SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Article

Statistical Methods in Medical Research
2019, Vol. 28(1) 248–262

DOI: 10.1177/0962280217720947
journals.sagepub.com/home/smm
SAGE

Competing risks modeling of cumulative effects of time-varying drug exposures

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Abstract

An accurate assessment of drug safety or effectiveness in pharmaco-epidemiology requires defining an etiologically correct time-varying exposure model, which specifies how previous drug use affects the hazard of the event of interest. An additional challenge is to account for the multitude of mutually exclusive events that may be associated with the use of a given drug. To simultaneously address both challenges, we develop, and validate in simulations, a new approach that combines flexible modeling of the cumulative effects of time-varying exposures with competing risks methodology to separate the effects of the same drug exposure on different outcomes. To account for the dosage, duration and timing of past exposures, we rely on a spline-based weighted cumulative exposure modeling. We also propose likelihood ratio tests to test if the cumulative effects of past exposure on the hazards of the competing events are the same or different. Simulation results indicate that the estimated event-specific weight functions are reasonably accurate, and that the proposed tests have acceptable type I error rate and power. In real-life application, the proposed method indicated that recent use of antihypertensive drugs may reduce the risk of stroke but has no effect on the hazard of coronary heart disease events.

Keywords

Survival analysis, competing risks, time-dependent covariates, simulations, pharmaco-epidemiology

1 Introduction

Post-marketing studies of the safety and effectiveness of drugs already being used in clinical practice are essential to improve prescribing practices and reduce risks of serious adverse events. Indeed, drugs are approved for therapeutic effects but many have serious unsuspected adverse effects, un-detected in pre-marketing trials.[1] Yet, population-based observational pharmaco-epidemiological studies that aim at assessing the putative associations of adverse events with drug exposures face several methodological challenges.[2–5] One important challenge, common to both clinical trials and observational studies of the effects of drug use, relates to the need to account for competing risks of other clinical endpoints, the occurrence of which may prevent the researchers' ability to observe the adverse event of primary interest.[3–5] Another challenge, specific to post-marketing pharmaco-epidemiological studies of drug safety or effectiveness is related to the need to account for the fact that, in real-life clinical practice, both the exposure status and its intensity (dose) vary between patients and also within patients over time.[2–3] The current paper is motivated by our belief that population-based studies of drug safety and effectiveness have to deal simultaneously with analytical challenges related to both time-varying drug exposures and competing risks. Accordingly, we first discuss each issue in more detail, and then propose a new flexible model that attempts to deal with both challenges.

In the vast majority of recent population-based pharmaco-epidemiological studies, exposure modeling has been limited to crude measures, such as current drug use or current dose.[6–9] Yet, an appropriate representation of the time-varying exposure is needed to understand how past dosage history affects the current risk,[10] which may help to achieve an optimal trade-off between therapeutic benefits and risks of adverse event.[3,11] Adequate modeling of such complex time-dependent exposures poses several challenges.[3,12–14] Indeed, prior knowledge about

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pharmaco-dynamics/kinetics of a given drug is usually not sufficient to formally determine how past and recent exposures/doses may affect the current hazard of the clinical event of interest[15] especially in the real-life clinical context, where actual users may have substantially different characteristics from the volunteers studied in pre-approval trials.[16] Yet, mis-specification of the model describing the association between a time-varying exposure and the hazard may lead to biased estimates and incorrect conclusions,[12,14] and may affect both the probability[17] and the timeliness of adverse effects detection.[18] Because the impact of past use of most drugs on health outcomes cumulates over time,[19,20] and because the relative importance of past doses likely depends on their timing,[14,19–24] the concept of *weighted* cumulative exposure (WCE) has been proposed as a comprehensive assessment of the impact of various aspects of time-varying exposure to medication in time-to-event analyses.[25] The WCE model defines the following aggregate time-dependent exposure metric

$$WCE(u) = \sum_{t \leq u}^{u} w(u-t)X(t) \tag{1}$$

where u is the current time when the hazard is evaluated; $t \leq u$ indexes times of exposure preceding u, $X(t)$ represents the past exposure intensity (e.g. drug dose) at time $t \leq u$; and the weight function $w(u-t)$ assigns the differential importance weights to past doses, depending on the time elapsed since the dose was taken $(u-t)$.

