paper on suicide-related outcomes [50].

Event dependent observation periods

The issue of event-dependent observation periods often arises since observation periods will typically end when a patient dies, so when an outcome carries high short-term mortality risk such as myocardial infarction or stroke, the end of observation may end early as a direct result of the outcome event. Event dependent observation periods can produce bias in either direction. This is often difficult to predict a priori, but the direction of bias depends upon whether risk periods tend to lie toward the beginning or the end of the observation period so can depend upon design choices. If most exposures occur toward the end of the observation period, and observation periods end early as a direct result of the event, estimates will be biased upward [101].

Appropriate SCCS studies for which death itself was the outcome have been discussed in the subsection above. Solutions are available that require researchers to include time after death within observation periods. One paper studied the association between stent placement and stroke or death (together as one outcome, and stroke alone in a separate analysis), but ended the observation period upon death [52]. This was a 'before and after' study, with the reference period 360 days before stent placement and risk periods over the 360 days after stent placement. Because there was no reference time after exposure, curtailing observation at death will have biased estimates upward. Moreover, time prior to stent replacement is immortal time [102], death cannot have occurred during this period otherwise the exposure, stent placement, could not have taken place.

27 papers studied myocardial infarction (MI) or stroke events, and of these 27, 17 papers mentioned that occurrence of an event could affect observation periods or post-event exposures. Following [35], we now recommend that a sensitivity analysis is undertaken excluding (or including an interaction term in the model for) patients that died due to the event [11, 101]. Where cause of death is unknown this could be all patients that died during observation or all patients that died within a certain time frame after the event. 9 of the 27 studies carried out such a sensitivity analysis. The first of these 27 papers to carry out such a sensitivity analysis appeared in 2009 [76], it was on acute bacterial pneumonia and acute coronary syndromes, where both exposure and outcome can be fatal. A fuller understanding of the issue did not come until a little later, in 2011, when an extension to the SCCS method that allows for event-dependent observation periods was published [9]. 11 of the 27 papers were published in the period 2004 to 2011, two of which carried out a sensitivity analysis excluding those who died [76, 87]. 15 of the papers were published in the period 2012 to 2016, 2 used the extension [9] either as the main analysis [53] or as a sensitivity analysis [82], 7 carried out a sensitivity analysis excluding those who died [33, 61, 70, 78-81], 1 discussed the issue only [24], leaving 5 papers with no mention of event-dependent observation periods [34, 37, 52, 97, 98]. However, sensitivity analysis results suggest that event-dependent observation periods rarely create such substantial bias as to change overall study conclusions.

Of course, event-dependent observation periods are not exclusive to MI and stroke outcomes, and 9 other papers discussed event-dependent observation periods. Six studies carried out a sensitivity analysis excluding those who died, the outcomes were: acute liver injury [36], fractures [35], falls [26], atrial fibrillation and flutter [64], pneumonia [38] and serious infections [65]. One study used the extension for a sensitivity analysis, the outcome was upper gastrointestinal bleeds [72]. They also carried out a sensitivity analysis by truncating the observation period at the event time, to help explore the effect of confounding by contraindication post event. One team carried out a simulation study to explore the impact of right censoring at first event [56].

Other sensitivity analyses

Many papers presented results from multiple primary analyses. Some sensitivity analyses have already been highlighted in the above subsections, such as excluding those who died due to the event, defining age groups differently and varying risk period lengths.

Various sensitivity analyses were undertaken that excluded a subset of cases: patients with some other exposure [28, 29, 50, 87, 89], patients with some other adverse event [63, 87, 89], those with uncertainty in dates [78], differing outcome definitions [39], those with overlapping risk periods [87], patients with exposures of a certain length [54, 103], patients with long hospitalization [33], patients that initiated exposure during hospitalization [34].

An additional assumption of the SCCS method is that events either arise according to a Poisson process, thus events within an individual must be independent of one another, or that events are unique and rare. In some studies repeated events within a pre-specified period were considered to belong to the same episode. For example, repeated stroke events within 28 days were grouped to be of the same episode [79]. On the basis of this Poisson assumption, sensitivity analyses were reported that took first events only [30, 54, 65, 70], restricted to patients with only one event [55] or took only incident events [39]. In a study with recurrences of myocardial infarction as the event, a sensitivity analysis of first recurrences i.e. second MI only was undertaken [33].

An interesting approach is to run an analysis on a separate control exposure to help validate results [35, 67]. For example, in a study on the association between glitazones (anti-diabetic treatment) and fractures, [35] also ran an analysis of a different antidiabetic treatment (sulphonylureas). This was to help check that initiating thiazolidinedione was not temporally correlated with other exposures that influence the risk of fractures.

Some comparisons with other statistical methods

Case-crossover

Similar to SCCS, the case-crossover design [104] is a within-person self-controlled study design. However, time centres on the time of the event (or a time window immediately preceding the event) and compares exposure status within this event window to referent windows prior to the event. Case and referent windows act as matched pairs. The case-crossover design does not include time after an event, so has the advantage that it does not matter whether exposures are influenced by past events as in a SCCS design, but can suffer different sources of bias [100].

