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Flexible modelling of vaccine effect in self-controlled case series models

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Summary:

The self-controlled case-series method (SCCS), commonly used to investigate the safety of vaccines, requires information on cases only and automatically controls all age-independent multiplicative confounders, while allowing for an age dependent baseline incidence.

Currently the SCCS method represents the time-varying exposures using step functions with pre-determined cutpoints. A less prescriptive approach may be beneficial when the shape of the relative risk function associated with exposure is not known a priori, especially when exposure effects can be long-lasting. We therefore propose to model exposure effects using flexible smooth functions. Specifically, we used a linear combination of cubic M-splines which, in addition to giving plausible shapes, avoids the integral in the log likelihood function of the SCCS model. The methods, though developed specifically for vaccines, are applicable more widely.

Simulations showed that the new approach generally performs better than the step function method. We applied the new method to two data sets, on febrile convulsion and exposure to MMR vaccine, and on fractures and thiazolidinedione use.

Key words:

exposure effect; M-splines; risk function; self controlled case series; smoothing; vaccines.

1. Introduction

The self controlled case series (SCCS) method is an epidemiological study design used to asses the association between time varying exposures and an adverse event of interest (Farrington, 1995). In the standard SCCS framework, exposure histories are collected for cases, namely individuals who experienced the event of interest at least once, over a defined period during which individuals are observed (the observation period). Appropriate conditioning enables an unbiased estimate of the relative incidence of the event to be obtained, this relative incidence being the ratio of the incidence rate in a predefined post-exposure risk period to the incidence rate at other times (the control period) within the observation period. The method implicitly controls for all measured and non-measured time independent confounding variables that act multiplicatively on the baseline incidence rate, but time-varying confounding variables should explicitly be modelled.

The focus of the present paper is the representation of the relative incidence associated with exposure within SCCS vaccine studies. There has been much work on flexible ways of modelling the exposure effect for standard study designs. These involve representing the exposure history as a convolution of past exposures that combines information about duration, intensity and timing of exposure in one summary measure, as proposed by (Breslow et al., 1983) and (Thomas, 1988). Letting $z(u)$ to be dose or intensity of exposure at time u and $w(u,t)$ a function that assigns weights to past exposures, the weighted cumulative exposure at time t is defined as

$$WCE(t) = \int_0^t z(u)w(u,t)du.$$

Within this context, interest has focused on modelling the weight function $w(u,t)$, whether by a priori parametric models (Vacek, 1997; Langholz et al., 1999; Abrahamowicz et al., 2006)

or spline models of varying complexity (Hauptmann et al., 2000, 2001; Berhane et al., 2008; Sylvestre and Abrahamowicz, 2009), with applications to environmental and drug exposures.

In the case of vaccines, a point exposure occurs at the age of vaccination c, so $z(u)$ is a Dirac delta function. Setting $w(u,t) = w(t-u)$ we obtain the WCE function

$$WCE(t) = w(t-c) \text{ for } t > c, \text{ 0 otherwise.}$$

While our focus is on vaccines, the approach we develop has broader applicability, as will be shown in one of our examples. In current SCCS methodology, $WCE(t)$ is represented by a step function, with pre-determined cutpoints. This is not biologically plausible and may incur losses in efficiency (Greenland, 1995; Weinberg, 1995; Zhao and Kolonel, 1992). Furthermore, a poor choice of cutpoints may be associated with cut-point bias and misclassification (Altman, 1991; Greenland, 1995). We therefore propose a more flexible way of modelling the exposure effect in SCCS studies. We represent the exposure-related relative incidence function (which is a function of time since exposure) as a linear combination of cubic M-spline basis functions, which are variants of B-splines.

The paper is organized in six sections. Section 2 briefly introduces likelihood function of the SCCS model, followed by the representation of the exposure-related relative incidence function as a linear combination of cubic M-splines in Section 3. Section 4 presents a simulation study conducted to evaluate performance of the new method and compare it with the existing step function approach. In Section 5 we present two applications of the new method, to febrile convulsions and MMR vaccine, and to fractures and thiazolidinedione use. And finally in Section 6 we make some final remarks.

2. The case series likelihood

Suppose that cases, indexed by i, $i = 1, ..., N$, are observed from age a_i to age b_i and experience a vector of exposures $x_i(t)$ at age t within the observation period. Events are

assumed to arise with rate $\lambda_i(t|x_i^t)$ where $x_i^t = \{x_i(s) : s \leqslant t\}$ represents the exposure history of individual i up to age t. Thus $x_i^{b_i}$ is the entire exposure history of individual i up to the end of their observation period.