Since, in most applications, prior knowledge is not sufficient to determine a specific analytical form, or shape, of the weight function $w(u-t)$, Sylvestre and Abrahamowicz[26] proposed a flexible method that uses cubic regression splines to estimate the weight function directly from the data. Recent applications of the flexible WCE model in time-to-event analyses yielded new insights regarding adverse effects of several drugs.[10,27–30]

In all aforementioned real-life applications, $WCE(u)$ was included as a time-dependent covariate in the multivariable Cox proportional hazards model, to estimate the adjusted effect of time-varying drug exposure on the hazard of the *single* adverse event of interest. However, studies of drug safety and/or effectiveness must account for competing risks since the occurrence of the adverse event of interest is almost always prevented by the main outcome of the time-to-event analysis, or other adverse events.[4] Indeed, the use of the same drug may affect the risks of more than one adverse event,[1] and the impact of drug exposure may vary across different outcomes[31] (involving different biological mechanisms). For example, WHO classification of adverse events includes both (a) acute events, whose risks depend mostly on very recent exposures or doses and (b) long-term, lagged or cumulative effects, which may depend on exposure history extending over several months or even years. The need to use the competing risks approach to account for different associations of drug exposure history with alternative "competing" events has been emphasized in several recent methodological reviews.[3,4,32,33] For example, competing risks analyses should be the approach of choice while assessing the associations of drug use with deaths,[3,4,32,33] as the same drug may affect differently mortality due to different causes.[3] Furthermore, the competing risks analysis offers a straightforward way to avoid using the "composite endpoints", such as, e.g. (i) occurrence of coronary heart disease or stroke or (ii) death of any cause or cancer recurrence, which may be inappropriate if the effects of a drug vary substantially across different "component events".[34,35]

In this paper, we attempt to simultaneously address challenges related to both: (a) the need for flexible modeling of the cumulative effects of time-varying exposures and (b) competing risks. To this end, we develop, and validate in comprehensive simulations, a new approach that extends the flexible WCE approach[26] to modeling of separate cumulative effects of the same drug exposure on the hazards of different "competing" outcomes. In particular, we rely on hazards-based approach to model competing risks,[4] as described by Holt,[36] Putter et al.,[37] and Andersen and Borgan,[38] and extend it to flexible modeling of the cumulative effects of time-varying exposures. Section 2 first introduces the basic concepts of the competing risks methodology, and then describes how we adapt it to develop the flexible competing risks WCE model. Section 3 describes the methods of the simulations, designed to assess the performance of the proposed model, while Section 4 summarizes the simulation results. Section 5 illustrates a real-life application of this new method, to re-assess, and compare separate cumulative effects of past doses of selected antihypertensive drugs on the hazards of: (i) serious coronary heart disease events *versus* (ii) stroke. We conclude the paper with a discussion.

2 Methods

2.1 Competing risks setting

In competing risks setting, each subject is followed until the first occurrence of the earliest among the $K \geq 2$ different types of mutually exclusive events or until a censoring time.[39,40]

The event-specific hazard function $\lambda_{i,k}(t)$ represents the instantaneous risk of the occurrence of event k, $k=\{1,\ldots,K\}$, given that the subject i did not experience any event until time t (implying $T_i \geq t$ where T_i is the time of the first event for this subject)

$$\lambda_{i,k}(t) = \lim_{dt\to 0}\left\{\frac{P(t \leq T_i < t+dt, K=k|T_i \geq t)}{dt}\right\} \tag{2}$$

Holt[36] and Andersen and Borgan[38] showed that the usual survival methods, developed for analyses limited to a single endpoint, such as Cox PH model and its flexible extensions, could be extended to the competing risks setting since the cause-specific hazards are identifiable. The analyses should consider all the competing risks. One approach is to fit K separate models, each corresponding to one of the K competing events, with censoring at each of the remaining events.[37] An alternative is to estimate a single competing risks model that simultaneously estimates the hazards of each of the competing events.[37] This approach may be conveniently implemented using the data augmentation approach as described by Lunn and McNeil,[41] and expanded by Belot et al.[42] to flexible modeling of baseline hazards and of time-dependent effects of time-invariant covariates.

2.2 Flexible WCE model for competing risks analyses

In this section, we extend the flexible modeling of cumulative effects of a time-varying exposure to competing risks approach, and, at the same time, relax the original proportionality assumption.[42] Suppose, for subject i, individual exposure intensity or dose $X_i(t)$ varies over follow-up time t. We propose to represent the joint effect of past exposures on the hazard of a given event k at time u, for subject i, by the time-dependent WCE metric[25]

$$WCE_{k,i}(u) = \sum_{t}^{u} w_k(u-t)X_i(t) \tag{3}$$

where $X_i(t)$, $t \leq u$, represent the individual dose at time t, and the weight function $w_k(u-t)$ assigns weights to past doses, depending on the time elapsed since they were taken $(u-t)$.