Both a SCCS and a case-crossover analysis were presented in four pharmacoepidemiology studies. All four studies reported multiple results, but a single 'headline' result was extracted for each study and is presented in Table 3, along with exposure risk and baseline reference windows used in the SCCS design (defined in relation to exposure), and case and referent windows used in the case crossover design (defined in relation to event).

Table 3. A headline result from articles reporting dual self-controlled case series and case crossover analyses; including exposure risk and reference periods used in the SCCS analysis, and case and referent windows used in the case crossover analysis.

Exposure (Outcome) [Reference]	SCCS			Case crossover		
	RI (95% CI)	Exposure risk period	Reference periods	OR (95% CI)	Case window	Referent window(s)
Antibiotics (liver injury) [23]	10.01 (6.59–15.18)	0-7 days	before prescription and 30+ days after last use	3.05 (2.06–4.53)	14 days	4 x 14 days immediately before case period
Antidepressants (hip, femur fracture) [56]	1.41 (1.32, 1.49)	current use (prescription + 30 days)	before prescription and 60+ days after last use	2.24 (2.04–2.47)	1 day	4 x 1 day, 91, 182, 273, 365 days before event
Compound analgesics (RTAs) [69]	2.06 (1.84, 2.32)	1-28 days following prescription	4+ weeks before prescription and 24+ weeks after last use	1.16 (1.04, 1.29)	28 days	29-56 days before event
Benzodiazepine (Fracture) [103]	1.46 (1.28-1.66)	0-4 weeks following prescription	0-4 weeks before prescription	1.39 (1.25-1.54)	1 day of event	150 days before event

RI: relative incidence, OR: odds ratio, CI: confidence interval.

Similar results for the two methods were found by Hwang et al [103]. In additional case-crossover analyses other referent days were used (90, 120 days before event), but results varied little.

Results contrasted in Brauer et al [23], but the case-crossover result presented will be biased downward by a 'carry-over effect'. Here, the SCCS analysis suggested an excess risk persisted in washout periods 20-30 days following exposure, this time would be 'unexposed' in the case-crossover analysis presented in Table 3, so this estimate is biased downward. Case-crossover estimates increased when a gap between referent and case windows was included in a sensitivity analysis. Also note that the SCCS exposure risk window is shorter than the case-crossover case window and this makes direct comparison more difficult. The case-crossover results presented in Gibson et al [69] will be similarly affected by a carry-over effect: case-crossover analyses included other referent windows and results varied (no primary analysis was identified so we reported the first), using a referent window of 113-140 days yielded a slightly higher OR of 1.26 (1.12, 1.41). Note that compound analgesics were only one class of medication studied in [69] and the gap between SCCS and case-crossover results varied, but case-crossover and SCCS were generally in agreement where no association was found.

De Groot et al [56] found the association to be higher in case-crossover analyses. They explained this by a selection bias in the case-crossover analysis in which discordant cases tended to have short-term exposure, while concordant cases tended to have long-term exposures. Long term users appeared to have a more stable risk. Only cases with discordant exposure statuses at the case and referent

windows contribute to a case-crossover analysis, while all cases contribute to a SCCS analysis. However, some bias in SCCS estimates may have arisen due to deaths post-event, which could be in either direction. Universally long-term use medications can make for problematic exposures in case-crossover studies [105]; while SCCS can provide unbiased estimates with longer exposures, power reduces with longer exposure risk windows [99].

Case-control

Four pharmacoepidemiology papers, and one paper with infection exposures used both a SCCS and case-control analysis. One or two headline results for each study are presented in Table 4, along with sample sizes.

Table 4. One or two headline results from papers that analysed the same data using both SCCS and case-control methods, including numbers of cases and controls used in each analysis.

Exposure (Outcome) [Reference]	Population & exposures comparable	SCCS		Case control		
		RI (95% CI)	cases	OR (95% CI)	cases	controls
Antipsychotics (MI) [23]	Yes	2.82(2.0–3.99)	1,546	3.19 (1.9–5.37)	27,861	108,234
TCA, SSRI (hip fracture) [41]	Yes	2.30 (1.82, 2.90) 1.96 (1.35, 2.83)	3,958 1,673	4.76 (3.06, 7.41) 6.30 (2.65, 14.97)	16,341	29,889
Concurrent NSAID and SSRI (GI bleed) [68]	Yes	3.25 (1.95, 5.42)	8,130	2.93 (2.25, 3.82)	11,261	53,156
TCA, SSRI (MI) [42]	Yes	1.44 (1.09, 1.90) 1.94 (1.40, 2.68)	6,735 4,132	2.07 (1.50, 2.86) 2.66 (1.81, 3.92)	63,512	378,886
Acute bacterial pneumonia (ACS) [76]	Yes	47.6 (24.5,92.5)	37	7.8 (3.1, 19.4)	206	395

RI: relative incidence, OR: odds ratio, CI: confidence interval, cases: number of cases, controls: number of controls.

In all papers the exposure definition used in the case-control study matched with the exposure risk period used in the SCCS study. The cases included in the analyses were from the same population, but in all papers only the exposed cases were included in the SCCS analysis, hence the smaller sample sizes reported for SCCS in Table 4. Similar results would not necessarily be expected from SCCS and case control analyses as the underlying models differ and the separate control population used in a case-control study is very different to the baseline/reference time windows used in SCCS. However, the results from the SCCS and case-control analyses were similar in [23] and [68].