The SCCS conditional likelihood is obtained by conditioning on the number of events, n_i, experienced by an individual i during their observation period $(a_i, b_i]$. Three assumptions are required: (1) events arise in a non-homogenous Poisson process; (2) $\lambda_i(t|x_i^t) = \lambda_i(t|x_i^{b_i})$, which implies that conditioning on n_i does not affect $\lambda_i(t|x_i^{b_i})$; and (3) censoring of individuals at the end of the observation period occurs completely at random, so that the occurrence of the event of interest must not censor or affect the observation period (Farrington, 1995; Farrington and Whitaker, 2006; Whitaker et al., 2006; Weldeselassie et al., 2011). Departures from these assumptions are discussed in (Farrington et al., 2009, 2011).

Suppose that the event intensity is parameterized as a proportional incidence model of the form

$$\lambda_i(t|x_i^t) = \varphi\psi(t)\exp\left\{\gamma_i + x_i(t)^T\beta\right\},$$

where φ is the underlying incidence at some reference age, γ_i is a sum of fixed and random individual effects, and $\psi(t)$ is the age-specific relative incidence function. The SCCS conditional likelihood function is then given by

$$L = \prod_{i=1}^{N}\prod_{j=1}^{n_i}\frac{\psi(t_{ij})\exp\left\{x_i(t_{ij})^T\beta\right\}}{\int_{a_i}^{b_i}\psi(t)\exp\left\{x_i(t)^T\beta\right\}dt}, \tag{1}$$

where t_{ij} is age at the j^{th} event for individual i . From this we can see that SCCS has two major features (1) it automatically controls for all time-independent confounding covariates that act multiplicatively (since these cancel out), and (2) only cases (individuals with at least one event) need to be included in the analysis (since terms with $n_i = 0$ contribute 1 to the likelihood). Note also that, without loss of generality, equation (1) can be rewritten with $n_i = 1$ by simply replicating individuals with more than one event (this is a consequence of the independence stemming from the Poisson assumption).

3. Smooth exposure effect

In this paper we approximate the exposure related relative incidence function by spline functions. This allows us to provide smooth estimates with continuous first two derivatives. Splines are flexible enough to represent a variety of clinically plausible shapes (Smith, 1979). To begin with, we specify a nominal risk period over which the exposure-related relative incidence function can be different from 1; outside this interval (which may be unbounded to the right), the function will take the value 1. The argument of this function is time since start of exposure (in our case, vaccination).

The exposure-related relative incidence function is required to be a positive function. Therefore, we use a linear combination of M-spline basis functions, which are variants of B-splines. An M-spline of order q is thus a positive function constructed by combining pieces of polynomial functions of degree $q-1$ connected at knots (Ramsay, 1988; Ghebremichael-Weldeselassie et al., 2013). To keep positivity of the M-splines when combined linearly, we constrain their coefficients to be positive. Therefore, the function representing the exposure effect in equation (1), $\exp\left\{x_i(t_{ij})^T\beta\right\}$, will be replaced by a function of time since exposure represented as a linear combination of M-splines of order 4:

$$\omega(t-c) = \begin{cases} \sum_{l=1}^{m} g(\beta_l) M_l(t-c), & c \leqslant t \leqslant d \\ 1, & \text{otherwise,} \end{cases}$$

where $g(\beta_l)$ are parameters to be estimated that determine the shape of the function, c is age at start of exposure, d is age at end of the nominal risk period and m is the number of M-spline functions. We shall choose $g(\beta_l) = \beta_l^2$ to ensure positivity of the function. The value m depends on the number of interior knots and the order of M-splines chosen: $m =$ number of interior knots + order. Usually a number of interior knots between 8 and 12 is sufficient (Joly et al., 1998). We choose equidistant knots between 0 and $d-c$, inclusive, and add an extra $q-1$ equidistant knots below the minimum and above the maximum knots to

construct the M-spline basis functions. When $d = \infty$ we set it equal to the maximum value of the b_i.

Replacing the exposure effect in equation (1) by a linear combination of cubic M-splines, the log likelihood function is

$$l = \sum_{i=1}^{N}\sum_{j=1}^{n_i} \log\left(\frac{\psi(t_{ij})(\sum_{l=1}^{m}\beta_l^2 M_l(t_{ij}-c_i))^{I(a_i\leqslant t_{ij}\leqslant d_i)}}{\int_{a_i}^{b_i}\psi(t)(\sum_{l=1}^{m}\beta_l^2 M_l(t-c_i))^{I(a_i\leqslant t\leqslant d_i)}dt}\right). \tag{2}$$

The age-specific relative incidence is represented by a step function, as in the standard SCCS method. Thus, we subdivide the observation period of each case into intervals $(l_{ih}, u_{ih}]$, h indexing the age group, with age-specific relative incidence $\exp(\alpha_h)$. Without loss of generality, we can choose these intervals to be sufficiently narrow (by splitting them) that they are properly contained in $(c_i, d_i]$ or its complement in $(a_i, b_i]$. The log likelihood is then:

$$l = \sum_{i=1}^{N}\sum_{j=1}^{n_i} \log\left(\frac{\exp(\alpha_{h(i,j)})(\sum_{l=1}^{m}\beta_l^2 M_l(t_{ij}-c_i))^{I(c_i\leqslant t_{ij}\leqslant d_i)}}{\sum_h \exp(\alpha_h)\int_{l_{ih}}^{u_{ih}}(\sum_{l=1}^{m}\beta_l^2 M_l(t-c_i))^{I(c_i\leqslant l_{ih}<d_i)}dt}\right). \tag{3}$$

where $h(i,j)$ is the age interval containing t_{ij}.