Because in most pharmaco-epidemiological applications there is no sufficient knowledge to determine the functional form of the weight function,[12] we adapt the flexible modeling approach of Sylvestre and Abrahamowicz,[26] who use (un-penalized) cubic regression B-splines to model the weight function

$$w_k(u-t) = \sum_{j=1}^{m} \theta_{kj}B_j(u-t) \tag{4}$$

where B_j, $j=\{1,\ldots,m\}$ represent the m functions in the cubic B-spline basis, common for all events $k=\{1,\ldots,K\}$, while θ_{kj}, $j=\{1,\ldots,m\}$ are the estimable coefficients, related to event k, for the respective splines in this basis.

The spline basis is defined over a time window [0, a], where user-specified parameter a represents the maximum length of etiologically relevant exposure time window over which past exposures may affect current hazard. In other words, past doses $X(t)$ at $t<(u-a)$ are a priori assumed to have no impact on the hazard at time u and, thus, are assigned the weights of 0. The values of l interior knots, with $l=1$, 2 or 3 (with higher l implying more flexible weight function), are a priori fixed, and typically uniformly distributed within the time window [0, a].[26]

An extension to competing risks analyses of the WCE model implies modeling the kth event-specific hazard of for subject i as follows

$$\lambda_{i,k}\left(u\middle|\left\{X_i(t),Z_i(u)\right\}\right) = \lambda_{0k}(u)\exp\left[\beta_k\sum_{t\leq u}^{u}\sum_{j=1}^{m}\theta_{kj}B_j(u-t)X_i(t) + \sum_{s=1}^{p}\mu_{ks}Z_{i,s}(u)\right] \tag{5}$$

where $\lambda_{0k}(u)$ represents the event-specific "baseline" hazard function for the event k at time u, i.e. the hazard of a subject not exposed at all during the time window $[u-a, u]$, with covariate vector $\mathbf{Z}_i(u)=0$, and μ_{ks} represents the vector of the log hazard ratio (HR) for the set of covariates $Z_{is}(u)$, that may include both time-dependent covariates and time-fixed covariates. Finally, $\beta_k\sum_{t\leq u}^{u}\sum_{j=1}^{m}\theta_{kj}B_j(u-t)X_i(t)$ represents the adjusted log HR, for event k, estimated using the WCE metric, for individual i at time u.

However, the model in (5) is non-identifiable, as an infinite number of the combinations of the values of β_k and of the vector of the spline coefficients θ_{kj} will yield the same product.[17,26] To avoid such identification problems, we re-parametrize the model by defining $\gamma_{kj} = \beta_k \theta_{kj}$, and use artificial time-dependent covariates, which allow estimation of different flexible time-varying survival analytical models using standard software for fitting Cox model with time-dependent covariates.[26,43] Specifically, we define a series of $4 + l$ (where l represents the number of interior knots) artificial time-dependent covariates

$$D_{i,j}(u) = \sum_{t}^{u} B_j(u - t) X_i(t) \tag{6}$$

For each subject i, each $D_{i,j}(u)$ in (6) is calculated as a function of (i) pre-defined cubic B-spline basis $B_j(u - t)$, $j = 1, \ldots, l + 4$, and (ii) doses $X_i(t)$ the subject received during the relevant time window $t \in [u - t,\ u]$. Once the matrix D_i is calculated, we fit a *single* flexible competing risks WCE model, that simultaneously estimates the hazards of each of the competing events, by using data augmentation[41]

$$\lambda_{i,k}\left(u \middle| \{X_i(u), Z_i(u)\}\right) = \lambda_{0k}(u) \exp\left[\sum_{j=1}^{m} \gamma_{kj} D_{i,j}(u) + \sum_{s=1}^{p} \mu_{ks} Z_{i,s}(u)\right] \tag{7}$$

The functions $\log[\lambda_{0k}(u)]$, $k = \{1, \ldots, K\}$ are modeled by cubic regression B-splines with one interior knot, located at the median of the un-censored event times.[42] A procedure based on split data is used to obtain full maximum likelihood estimation. This procedure allows approximation of the contribution of each individual to the full log-likelihood by a sum of Poisson terms on time interval that is sufficiently small for the assumption of a constant hazard to be acceptable.[42] Fitting a single model, that specifies each of the event-specific weight function and estimates them simultaneously, facilitates both the interpretation of the estimates and the testing of the relevant hypotheses discussed in Section 2.4. An alternative parameterization of equation (7) is discussed in Section 1 of the Supplementary Material.