In the papers by [41] and [42] a higher risk was found in case-control analysis than in the SCCS analysis; both papers considered antidepressant exposures. Hubbard et al [41] considered selection and indication biases to be an issue in the case-control analysis. Tata et al [42] expressed concern about the inability of either design to control for the changing severity of depression over time, but

considered control of fixed confounders an advantage of SCCS. SCCS results could potentially be affected by event dependent exposures (reverse causality), the event leading to depression and prescription of an antidepressant, which would attenuate results.

Though estimates differ considerably in the study by Corrales-Medina et al [76], authors were reassured by the fact that both analyses indicated a strong positive association. The study size was much smaller than that of the pharmacoepidemiology studies. (Note that this study was labelled 'cohort' in the paper but appears to be analysed as a case-control study).

Cohort

A number of papers presented both a cohort and a SCCS analysis. One headline (or most comparable) result for each analysis for the majority of these papers is shown in Table 5, along with sample sizes. Table 5 does not include results for three papers that included both cohort and SCCS analyses, namely [25] in which a large volume of results for multiple exposures and outcomes were presented with no clear headline result, [96] in which the cohort and SCCS analyses were on different outcomes to explore different aspects of the study, and [60] who reported only raw incidence rates for the cohort.

Table 5. A headline result from papers that analysed the same data using both SCCS and cohort methods, including numbers of cases and controls used in each analysis.

Exposure (Outcome) [Reference]	**Population & exposure periods comparable**	**SCCS**		**Other Study Type**	
		RI (95% CI)	**cases**	**RR (95% CI)**	**SS**
Tamsulosin (hypotension) [30]	Reference windows differ	2.56 (2.15, 3.05)	2,248	2.12 (1.29, 3.04)	324,255
Antihypertensives (generic vs brand name) (treatment discontinuation) [31]	Yes	1.01 (0.96, 1.11)	804	1.00 (0.98, 1.02)	101,618
Clopidogrel and PPI interaction (MI) [70]	Yes, except for pre-exposure	0.75 (0.55, 1.01)	-	1.41 (1.31, 1.52)	24,471
Inflammatory bowel disease (VTE) [91]	Yes	4·5 (2·6, 7·8)	304	3·4 (2·7, 4·3)	85,428
Bupropion (sudden death) [43]	Reference windows differ	0.50 (0.12, 2.05)	121	0.40 (0.10, 1.60)	9,329
Antidepressants (work-related injuries) [57]	Yes, except for pre-exposure	1.15 (1.02, 1.29)	2,238	1.14 (1.07, 1.22)	66,238

Antipsychotics (MI) [49]	Reference windows differ	1.78 (1.26, 2.52)	804	2.19 (1.11, 4.32)	21,938
PPIs (Pneumonia) [38]	Yes, except for pre-exposure	3.07 (2.69, 3.50)	6,775	3.24 (2.50, 4.19)	105,467
Clarithromycin (MI) [24]	SCCS on a sub-cohort of cases. Reference windows differ.	3.38 (1.89, 6.04)	740	3.66 (2.82, 4.76)	326,781
Colchicine (CD infection) [59]	Reference windows differ	1.24(1.03, 1.49)	-	1.44(1.15, 1.97)	386,110

RI: relative incidence, RR: relative risk, CI: confidence interval, cases: number of cases, SS: sample size.

We checked the studies for comparability. All explored the same hypothesized exposure risk window. Wong et al [24] used only a subset of cases from the cohort population in the SCCS analysis, for whom the underlying disease for which the medication exposure is prescribed would not be expected to temporally trigger the outcome. For all other studies in Table 5, either all cases (both exposed and unexposed), or all exposed cases were extracted from the cohort for the SCCS analysis; though some papers did not explicitly state which. Corrao et al [31] compared two exposure types (rather than one exposure type to unexposed reference periods) and included only those that were exposed to both types in the SCCS analysis. Reference periods used in the cohort and SCCS analyses differed in 5 studies [24, 30, 43, 49, 59]. Reference periods were similar in 5 studies [31, 38, 57, 70, 91], though some included a pre-exposure 'risk' period in the SCCS study.

Many of the results in Table 5 demonstrate comparable findings from the cohort and SCCS analyses, with non-conflicting overall conclusions and most often overlapping confidence intervals. The main exception with conflicting results is on the association between Clopidogrel and proton pump inhibitor interaction and myocardial infarction [70]. It was concluded that it is likely that unadjusted confounding remained in the cohort study, either from illnesses that they were unable to measure, or through systematic differences in the severity of underlying disease. Studies often report unadjusted cohort analysis results, as well as adjusted results (that we have reported in table 5); [57] and [38] present neat examples of how unadjusted cohort results became more aligned with SCCS results after adjustment.

The cohort and SCCS results were well aligned in [24], though additional cases were present in the cohort. Additionally a case-crossover analysis was carried out, for which OR = 2.20 (1.23, 3.95), a weaker association than that suggested by the SCCS or cohort analyses.