The integral in the denominator of the log likelihood function (3) can be replaced by a linear combination of integrated splines (I-splines) since the integral of an M-spline function of order q can be expressed as an I-spline of order $q+1$. Hence, denoting the length of interval h for the i^{th} individual by $e_{ih} = u_{ih} - l_{ih}$, our log likelihood function will be:

$$l = \sum_{i=1}^{N}\sum_{j=1}^{n_i} \log\left(\frac{\exp(\alpha_{h(i,j)})(\sum_{l=1}^{m}\beta_l^2 M_l(t_{ij}-c_i))^{I(c_i\leqslant t_{ij}\leqslant d_i)}}{\sum \exp(\alpha_h)(e_{ih})^{(1-I(c_i\leqslant l_{ih}<d_i))}(\sum_{l=1}^{m}\beta_l^2 I_l(u_{ih}-c_i) - \sum_{l=1}^{m}\beta_l^2 I_l(l_{ih}-c_i))^{I(c_i\leqslant l_{ih}<d_i)}}\right). \tag{4}$$

To estimate the parameters of interest from the log likelihood (4), we introduce a penalty term that controls the smoothness of the exposure-related relative incidence function. As in O'Sullivan (1986, 1988) the penalty is based on the second derivative of the linear combination of cubic M-splines. Thus, the penalized log likelihood function is:

$$\begin{aligned} pl &= l - \lambda\int(\sum_{l=1}^{m}\beta_l^2 M_l^{''}(u))^2 du \\ &= l - \lambda((\boldsymbol{\beta_l^2})^T \mathbf{A}\boldsymbol{\beta_l^2}) \end{aligned} \tag{5}$$

where l is the log likelihood in (4), $\mathbf{A}$ is an $m \times m$ matrix with (r, l) element $\int M_r^{"}(u) M_l^{"}(u) du$ and $\lambda \geqslant 0$ is a smoothing parameter that controls the balance between smoothness of the function and fit to the data. One can also use a difference penalty as in (Eilers and Marx, 1996). We choose the smoothing parameter by maximizing an approximate cross-validation score, as proposed by (O'Sullivan, 1988), while keeping the age effect to be constant (i.e. setting the $\alpha_h = 0$). Once λ is chosen we maximize the penalized log likelihood function to estimate the parameters relating to age and exposure effects. The approximate cross-validation score maximized to obtain the optimum smoothing parameter is

$$\bar{V}(\lambda) = l(\hat{\boldsymbol{\beta}}) - \text{tr}([\hat{H} - 2\lambda \mathbf{S}]^{-1} \hat{H}), \tag{6}$$

where $\hat{H}$ is the likelihood component of the hessian evaluated at the penalized MLE, $\hat{\boldsymbol{\beta}}$, and $2\lambda\mathbf{S}$ is the penalized component of the hessian (see (Ghebremichael-Weldeselassie et al., 2013; Joly et al., 1998) for more details). Since we use β_l^2 to keep positivity of the spline function the matrix $\mathbf{S} = 4\left(\mathbf{A}\text{o}(\boldsymbol{\beta}\boldsymbol{\beta}^T)\right) + 2(\text{diag}(\mathbf{A}\boldsymbol{\beta}^2))$ (Ghebremichael-Weldeselassie et al., 2013).

3.1 *Approximate confidence Bands*

Following (O'Sullivan, 1988) and (Joly et al., 2002), we use a Bayesian-like technique to generate confidence bands for the exposure related relative incidence estimators. Considering the penalized log-likelihood function (5) to be a posterior log-likelihood for $\boldsymbol{\beta}$ and the penalty term to be a prior log-likelihood, the approximate covariance of $\hat{\boldsymbol{\beta}}$ is $\hat{V}_{pl}$, where $\hat{V}_{pl}$ is the negative of the inverted hessian of pl evaluated at the penalized maximum log-likelihood estimates. Our approximation of the exposure-related relative incidence function used $g(\beta_l) = \beta_l^2$ to keep positivity of the function, we therefore need to know the covariance of β_{rl}^2. The required covariance matrix can be obtained using the delta method as

$\hat{V}_{tr} = 4\text{diag}(\hat{\boldsymbol{\beta}})[\hat{V}_{pl}](\text{diag}\hat{\boldsymbol{\beta}})^T$. Hence an approximate 95% confidence interval for the exposure-related relative incidence at a point τ is

$$\hat{\omega}(\tau) \pm 1.96\sqrt{M(\tau)^T \hat{V}_{tr} M(\tau)}$$

where τ is time since first exposure and $M(\tau)^T = (M_1(\tau), \ldots, M_m(\tau))$.