In real-life applications, it is often difficult to determine a priori both (a) the length of the time window $[u - a,\ u]$ over which past exposures may be still relevant for the current hazard at time u; and (b) how much flexibility is necessary to capture the underlying weight functions $w(u - t)$ without incurring substantial over-fit bias. Therefore, as in previous publications, we recommend fitting a limited number of alternative versions of model (7), corresponding to combinations of (a) two to four different time windows and (b) 1, 2 or 3 interior knots.[17,26] Then, we use the Akaike information criterion (AIC)[44] to select the best-fitting WCE model (7).

2.3 The weight function and its constraints

In many applications, it may be a priori evident that the weight function $w_k(u - t)$ should smoothly decay to 0 at one or both ends of the support interval $[0,\ a]$. This will imply imposing some boundary constraints on the estimate.[26] For example, if the value of $X(u - a)$ is assumed to have no impact on the current risk at u, the weight function and its first derivative can be both constrained to be equal to zero at $t = u - a$, simply by constraining the two last spline coefficients to zero: $\theta_{k,m-1} = \theta_{k,m} = 0$. Similarly, if the lagged exposure effect is assumed[45] so that the current value $X(u)$ has no impact on the current hazard, similar constraints can be imposed on the two first coefficients: $\theta_{k,1} = \theta_{k,2} = 0$. If the aforementioned constraints seem plausible but not a priori necessary, likelihood ratio tests (LRT) with 2 to 4 degrees-of-freedom (df) can be used to test if the unconstrained model offers a significantly better fit than the model with constraints at, respectively, one or both ends of the support interval.[26] The results of such LRT may, by themselves, provide useful model diagnostics. For example, the rejection of the null hypothesis for the constraint at $(u - a)$ may indicate that the pre-specified support window $[0,\ a]$ is too short to capture the full impact of past exposures,[26] suggesting extending the time window to a more distant past.

2.4 Hypothesis testing

In the competing risks setting, one question of potential practical and etiologic interest is whether the exposure has the same or different effects on each of the alternative events.[46,47] In our context of modeling cumulative effects, this question requires assessing whether the ways the effects of past exposures cumulate over time are different between the competing events. To this end, in the case of two competing events, $k = \{1,\ 2\}$, we need to

discriminate between three alternative WCE models. The simplest Model 1 assumes that both weight functions are identical $w_1(u\text{-}t) = w_2(u-t)$

$$\lambda_{ik}\left(u\middle|\left\{X_i(u), Z_i(u)\right\}\right) = \lambda_{0k}(u)\exp\left[\beta_{\text{mod.1}}WCE(u) + \sum_{s=1}^{p}\mu_{ks}Z_{i,s}(u)\right] \tag{8}$$

The intermediate Model 2 assumes that the relative importance of exposures that occurred at different times in the past $(u-t)$ is the same for both events, but the strength of the resulting WCE varies between the two events. Formally, this implies that the two weight functions have the same shape, i.e. are proportional to each other $w_2(u-t) = C.w_1(u-t)$, with $C \neq 1$. To implement Model 2, we use a two-stage approach. At the first stage, we fit the Model 1. Then, we consider the resulting estimated "common" weight function as a known ("fixed") covariate, i.e. assign to each subject, at each time, the value of $WCE(u)$ calculated using the spline coefficients estimated at stage 1. Finally, at stage 2 we fit the model in equation (9) where only the two coefficients $\beta_{\text{mod.2}}$ and $\beta_{\text{mod.2.2}}$ are estimated, in addition to covariate effects

$$\lambda_{ik}\left(u\middle|\left\{X_i(u), Z_i(u)\right\}\right) = \lambda_{0k}(u)\exp\left\{\beta_{\text{mod.2}}[\beta_{\text{mod.1}}WCE(u)] + \beta_{\text{mod.2.2}}\delta_2[\beta_{\text{mod.1}}WCE(u)] + \sum_{s=1}^{p}\mu_{ks}Z_{i,s}(u)\right\} \tag{9}$$

Finally, Model 3 assumes that the two weight functions are "qualitatively" different, i.e. have different shapes, implying the relative importance of exposure intensity observed at different times does vary depending on the endpoint event. Model 3 simply estimates two separate weight functions

$$\lambda_{ik}\left(u\middle|\left\{X_i(u), Z_i(u)\right\}\right) = \lambda_{0k}(u)\exp\left\{\beta_{\text{mod.3.1}}\delta_1 WCE_1(u) + \beta_{\text{mod.3.2}}\delta_2 WCE_2(u) + \sum_{s=1}^{p}\mu_{ks}Z_{i,s}(u)\right\} \tag{10}$$