Conclusion

Application of SCCS methods is growing and becoming more varied since their first introduction for vaccine safety studies in 1995 [2]. The studies reviewed were largely methodologically sound, with a couple of exceptions [31, 52]. Two previous reviews of case-only studies [15, 16] implied that the exposure should be transient and the event acute. Indeed, the SCCS method works best when these

are the case, but it can still give good results for any study with clear temporal hypotheses. These conditions may, however, be more important for case-crossover studies that were also included in these reviews. More important to SCCS are the assumptions of event-dependent exposures and observation periods. These are often well considered and analyses adapted accordingly or sensitivity analyses performed, though this is not always the case.

We found that a rigorous definition of age groups was frequently not given. It is good practice to ensure that sufficient detail is given so that studies are reproducible. Age was also frequently not adjusted for. That events do not vary with age over the observation period is a strong assumption to make unless observation periods are short, and can impact on exposure estimates considerably [14].

It is possible that a handful of papers will have been missed by our search criteria, but by searching for references to all the main SCCS papers, we believe that we will have captured the vast majority, even where SCCS was used only for a secondary analysis. A limitation is that we did not extend the review to other methods that are special cases of the self-controlled case series design, such as the self-controlled risk interval design.

References

1. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: The self-controlled case series method. Statistics in Medicine. 2006;25(10):1768-97. doi: 10.1002/sim.2302.
2. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics. 1995;51(1):228-35. doi: 10.2307/2533328.
3. Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice. Epidemiology and Infection. 2011;139(12):1805-17. doi: 10.1017/S0950268811001531.
4. Farrington CP. Control without separate controls: Evaluation of vaccine safety using case-only methods. Vaccine. 2004;22(15-16):2064-70. doi: 10.1016/j.vaccine.2004.01.017.
5. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: A comparative evaluation. American Journal of Epidemiology. 1996;143(11):1165-73.
6. Farrington CP, Whitaker HJ. Semiparametric analysis of case series data. Journal of the Royal Statistical Society Series C: Applied Statistics. 2006;55(5):553-94. doi: 10.1111/j.1467-9876.2006.00554.x.
7. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures [Article]. 2009 [cited 10 1]. 3-16].
8. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Statistics in Medicine. 2006;25(15):2618-31. doi: 10.1002/sim.2477.
9. Paddy Farrington C, Anaya-Izquierdo K, Whitaker HJ, Hocine MN, Douglas I, Smeeth L. Self-controlled case series analysis with event-dependent observation periods. Journal of the American Statistical Association. 2011;106(494):417-26. doi: 10.1198/jasa.2011.ap10108.
10. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Statistical Methods in Medical Research. 2009;18(1):7-26. doi: 10.1177/0962280208092342.
11. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ (Clinical research ed). 2016;354:i4515. doi: 10.1136/bmj.i4515.
12. Ghebremichael-Weldeselassie Y, Whitaker HJ, Farrington CP. Flexible modelling of vaccine effect in self-controlled case series models. Biometrical Journal. 2016;58(3):607-22. doi: 10.1002/bimj.201400257.
13. Ghebremichael-Weldeselassie Y, Whitaker HJ, Farrington CP. Spline-based self-controlled case series method. Statistics in Medicine. 2017;36(19):3022-38. doi: 10.1002/sim.7311.
14. Ghebremichael-Weldeselassie Y, Whitaker HJ, Paddy Farrington C. Self-controlled case series method with smooth age effect. Statistics in Medicine. 2014;33(4):639-49. doi: 10.1002/sim.5949.