Alternatively, to ensure that the confidence bands lie above zero, they can be obtained on the log scale as

$$\hat{\omega}(\tau) \exp\{\pm 1.96\sqrt{M(\tau)^T \hat{V}_{tr} M(\tau)}/\hat{\omega}(\tau)\}.$$

4. Simulation study

To evaluate the performance of the new approach and compare it with the standard SCCS model, we conducted a simulation study. The number of cases was fixed at 1000. The length of the observation period for all cases was chosen to be 730 days, where age at start of observation $a_i = 0$ days and age at end of observation $b_i = 730$ days for all cases. Ages at vaccination c_i were uniformly distributed and generated from a beta distribution.

Four different scenarios of true exposure-related relative incidence functions were considered, generated from beta densities (Figure 1). The risk periods considered in all scenarios were all of length 49 days. The effect of age was represented using a step function in which we used 6 equal age groups with true relative incidence rates $1, 2, 5, 8, 10$ and 15.

[Figure 1 about here.]

Marginal number of events per individual were generated the truncated from Poisson distribution. A multinomial distribution was used to identify in which interval within the observation period the event occurred and then a uniform distribution was used to generate event ages within this interval. For each scenario 100 samples of 1000 cases were generated in this way. These simulated data were then analysed using both the standard SCCS and the new approach with risk periods totalling 49 days following exposure (as simulated) or with

an extended nominal risk period of 98 days. In the standard SCCS, the risk period of 49 days following an exposure was divided in to 7 groups of length 7 days (with 7 parameters). We also used an extended nominal risk period of 98 days, and fitted a standard SCCS model with 14 7-day groups (and 14 parameters). In addition, we fitted the standard SCCS model with 49-day risk intervals (and hence 1 or 2 parameters, according to the nominal risk period). In all the spline-based analyses we used 9 interior knots and the approximate cross-validation score was employed to choose the smoothing parameter.

[Figure 2 about here.]

Figure 2 shows the estimated exposure-related relative incidence curves obtained by fitting the spline-based method to the 100 randomly selected samples. The top row in the figure presents results obtained when the risk period is kept at 49 days post exposure (which is equal to the risk period used to simulate the data) and in the bottom row are the results when a nominal risk period of 98 days was used. The results show that the shapes of the true relative incidence curves (white lines) were captured well by most of the estimated curves and are all are included within the range of estimated curves in all scenarios.

[Table 1 about here.]

Table 1 shows that the mean integrated square errors (MISE) are all lower for the spline method than the standard method, except for scenario 2, in which the true exposure-related relative incidence was constant. For this scenario, the correctly specified step function model (with 1 or 2 parameters), though interestingly not the over-specified step function model (with 7 or 14 parameters), outperforms the spline model. Comparable if slightly degraded results were obtained for scenarios 1, 3 and 4 with the 98-day nominal risk period as with the correct 49-day risk period. For scenario 2, the spline method produced much worse results with 98 day compared to 49 day risk periods.

Figure 3 shows the bias (top row) and variability (standard deviation, bottom row) of

estimates from the standard (with 7 parameters) and spline-based SCCS methods with a 49 day nominal risk period. The bias of the standard method has a saw-tooth appearance in scenarios 1, 3 and 4 related to discontinuities at the cutpoints, whereas the spline method occasionally showing some bias at endpoints, notably for scenarios 2 and 3. The spline method produces lower standard deviations, except at the endpoints.

[Figure 3 about here.]

5. Applications

5.1 *Febrile convulsion and MMR vaccine*

The new approach was applied to data on febrile convulsions and measles/mumps/rubella (MMR) vaccine. The dataset comprises 2389 children aged between 28 and 730 days in the period 1991-1994. They experienced 3826 febrile convulsion events in total. In this example we used 50 days post MMR vaccine for all cases to represent the exposure effect with splines. Since all individuals have the same nominal risk period of 50 days, we defined 12 equidistant inner knots between 0 and 50 days. Age was included in the model as a step function. There were 21 age groups of length 30 days while the first and last groups were of length 32 and 40 days respectively. A linear combination of cubic M-splines was used to represent the MMR-related relative incidence function. The value of the smoothing parameter selected by the approximate cross-validation score was 0.031. We present the relative incidence function estimated by maximizing the penalized log likelihood function (5) along with its approximated confidence bands in Figure 4. The figure shows no risk of febrile convulsion in the first 3 days post MMR vaccination and a borderline non-significant relative incidence of 1.248 at the 4^{th} day. However, there is a significantly increased risk between 5 and 11 days after exposure to the vaccine. The relative incidence at the 5th day is 1.922 and increases smoothly to 3.647 at the 8th day and then the risk decreases to 1.244 at 12 days since exposure. There is also an increased risk of febrile convulsion due to MMR vaccine between 19 and 21 days post vaccination. At all other times after vaccination there is no significantly increased risk of febrile convulsion.