The three models are nested. Model 1 is a special case of Model 2, with $\beta_{\text{mod.2}} = 1$ and $\beta_{\text{mod2.2}} = 0$. Model 2 is a special case of Model 3, where $\beta_{\text{mod.3.1}} = \beta_{\text{mod.2}} \times \beta_{\text{mod.1}}$ and $\beta_{\text{mod.3.2}} = \beta_{\text{mod.1}}(\beta_{\text{mod.2}} + \beta_{\text{mod.2.2}})$, which would imply $C = 1 + \frac{\beta_{\text{mod2.2}}}{\beta_{\text{mod2}}}$. The three models use, respectively, $(2m+q)$, $(2m+q+1)$, and $(2m+2q)$ df to model the WCE effects, m and q representing the number of coefficients used to model, respectively, each of the baseline hazards and a single weight function. Thus, their respective deviances can be compared using LRT with either 1 df (Model 2 vs. Model 1) or $(q-1)$ df (Model 3 vs. Model 2). In simulations, we assess the type I error rates and/or the empirical power of the resulting LRTs, under different assumptions about the "true model".

3 Simulation studies

To validate our model, we simulated a hypothetical prospective cohort study of the associations between time-varying exposure to a single drug and times to two competing events. The cohort consisted of 500 new users of the drug, and time zero was defined as the first day of the drug use. Individuals could interrupt and resume their treatment repeatedly. The follow-up was limited to one year. Section 2 of the Supplementary Material provides details of the generation of the matrix of individual time-varying patterns of daily drug doses, which was kept fixed across the simulations. The three sub-sections below describe (i) the selection of alternative weight functions and parameters used in different data-generation scenarios, (ii) the generation of event times conditional on the WCE, calculated using the weight function selected in step (i) and (iii) how the simulated datasets were analyzed.

3.1 Weight functions

In all simulations, the current hazards for both events were assumed to depend on the current value of the time-varying covariate representing the WCE, which aggregated the information on the doses taken by a given subject in the past half a year (180 days), using equation (3) with the pre-specified event-specific weight functions. We considered seven different scenarios, each corresponding to a different pair of the "true" weight functions for the two competing events ($k = \{1, 2\}$). Each weight function $w_k(u-t)$ shows the relative impact of doses taken $(u-t)$ days ago on the hazard for event k at time u. This determines also how the impact of current dose changes with increasing time since exposure.[48] Details are provided in Section 3 of the Supplementary Material. The weight functions for the different scenarios are shown in Figure 1.

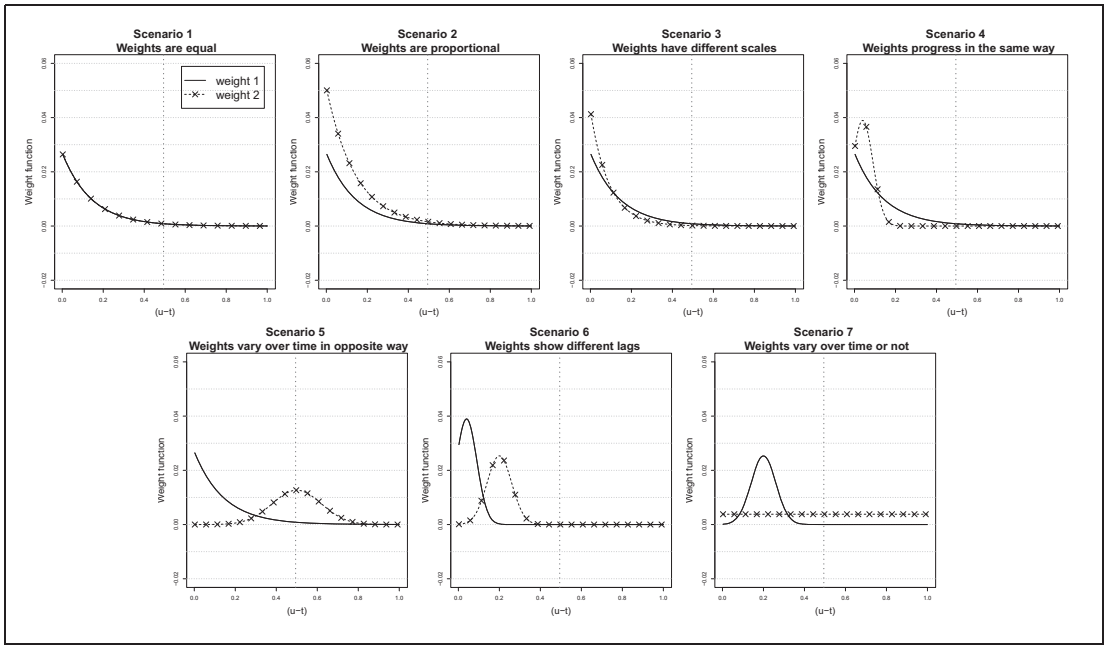

Figure 1. Weight functions for each scenario: weight1 is represented by the solid curve and weight2 is represented by the dashed line with crosses. The vertical line indicates the boundary of the time window [1, 180/364].