15. Gault N, Castañeda-Sanabria J, De Rycke Y, Guillo S, Foulon S, Tubach F. Self-controlled designs in pharmacoepidemiology involving electronic healthcare databases: A systematic review. BMC Medical Research Methodology. 2017;17(1). doi: 10.1186/s12874-016-0278-0.
16. Nordmann S, Biard L, Ravaud P, Esposito-Farèse M, Tubach F. Case-Only Designs in Pharmacoepidemiology: A Systematic Review. PLoS ONE. 2012;7(11). doi: 10.1371/journal.pone.0049444.
17. Ryan PB, Madigan D, Stang PE, Marc Overhage J, Racoosin JA, Hartzema AG. Empirical assessment of methods for risk identification in healthcare data: Results from the experiments of the Observational Medical Outcomes Partnership. Statistics in Medicine. 2012;31(30):4401-15. doi: 10.1002/sim.5620.
18. Pouwels KB, Mulder B, Hak E. Moderate concordance was found between case-only and parallel group designs in systematic comparison. Journal of clinical epidemiology. 2016;71:18-24. doi: 10.1016/j.jclinepi.2015.09.018.
19. Baker MA, Lieu TA, Li L, Hua W, Qiang Y, Kawai AT, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. American Journal of Epidemiology. 2015;181(8):608-18. doi: 10.1093/aje/kwu322.
20. Lumley T, Levy D. Bias in the case-crossover design: Implications for studies of air pollution. Environmetrics. 2000;11(6):689-704. doi: 10.1002/1099-095X(200011/12)11:6<689::AID-ENV439>3.0.CO;2-N.
21. Chui CSL, Man KKC, Cheng CL, Chan EW, Lau WCY, Cheng VCC, et al. An investigation of the potential association between retinal detachment and oral fluoroquinolones: A self-controlled case series study. Journal of Antimicrobial Chemotherapy. 2014;69(9):2563-7. doi: 10.1093/jac/dku145.
22. Ueyama H, Hinotsu S, Tanaka S, Urushihara H, Nakamura M, Nakamura Y, et al. Application of a self-controlled case series study to a database study in children. Drug Safety. 2014;37(4):259-68. doi: 10.1007/s40264-014-0148-9.
23. Brauer R, Ruigómez A, Klungel O, Reynolds R, Feudjo Tepie M, Smeeth L, et al. The risk of acute liver injury among users of antibiotic medications: A comparison of case-only studies. Pharmacoepidemiology and Drug Safety. 2016;25:39-46. doi: 10.1002/pds.3846.
24. Wong AYS, Root A, Douglas IJ, Chui CSL, Chan EW, Ghebremichael-Weldeselassie Y, et al. Cardiovascular outcomes associated with use of clarithromycin: Population based study. BMJ (Online). 2016;352. doi: 10.1136/bmj.h6926.
25. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: Population based cohort study using the QResearch database. BMJ (Online). 2010;340(7758):1232. doi: 10.1136/bmj.c2197.
26. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: Self-controlled case series. Pharmacoepidemiology and Drug Safety. 2011;20(8):879-84. doi: 10.1002/pds.2176.
27. Ramsay EN, Roughead EE, Ewald B, Pratt NL, Ryan P. A self-controlled case series to assess the effectiveness of beta blockers for heart failure in reducing hospitalisations in the elderly. BMC Medical Research Methodology. 2011;11. doi: 10.1186/1471-2288-11-106.
28. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Archives of Internal Medicine. 2012;172(22):1739-44. doi: 10.1001/2013.jamainternmed.469.
29. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH. The risk of falls on initiation of antihypertensive drugs in the elderly. Osteoporosis International. 2013;24(10):2649-57. doi: 10.1007/s00198-013-2369-7.
30. Bird ST, Delaney JAC, Brophy JM, Etminan M, Skeldon SC, Hartzema AG. Tamsulosin treatment for benign prostatic hyperplasia and risk of severe hypotension in men aged 40-85 years in the United States: Risk window analyses using between and within patient methodology. BMJ (Online). 2013;347. doi: 10.1136/bmj.f6320.

31. Corrao G, Soranna D, La Vecchia C, Catapano A, Agabiti-Rosei E, Gensini G, et al. Medication persistence and the use of generic and brand-name blood pressure-lowering agents. Journal of Hypertension. 2014;32(5):1146-53. doi: 10.1097/HJH.0000000000000130.
32. Lai CL, Kuo RNC, Chen HM, Chen MF, Chan KA, Lai MS. Risk of hip/femur fractures during the initiation period of α-adrenoceptor blocker therapy among elderly males: A self-controlled case series study. British Journal of Clinical Pharmacology. 2015;80(5):1208-18. doi: 10.1111/bcp.12671.
33. Di Bartolomeo S, Marino M, Guastaroba P, Valent F, De Palma R. Self-controlled case-series study to verify the effect of adherence to Beta-blockers in secondary prevention of myocardial infarction. Journal of the American Heart Association. 2015;4(1):e001575. doi: 10.1161/JAHA.114.001575.
34. Lai CL, Kuo RNC, Chen HM, Chen MF, Chan KA, Lai MS. Risk of ischemic stroke during the initiation period of α-blocker therapy among older men. CMAJ. 2016;188(4):255-60. doi: 10.1503/cmaj.150624.
35. Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: A self-controlled case-series study. PLoS Medicine. 2009;6(9). doi: 10.1371/journal.pmed.1000154.
36. Douglas IJ, Langham J, Bhaskaran K, Brauer R, Smeeth L. Orlistat and the risk of acute liver injury: Self controlled case series study in UK Clinical Practice Research Datalink. BMJ (Online). 2013;346(7906). doi: 10.1136/bmj.f1936.
37. Juurlink DN, Dormuth CR, Huang A, Hellings C, Paterson JM, Raymond C, et al. Proton pump inhibitors and the risk of adverse cardiac events. PLoS ONE. 2013;8(12). doi: 10.1371/journal.pone.0084890.
38. Ramsay EN, Pratt NL, Ryan P, Roughead EE. Proton pump inhibitors and the risk of pneumonia: A comparison of cohort and self-controlled case series designs. BMC Medical Research Methodology. 2013;13(1). doi: 10.1186/1471-2288-13-82.
39. Li X, Zhang Z, Duke J. Glucagon-like peptide 1-based therapies and risk of pancreatitis: A self-controlled case series analysis. Pharmacoepidemiology and Drug Safety. 2014;23(3):234-9. doi: 10.1002/pds.3542.
40. Nylund CM, Eide M, Gorman GH. Association of clostridium difficile infections with acid suppression medications in children. Journal of Pediatrics. 2014;165(5):979-84.e1. doi: 10.1016/j.jpeds.2014.06.062.
41. Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. American Journal of Epidemiology. 2003;158(1):77-84. doi: 10.1093/aje/kwg114.
42. Tata LJ, West J, Smith C, Farrington P, Card T, Smeeth L, et al. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. Heart. 2005;91(4):465-71. doi: 10.1136/hrt.2004.037457.
43. Hubbard R, Lewis S, West J, Smith C, Godfrey C, Smeeth L, et al. Bupropion and the risk of sudden death: A self-controlled case-series analysis using The Health Improvement Network. Thorax. 2005;60(10):848-50. doi: 10.1136/thx.2005.041798.
44. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: Self controlled case series study. BMJ. 2008;337(7670):616-8. doi: 10.1136/bmj.a1227.
45. Pratt NL, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for stroke associated with antipsychotic use in the elderly: A self-controlled case series. Drugs and Aging. 2010;27(11):885-93. doi: 10.2165/11584490-000000000-00000.
46. Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Serotonin-norepinephrine reuptake inhibitor antidepressants and the risk of falls in older people: Case-control and case-series analysis of a large UK primary care database. Drugs and Aging. 2011;28(11):895-902. doi: 10.2165/11592860-000000000-00000.
47. Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: A self-controlled case-series