[Figure 4 about here.]

Figure 5 compares the effects of exposure to MMR vaccine estimated by the standard SCCS (step function) and the spline based (smooth function) methods. The standard model was fitted by defining 10 exposure groups with cut points at $6, 11, 18, 22, 26, 30, 36, 40$ and 45

days since vaccination and 21 age groups as described above. The results given by the two methods are similar, though different categorizations give different results for the standard method.

[Figure 5 about here.]

5.2 *Fractures and Thiazolidinediones*

The methods developed in the present paper can be applied more widely. We illustrate this with data on fractures and thiazolidinediones, which were analysed by (Douglas et al., 2009) using the standard case series method. The aim of the study was to investigate whether there is an increased risk of fracture associated with the use of thiazolidinediones, a class of medicines used to treat type 2 diabetes. The data used in the analysis were primary care computerized clinical records from the United Kingdom-based General Practice Research Database (GPRD). 1819 patients aged about 40 years or older prescribed at least one thiazolidinedione and with at least one fracture were included in the analysis. The data included patients with multiple fractures: 283 (16%), 64 (4%), and 25 (1%) had two, three, and four or more fractures, respectively. Multiple fractures were includedin the analysis if the fractures happened at different sites or at the same site but at least 6 months apart.

In (Douglas et al., 2009) the authors defined the control period to be from start of observation period until first prescription of a thiazolidinedione and the risk period was from age at start of thiazolidinedione use until age at end of observation period. The length of exposure following each individual prescription was calculated using information recorded in the GPRD on pack size and dosing frequency. Thiazolidinedione treatment was assumed to be continuous where any apparent treatment break was less than 60 days, to allow for partial noncompliance and situations where patients may have built up treatment stocks (Douglas et al., 2009). Age at end of observation was then taken to be age at the earliest of any treatment break longer than 60 days or the end of recorded follow up in the database.

The mean duration of control periods prior to thiazolidinedione use was 9.5 years, and the mean duration of exposure to a thiazolidinedione was 2.3 years.

Unlike vaccines, thiazoledinediones are not point exposures, however we can use a similar approach as with vaccines since $z(u) = z$ for $u > c$, the age at first thiazeledinedione, so $WCE(t) = z \int_c^y w(t-u)du$. We reanalyzed the data using the new version of SCCS where time since exposure is represented by a linear combination of M-splines. In our analysis, we used the same exposure risk periods as in (Douglas et al., 2009). The maximum duration of exposure to thiazolidinedione was 2364 days. Hence our exposure-related relative incidence function was represented by a linear combination of cubic M-splines defined between 0 and 2364 days since first exposure. We chose 14 equidistant knots between 0 and 2364 days inclusive, i.e we have 16 M-spline basis functions. The time-varying confounding covariate age was taken into account using a piecewise constant function with 42 age groups: the first age group is less than 14610 days (40 years) of age, followed by 5 age groups of length two years, 28 groups of 1 year length, 7 groups of length two years and the last age group with age greater than 33603 days.

To estimate the parameters we first selected the optimum smoothing parameter, λ, that maximizes the approximate cross-validation score in equation (6). This optimum λ was 288. We then maximized the penalized log likelihood function in (4) for fixed $\lambda = 288$ to get the required parameters. The estimated exposure relative incidence function and its approximate confidence bands are presented in Figure 6.

[Figure 6 about here.]

From Figure 6, it can be seen that the relative incidence of fracture due to thiazolidinedione use increases as time since exposure increases. There is no significant increased risk of fracture in the first two months of exposure and the relative incidence is borderline significant from two months to about 1 year and half, but there is a significantly increased risk of fracture

due to exposure to thiazolidinedione thereafter, and the maximum relative incidence of 2.103 is reached after about 5 years of exposure. The relative incidence may start to decrease and the confidence bands widen after 5 years.

In their parametric SCCS analyis, (Douglas et al., 2009), defined five exposure groups of $(0-1), (1-2), (2-3), (3-4)$ and $(4-7)$ years since first exposure and obtained relative incidence estimates of $1.26, 1.49, 1.70, 2.31$, and 2.00 respectively. We repeated the analysis but with a different number and length of exposure groups. We divided the time since first exposure in to 13 groups of lengths 6 to 9 months. Results from this analysis are presented in Figure 7 and are similar to those obtained by the spline method.

[Figure 7 about here.]