3.2 Events generation

We adapted, to the competing risks setting, the "permutational algorithm" (PA)[43,49] proposed to generate survival time conditional on time-varying exposure, according to a pre-specified model.[50] The algorithm is particularly useful if the true exposure-hazard association is too complex to use standard techniques, such as the inversion method.[43,49] The crux of the algorithm is to perform matching of (i) the n observed times T_j, $j = 1, \ldots, n$, corresponding to either one of the events k, $k = \{1, \ldots, K\}$ or censoring, with (ii) each of the n independently generated vectors of possibly time-varying covariate values $X_s(t)$, $s = 1, \ldots, n$.[49] The matching is performed so that the probability of different covariate vectors being matched with a given event are consistent with the partial likelihood of the data-generating "true" model.[43,51,52] Accordingly, in the setting with time-varying covariates, the probabilities of matching the event at time T_j, to each of the vectors of the current covariate values $X_s(T_j)$, for subjects who remain at risk until T_j, are proportional to their individual hazards at T_j, calculated according to the "true" model.[50]

The steps we implemented to adapt the PA to the competing risks setting and details regarding the choice of (i) distributions of event and censoring times and (ii) relevant parameters are provided in, respectively, Sections 4 and 5 of the Supplementary Material.

3.3 Analysis of the simulated datasets

For each simulated scenario, we generated 300 independent data sets of size $n = 500$. All simulations were performed using a customized program in R software.

For each of the 300 samples, we estimated four alternative WCE models that differed in whether the right boundary constraints, $w(a) = w'(a) = 0$, were imposed on the estimated weight function(s) for both, either, or none of the two events. In addition, for each type of the WCE model, we varied the number of interior knots for the weight functions in equation (4) from 1 to 3. We then used the minimum AIC to select the best-fitting model among the 12 (4×3) alternative WCE models. Regardless of the true data-generating weight function, which remains unknown in real-life applications, we assumed that the user would select a six-month interval as the maximum time window of potentially etiologically relevant exposures. Accordingly, we a priori set $a = 0.5$ year for all spline estimates of the weight function, across all models estimated in our simulations. Notice that this over-estimates the true duration of the exposure effects for most of the scenarios but under-estimates it for event $k = 2$ in scenario 5 (Figure 1).

3.3.1 Strength of the exposure effect

To assess the accuracy of the estimated strength of the exposure effect, we focus on the overall impact of being exposed at $X(t)=1$ during the entire one-year time-window. To this end, we use the estimates of the spline coefficients for each of the two event-specific weight functions, $\hat{\gamma}_{kj}$, $k=\{1,2\}$, to reconstruct the estimated values of $\beta_{1,wce}$ and $\beta_{2,wce}$ as[26]

$$\hat{\beta}_{k,WCE}=\sum_{\tau=0}^{a}\sum_{j=1}^{m}\hat{\gamma}_{kj}B_j(\tau) \tag{11}$$

Given equations (4) and (7), and the fact that each true weight function has been normalized (Section 3 of Supplementary Material), the values of $\hat{\beta}_{1,WCE}$ and $\hat{\beta}_{2,WCE}$ calculated from equation (11) should approximate, respectively, $\beta_{1,WCE}$ and $\beta_{2,WCE}$, that is, event-specific ln(HR) for patients always exposed to a dose $X_i(t)=1$, relative to those never exposed ($X_i(t)=0$ for all t).

Based on the distribution of the $\hat{\beta}_{1,WCE}$ and $\hat{\beta}_{2,WCE}$ estimates from the 300 samples for a given scenario, we assessed their relative bias, the empirical standard deviation, and the coverage probability of the 95% confidence intervals (see Section 6 of the Supplementary Material for details).

3.3.2 Weight functions

To assess the accuracy of the estimated weight functions, for each simulated sample, we plotted the 300 estimated normalized weight functions $w_k(u-t)$ for each event k against the corresponding true weight function. Furthermore, to facilitate visual assessment of the potential bias in the estimates, we also compared the true weight function with the mean of the 300 estimated functions.

4 Simulation results

In this section, we present the results for four simulated scenarios (three other scenarios are summarized in Section 7 of the Supplementary Materials). For each scenario, in Figure 2, we show the two event-specific estimated normalized weight functions, yielded by the minimum AIC model among models with 1–3 interior knots, separately for both the constrained and the unconstrained models, and summarize the findings regarding the estimated strength of the respective exposure effect in Table 1.