analysis in an Australian health care claims database. Drug Safety. 2011;34(7):567-75. doi: 10.2165/11588470-000000000-00000.
48. Dassanayake TL, Jones AL, Michie PT, Carter GL, McElduff P, Stokes BJ, et al. Risk of road traffic accidents in patients discharged following treatment for psychotropic drug overdose: A self-controlled case series study in Australia. CNS Drugs. 2012;26(3):269-76. doi: 10.2165/11599790-000000000-00000.
49. Pariente A, Fourrier-Réglat A, Ducruet T, Farrington P, Béland SG, Dartigues JF, et al. Antipsychotic use and myocardial infarction in older patients with treated dementia. Archives of Internal Medicine. 2012;172(8):648-53. doi: 10.1001/archinternmed.2012.28.
50. Wijlaars LPMM, Nazareth I, Whitaker HJ, Evans SJW, Petersen I. Suicide-related events in young people following prescription of SSRIs and other antidepressants: A self-controlled case series analysis. BMJ Open. 2013;3(9). doi: 10.1136/bmjopen-2013-003247.
51. Raman SR, Marshall SW, Haynes K, Gaynes BN, Naftel AJ, Stürmer T. Stimulant treatment and injury among children with attention deficit hyperactivity disorder: An application of the self-controlled case series study design. Injury Prevention. 2013;19(3):164-70. doi: 10.1136/injuryprev-2012-040483.
52. Chang CH, Lin JW, Lin CH, Chen HC, Hwang JJ, Lai MS. Effectiveness and safety of extracranial carotid stent placement: A nationwide self-controlled case-series study. Journal of the Formosan Medical Association. 2015;114(3):274-81. doi: 10.1016/j.jfma.2014.05.001.
53. Brauer R, Smeeth L, Anaya-Izquierdo K, Timmis A, Denaxas SC, Farrington CP, et al. Antipsychotic drugs and risks of myocardial infarction: A self-controlled case series study. European Heart Journal. 2015;36(16):984-92. doi: 10.1093/eurheartj/ehu263.
54. Man KKC, Chan EW, Coghill D, Douglas I, Ip P, Leung LP, et al. Methylphenidate and the risk of trauma. Pediatrics. 2015;135(1):40-8. doi: 10.1542/peds.2014-1738.
55. Mikolajczyk R, Horn J, Schmedt N, Langner I, Lindemann C, Garbe E. Injury prevention by medication among children with attention-deficit/Hyperactivity disorder a case-only study. JAMA Pediatrics. 2015;169(4):391-5. doi: 10.1001/jamapediatrics.2014.3275.
56. De Groot MCH, Candore G, Uddin MJ, Souverein PC, Ali MS, Belitser SV, et al. Case-only designs for studying the association of antidepressants and hip or femur fracture. Pharmacoepidemiology and Drug Safety. 2016;25:103-13. doi: 10.1002/pds.3850.
57. Kouvonen A, Vahtera J, Pentti J, Korhonen MJ, Oksanen T, Salo P, et al. Antidepressant use and work-related injuries. Psychological Medicine. 2016;46(7):1391-9. doi: 10.1017/S0033291715002925.
58. Hubbard R, Lewis S, Smith C, Godfrey C, Smeeth L, Farrington P, et al. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. Tobacco Control. 2005;14(6):416-21. doi: 10.1136/tc.2005.011387.
59. Young-Xu Y, Kakkar R, Mills P, Wegner CD. Effect of colchicine on clostridium difficile infection incidence, recurrence, and severity. Infectious Diseases in Clinical Practice. 2015;23(3):141-7. doi: 10.1097/IPC.0000000000000246.
60. Fardet L, Nazareth I, Whitaker HJ, Petersen I. Severe neuropsychiatric outcomes following discontinuation of long-term glucocorticoid therapy: A cohort Study. Journal of Clinical Psychiatry. 2013;74(4):e281-e6. doi: 10.4088/JCP.12m08034.
61. Pratt NL, Ramsay EN, Kemp A, Kalisch-Ellett LM, Shakib S, Caughey GE, et al. Ranibizumab and Risk of Hospitalisation for Ischaemic Stroke and Myocardial Infarction in Patients with Age-Related Macular Degeneration: A Self-Controlled Case-Series Analysis. Drug Safety. 2014;37(12):1021-7. doi: 10.1007/s40264-014-0231-2.
62. Pratt NL, Ramsay EN, Kalisch Ellett LM, Nguyen TA, Roughead EE. Association between ophthalmic timolol and hospitalisation for bradycardia. Journal of Ophthalmology. 2015;2015. doi: 10.1155/2015/567387.
63. Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L. Post-marketing assessment of the safety of strontium ranelate; a novel case-only approach to the early detection of adverse drug