6. Final remarks

We have proposed using regression splines to model the effect of point exposures due to vaccination, and drug-related exposures more widely, in the self-control controlled case series method. We model the exposure-related relative incidence function using as a linear combination of cubic M-splines. This approach avoids the limitations of the standard SCCS method that uses step functions with pre-specified cutpoints to assess the exposure effect.

Our spline-based SCCS method can be considered as a special case of weighted cumulative exposure models used in environmental epidemiology, which have also made good use of spline models (Hauptmann et al., 2000; Sylvestre and Abrahamowicz, 2009). These approaches have used information criteria to choose the knots in defining the B-spline basis functions. In our case, we intentionally selected a large number of knots and introduced a penalty term to the log likelihood function to avoid overfitting, the smoothing parameter being chosen by an approximate cross validation score (O'Sullivan, 1988; Joly et al., 1998, 2002).

Simulation studies showed that the new approach generally has a better performance than the use of step functions. The new method was applied to two data sets to investigate the association between febrile convulsions and MMR, and between fracture and thiazolidinedione use. The estimates obtained from the new method are consistent with the results from the standard SCCS method when the exposure groups are correctly specified. Increasing number of a priori defined exposure groups in standard SCCS model may help in capturing the true exposure-related relative incidence curve better, but at the cost of reduced efficiency. The new method is likely to be particularly useful in the absence of a clear, a priori hypothesis regarding the risk period. It can also be used to obtain an overall risk profile, or, if required, to specify risk periods upon which to base standard SCCS analyses in other data sets.

While our focus has been on developing methods for studying the safety of vaccines, they have wider applicability, as we have shown in our example on fractures and thiazolidinediones.

Further extension of the spline-based SCCS method to non-vaccine pharmacoepidemiology, notably to incorporate the effect of dose within a more general weighted cumulative exposure model framework, would be desirable.

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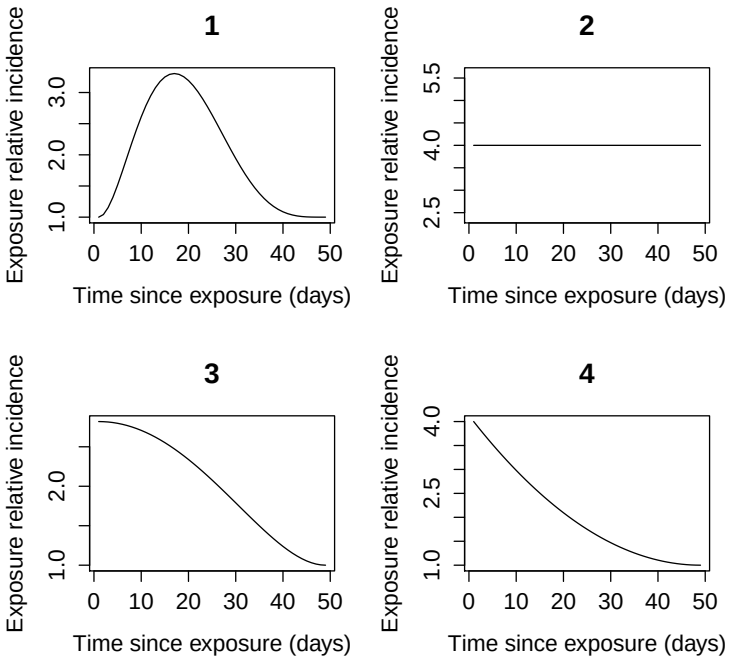


Figure 1. True exposure related relative incidence curves used in simulating the samples