Except for scenario 5, most estimates from individual samples recover well the true shape of each of the event-specific weight functions, even if there is a non-negligible sampling variation (Figure 2). As expected, the estimates from the unconstrained model show considerable over-fitting bias in the right tail of the curves, which is

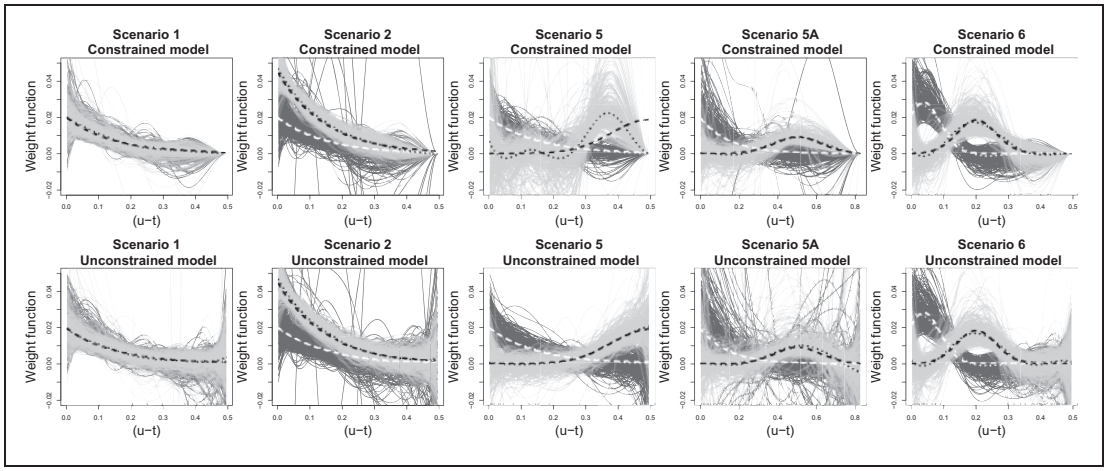

Figure 2. Estimated weight functions for the first event (dark-grey curves) and for the second event (light-grey curves) with their respective mean over the 300 samples (dotted curves) for the constrained models (top row) and for the unconstrained models (bottom row). The true weight functions are shown as the white dashed curve for the first event, and as black dashed curve for the second event (except for scenario 1, where the event-specific weight functions are identical). The estimated weight functions for the other scenarios are shown in Figure S1 of Supplementary Materials.

Table 1. Performance of the method over 300 samples for each scenario.

	True $\beta_{1,wce}$	True $\beta_{2,wce}$	Mean $\beta_{1,wce}$	SD $\beta_{1,wce}$	Relative bias (%)	Coverage rate (%)	Mean $\beta_{2,wce}$	SD $\beta_{2,wce}$	Relative bias (%)	Coverage rate (%)
Scenario 1: weight functions are the same										
Constrained model	1.386	1.386	1.316	0.277	−05.1	94.0	1.292	0.338	−06.8	93.7
Unconstrained model	1.386	1.386	1.358	0.329	−02.0	97.0	1.344	0.395	−03.1	93.7
Scenario 2: weight functions are the same										
Constrained model	1.386	2.079	1.279	0.337	−07.7	95.0	1.997	0.283	−04.0	94.3
Unconstrained model	1.386	2.079	1.319	0.397	−04.9	97.3	2.069	0.332	−00.5	96.7
Scenario 5: weight vary over time in opposite way when time window equals to 180 days										
Constrained model	1.386	1.386	1.317	0.249	−05.0	93.0	0.795	0.382	−42.7	59.3
Unconstrained model	1.386	1.386	1.325	0.297	−04.4	97.3	1.321	0.392	−04.7	94.3
Scenario 5A: weight vary over time in opposite way when time window equals to 300 days										
Constrained model	1.386	1.386	1.349	0.453	−02.7	95.0	1.323	0.558	−04.6	93.7
Unconstrained model	1.386	1.386	1.219	0.639	−12.1	94.0	1.210	0.763	−12.7	93.0
Scenario 6: weight functions with different lags										
Constrained model	1.386	1.386	1.345	0.306	−03.0	94.3	1.315	0.404	−05.1	93.3
Unconstrained model	1.386	1.386	1.362	0.348	−01.8	95.0	1.347	0.439	−02.8	93.3

SD: standard deviation.

avoided in the constrained estimates. Accordingly, unconstrained models also yield somewhat larger variance of the estimated WCE effects on the respective hazard (see "SD" columns in Table 1).