reactions. British Journal of Clinical Pharmacology. 2008;66(5):689-94+751. doi: 10.1111/j.1365-2125.2008.03273.x.
64. Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L. Oral bisphosphonates and risk of atrial fibrillation and flutter in women: A self-controlled case-series safety analysis. PLoS ONE. 2009;4(3). doi: 10.1371/journal.pone.0004720.
65. Wiese AD, Griffin MR, Stein CM, Mitchel EF, Grijalva CG. Opioid Analgesics and the Risk of Serious Infections among Patients with Rheumatoid Arthritis: A Self-Controlled Case Series Study. Arthritis and Rheumatology. 2016;68(2):323-31. doi: 10.1002/art.39462.
66. Correale J, Farez MF, Ysrraelit MC. Increase in multiple sclerosis activity after assisted reproduction technology. Annals of Neurology. 2012;72(5):682-94. doi: 10.1002/ana.23745.
67. Grosso A, Douglas I, Hingorani AD, MacAllister R, Hubbard R, Smeeth L. Inhaled tiotropium bromide and risk of stroke. British Journal of Clinical Pharmacology. 2009;68(5):731-6. doi: 10.1111/j.1365-2125.2009.03517.x.
68. Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJP, et al. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? Alimentary Pharmacology and Therapeutics. 2005;22(3):175-81. doi: 10.1111/j.1365-2036.2005.02543.x.
69. Gibson JE, Hubbard RB, Smith CJP, Tata LJ, Britton JR, Fogarty AW. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. American Journal of Epidemiology. 2009;169(6):761-8. doi: 10.1093/aje/kwn364.
70. Douglas IJ, Evans SJW, Hingorani AD, Grosso AM, Timmis A, Hemingway H, et al. Clopidogrel and interaction with proton pump inhibitors: Comparison between cohort and within person study designs. BMJ (Online). 2012;345(7869). doi: 10.1136/bmj.e4388.
71. Pottegård A, dePont Christensen R, Wang SV, Gagne JJ, Larsen TB, Hallas J. Pharmacoepidemiological assessment of drug interactions with vitamin K antagonists. Pharmacoepidemiology and Drug Safety. 2014;23(11):1160-7. doi: 10.1002/pds.3714.
72. Masclee GMC, Valkhoff VE, Coloma PM, De Ridder M, Romio S, Schuemie MJ, et al. Risk of upper gastrointestinal bleeding from different drug combinations. Gastroenterology. 2014;147(4):784-92.e9. doi: 10.1053/j.gastro.2014.06.007.
73. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. New England Journal of Medicine. 2004;351(25):2611-8. doi: 10.1056/NEJMoa041747.
74. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet. 2006;367(9516):1075-9. doi: 10.1016/S0140-6736(06)68474-2.
75. Corrales-Medina VF, Fatemi O, Serpa J, Valayam J, Bozkurt B, Madjid M, et al. The association between Staphylococcus aureus bacteremia and acute myocardial infarction. Scandinavian Journal of Infectious Diseases. 2009;41(6-7):511-4. doi: 10.1080/00365540902913460.
76. Corrales-Medina VF, Serpa J, Rueda AM, Giordano TP, Bozkurt B, Madjid M, et al. Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. Medicine. 2009;88(3):154-9. doi: 10.1097/MD.0b013e3181a692f0.
77. Dalrymple LS, Mohammed SM, Mu Y, Johansen KL, Chertow GM, Grimes B, et al. Risk of cardiovascular events after infection-related hospitalizations in older patients on dialysis. Clinical Journal of the American Society of Nephrology. 2011;6(7):1708-13. doi: 10.2215/CJN.10151110.
78. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, et al. Influenza infection and risk of acute myocardial infarction in england and wales: A CALIBER self-controlled case series study. Journal of Infectious Diseases. 2012;206(11):1652-9. doi: 10.1093/infdis/jis597.
79. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: A self-controlled case-series study. Clinical Infectious Diseases. 2014;58(11):1497-503. doi: 10.1093/cid/ciu098.