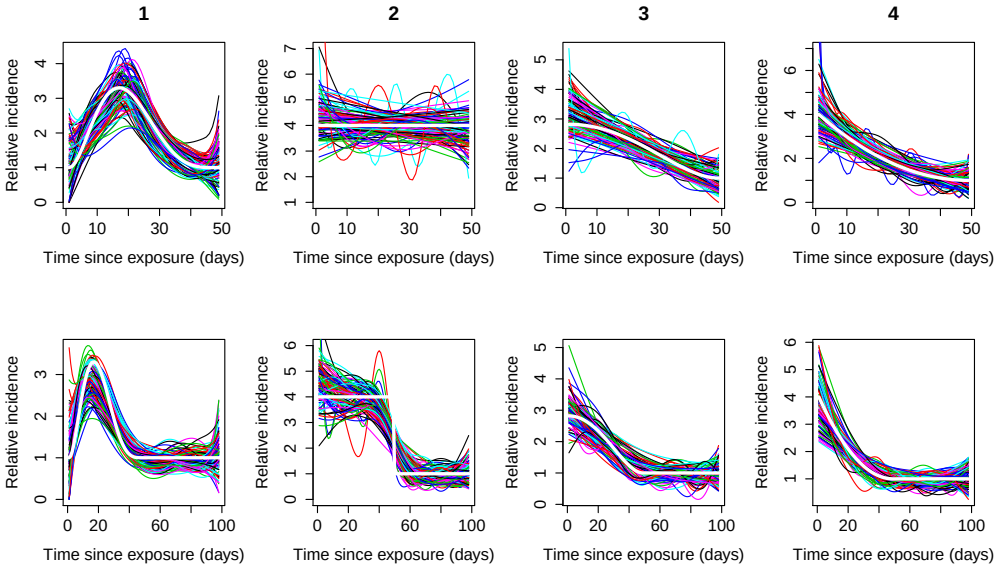


Figure 2. Estimated relative incidence curves obtained from fitting spline-based SCCS to 100 randomly selected samples with the true relative incidence function in thick white. Top row: 49 day nominal risk period; bottom row: 98 day nominal risk period.

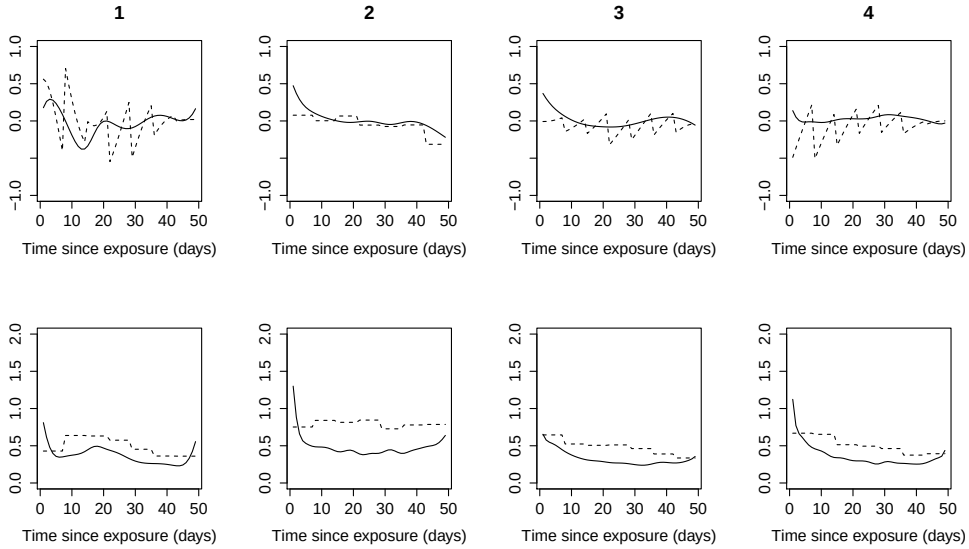


Figure 3. Bias (top row) and standard deviation (bottom row) of estimates obtained by fitting spline-based SCCS (solid lines) and standard SCCS (dotted lines).

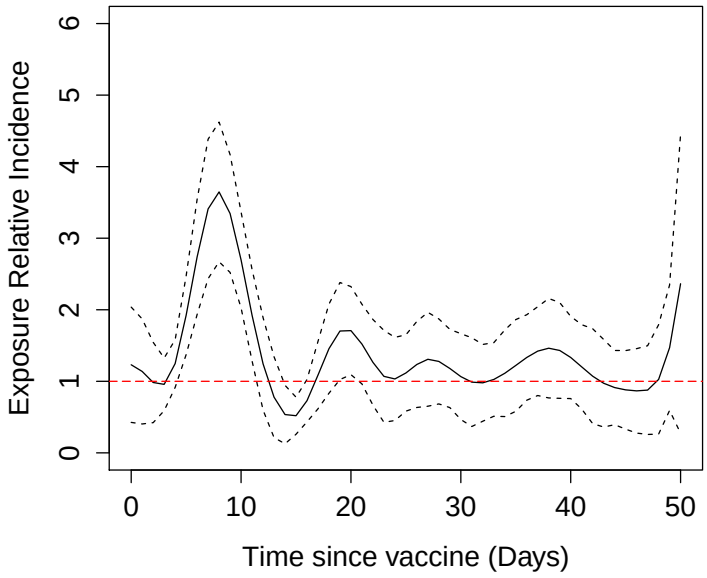
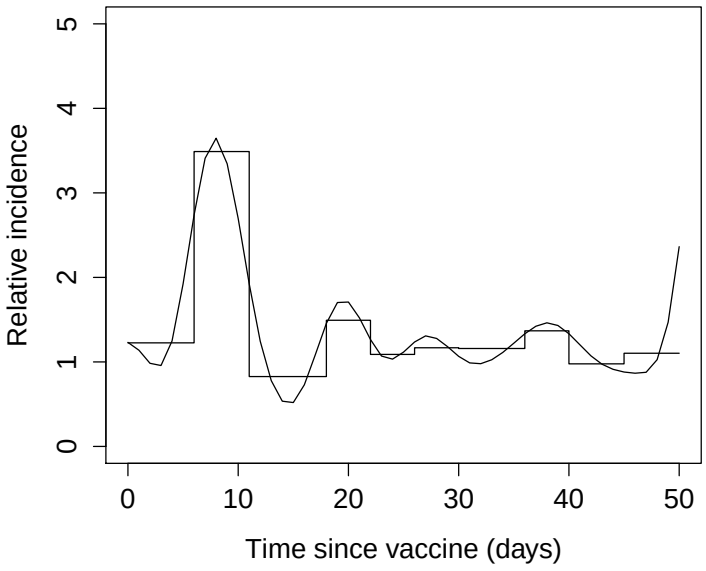