80. Connolly-Andersen AM, Hammargren E, Whitaker H, Eliasson M, Holmgren L, Klingström J, et al. Increased risk of acute myocardial infarction and stroke during hemorrhagic fever with renal syndrome: A self-controlled case series study. Circulation. 2014;129(12):1295-302. doi: 10.1161/CIRCULATIONAHA.113.001870.
81. Thomas SL, Minassian C, Ganesan V, Langan SM, Smeeth L. Chickenpox and risk of stroke: A self-controlled case series analysis. Clinical Infectious Diseases. 2014;58(1):61-8. doi: 10.1093/cid/cit659.
82. Minassian C, Thomas SL, Smeeth L, Douglas I, Brauer R, Langan SM. Acute Cardiovascular Events after Herpes Zoster: A Self-Controlled Case Series Analysis in Vaccinated and Unvaccinated Older Residents of the United States. PLoS Medicine. 2015;12(12). doi: 10.1371/journal.pmed.1001919.
83. Hansen AL, Bi P, Ryan P, Nitschke M, Pisaniello D, Tucker G. The effect of heat waves on hospital admissions for renal disease in a temperate city of Australia. International Journal of Epidemiology. 2008;37(6):1359-65. doi: 10.1093/ije/dyn165.
84. Nitschke M, Tucker GR, Hansen AL, Williams S, Zhang Y, Bi P. Impact of two recent extreme heat episodes on morbidity and mortality in Adelaide, South Australia: A case-series analysis. Environmental Health: A Global Access Science Source. 2011;10(1). doi: 10.1186/1476-069X-10-42.
85. Petersen I, Gilbert R, Evans S, Ridolfi A, Nazareth I. Oral antibiotic prescribing during pregnancy in primary care: UK population-based study. Journal of Antimicrobial Chemotherapy. 2010;65(10):2238-46. doi: 10.1093/jac/dkq307.
86. Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis in pregnancy: A national, primary care-based cohort and self-controlled case series study. American Journal of Respiratory and Critical Care Medicine. 2012;185(7):779-84. doi: 10.1164/rccm.201106-1083OC.
87. Minassian C, D'Aiuto F, Hingorani AD, Smeeth L. Invasive dental treatment and risk for vascular events: A self-controlled case series. Annals of Internal Medicine. 2010;153(8):499-506.
88. Hasegawa K, Tsugawa Y, Chang Y, Camargo CA. Risk of an asthma exacerbation after bariatric surgery in adults. Journal of Allergy and Clinical Immunology. 2015;136(2):288-94.e8. doi: 10.1016/j.jaci.2014.12.1931.
89. Shimada YJ, Tsugawa Y, Brown DFM, Hasegawa K. Bariatric Surgery and Emergency Department Visits and Hospitalizations for Heart Failure Exacerbation: Population-Based, Self-Controlled Series. Journal of the American College of Cardiology. 2016;67(8):895-903. doi: 10.1016/j.jacc.2015.12.016.
90. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. Chest. 2010;137(5):1091-7. doi: 10.1378/chest.09-2029.
91. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. The Lancet. 2010;375(9715):657-63. doi: 10.1016/S0140-6736(09)61963-2.
92. Burton C, Simpson C, Anderson N. Diagnosis and treatment of depression following routine screening in patients with coronary heart disease or diabetes: A database cohort study. Psychological Medicine. 2013;43(3):529-37. doi: 10.1017/S0033291712001481.
93. Harpaz R, Leung JW, Brown CJ, Zhou FJ. Psychological stress as a trigger for herpes zoster: Might the conventional wisdom be wrong? Clinical Infectious Diseases. 2015;60(5):781-5. doi: 10.1093/cid/ciu889.
94. Illingworth JL, Watson P, Xu S, Manford M, Ring H. A method for identifying associations between seizures and possible trigger events in adults with intellectual disability. Epilepsia. 2015;56(11):1812-8. doi: 10.1111/epi.13137.
95. Yom-Tov E, Borsa D, Hayward AC, McKendry RA, Cox IJ. Automatic identification of web-based risk markers for health events. Journal of Medical Internet Research. 2015;17(1):e29. doi: 10.2196/jmir.4082.

96. Prescott HC, Dickson RP, Rogers MAM, Langa KM, Iwashyna TJ. Hospitalization type and subsequent severe sepsis. American Journal of Respiratory and Critical Care Medicine. 2015;192(5):581-8. doi: 10.1164/rccm.201503-0483OC.
97. Park SJ, Choi NK, Yang BR, Park KH, Woo SJ. Risk of stroke in retinal vein occlusion. Neurology. 2015;85(18):1578-84. doi: 10.1212/WNL.0000000000002085.
98. Park SJ, Choi NK, Yang BR, Park KH, Lee J, Jung SY, et al. Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion. Ophthalmology. 2015;122(11):2336-43e2. doi: 10.1016/j.ophtha.2015.07.018.
99. Musonda P. The self controlled case series method: perfonrmance and design in studies of vaccine safety. Phd Thesis, the Open University. 2006.
100. Maclure M, Fireman B, Nelson JC, Hua W, Shoaibi A, Paredes A, et al. When should case-only designs be used for safety monitoring of medical products? Pharmacoepidemiology and Drug Safety. 2012;21(SUPPL. 1):50-61. doi: 10.1002/pds.2330.
101. Whitaker HJ, Ghebremichael-Weldeselassie Y, Farrington CP. On investigating the assumptions of the self-controlled case series method. 2017.

102. Suissa S. Immortal time bias in pharmacoepidemiology. American Journal of Epidemiology. 2008;167(4):492-9. doi: 10.1093/aje/kwm324.
103. Hwang JS, Oh SH, Oh KS, Lee KU, Woo JM, Lee BC, et al. Association of fracture risk with benzodiazepine among adults in South Korea. International Journal of Clinical Pharmacology and Therapeutics. 2015;53(2):163-71. doi: 10.5414/CP202134.
104. Maclure M. The case-crossover design: A method for studying transient effects on the risk of acute events. American Journal of Epidemiology. 1991;133(2):144-53.
105. Hallas J, Pottegård A, Wang S, Schneeweiss S, Gagne JJ. Persistent user bias in case-crossover studies in pharmacoepidemiology. American Journal of Epidemiology. 2016;184(10):761-9. doi: 10.1093/aje/kww079.