Figure 4. Smooth estimate of the relative incidence function related to exposure to MMR vaccine (bold line) and 95% confidence bands(doted lines).



and spline.pdf

Figure 5. Relative incidence functions related to MMR vaccine estimated from fitting the standard model with 10 exposure groups (step function) and spline-based SCCS (smooth function).

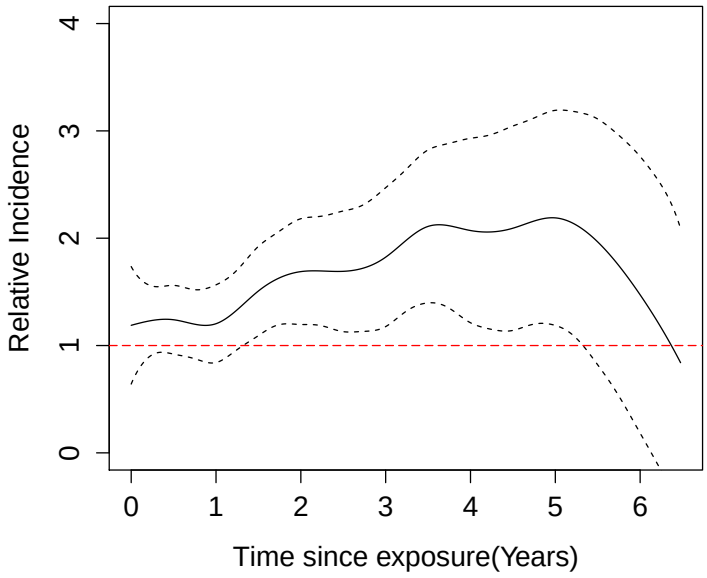


Figure 6. Relative incidence function estimate related to thiazolidinedione use (bold line) and 95% confidence intervals (dotted lines).

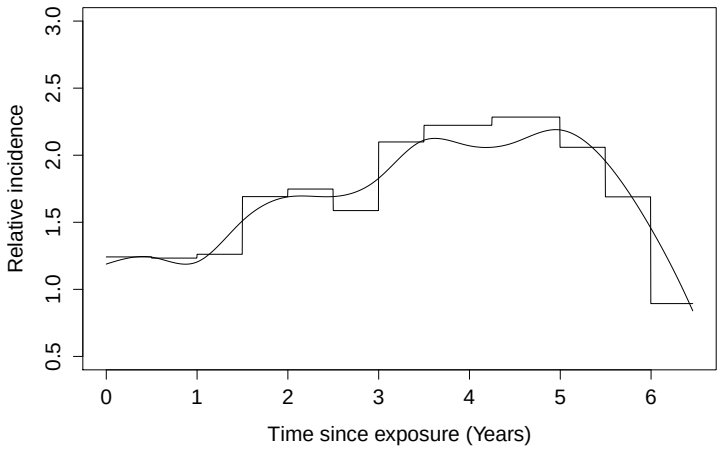


Figure 7. Relative incidence functions related to thiazolidinedione use estimated from fitting the standard model with 13 exposure groups (step function) and the spline-based SCCS (smooth function).

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Table 1

Mean integrated square error (MISE) and standard deviation (SD) obtained from spline-based and standard SCCS models. Each simulated data set was fitted twice by the two methods with nominal risk periods of 49 and 98 days

	Spline-based SCCS		Standard SCCS with groups of length 7 days		Standard SCCS with groups of length 49 days	
Scenario	MISE	SD	MISE	SD	MISE	SD
Potential risk length of 49 days						
1	7.982	5.685	14.993	8.202	37.934	3.494
2	9.575	10.190	31.368	16.434	5.498	7.559
3	5.453	5.625	12.338	6.207	22.388	2.924
4	6.478	8.376	14.650	7.300	43.490	4.593
Potential risk length of 98 days						
1	14.875	7.096	20.072	7.926	38.121	3.414
2	34.112	13.747	38.750	18.549	8.012	10.127
3	6.439	5.283	20.000	18.791	22.654	2.659
4	8.151	6.823	19.037	8.201	44.232	3.059