In most scenarios presented in Table 1, except scenario 5, both constrained and unconstrained models provide reasonably accurate WCE-based estimates of the total impact of being always exposed at a constant dose $X(t) = 1$ on the hazards of each event, with relative bias below 10% for both models, though the constrained estimates are typically slightly more biased. For these scenarios, low bias and accurate Monte-Carlo-based variance estimates result in the coverage probability of the 95% confidence intervals uniformly above 90% (Table 1). In all cases, except scenario 5, the LRT results indicate that in more than 90% of the simulated samples the unconstrained model does not improve the fit to data significantly over a more parsimonious constrained model (Table S2 of the Supplementary Material). This is encouraging as in all these scenarios the true weight function does, indeed, decay to 0 before the end of the *a priori* selected exposure time window of 180 days, which is consistent with the right boundary constraints.

In contrast, in scenario 5, relaxing the right boundary constraints reduced significantly ($p < 0.05$) the model deviance in around 80% of the simulated samples (Table S2 of the Supplementary Material), indicating the unconstrained model fits the data better. These results were expected since the true weight function for the second event $k = 2$ does not reach 0 at the end of the pre-specified time window [0;180 days], as for this event doses taken up to 290 days ago do affect the current hazard (Figures 1 and 2—scenario 5). Accordingly, in scenario 5, the constrained models yielded considerably biased estimates of the exposure effect $\beta_{2,WCE}$, with relative biases (−42.7%) several times higher than for any other scenario (Table 1), and very low coverage probability (59.3%). Together, the findings that (i) the unconstrained model fits significantly better, and (ii) that the corresponding unconstrained estimates of the weight function for the second event seem to reach their maxima around the end of the pre-specified 180-days exposure window, suggest that this window may be too short to capture the full impact of prior exposure. Therefore, in scenario 5A, we re-analyzed the data from scenario 5 while assuming a wider time window, expanded up to 300 previous days. With this new time window, which covers the entire period during which previous doses do affect the current hazards for both events (Figure 2), a better fit was provided by the constrained models in more than 90% of the simulated samples. As shown in Figure 2—scenario 5A, the resulting estimates, constrained to decay to 0 at 300 days, recovered very well the true weight functions for either event, and the constrained models estimate the total exposure impact with only a minimal (<5%) bias and accurate confidence intervals (Table 1). Thus, scenarios 5 and 5A illustrate how comparing the constrained versus unconstrained models, in terms of both the weight functions estimates and deviances, can provide useful model diagnostics and correct for a possibly suboptimal choice of the length of the exposure window.

Table 2. Proportion of rejection of H_0 when fixing a priori the number of knots in the B-splines for each events (we remove scenario 5 since scenario 5A is the same but using a bigger time window).

	True hypothesis	LRT (H_0) Model 1 (Identical w_k) (H_1) Model 2 (Proportional w_k)	LRT (H_0) Model 2 (Proportional w_k) (H_1) Model 3 (Different w_k)
Scenario 1	Identical w_k	04.0	08.3
Scenario 2	Proportional w_k	72.7	04.0
Scenario 5A	Different w_k	99.0	80.0
Scenario 6	Different w_k	98.3	99.7

LRT: likelihood ratio test.

Finally, the LRT tests proposed in Section 2.4 were found to discriminate well between situations where the two event-specific weight functions were (i) the same (Model 1, assumed in scenario 1), (ii) proportional to each other but with different effect strengths (Model 2, assumed in scenario 2), or (iii) of different shapes (Model 3, assumed in scenarios 5, 5A and 6). Indeed, Table 2 shows that in most scenarios, the tests comparing (i) Model 2 (H_1) versus Model 1 (H_0), and (ii) Model 3 (H_1) versus Model 2 (H_0), had empirical type I error rates close to the nominal $\alpha = 5\%$, and satisfactory power ($1 - \beta$) between 72.7% and 99.7%. Notice that in Table 2, (i) we present the results only for the constrained models since, as discussed above, relaxing the constraints rarely improved significantly the model's deviance and (ii) to avoid inflation of type I error due to un-accounted for additional variance induced by data-dependent choices,[43,53] we a priori fixed the number of interior knots for all weight functions.

5 Application to re-assess the effectiveness of thiazide diuretics in preventing cardiovascular events

5.1 Data source

We applied our flexible competing risks WCE model to assess the effectiveness of a class of frequently prescribed antihypertensive drugs, thiazide diuretics (TD), in preventing (i) serious coronary heart disease (CHD) events (acute myocardial infarction, unstable angina, congestive heart failure) versus (ii) stroke.

Separating the potential associations of TD use with these two competing events may be important. Firstly, whereas most clinical trials and epidemiological studies of drugs prescribed to reduce cardiovascular risks use the composite endpoints, which combine CHD and/or stroke, and possibly other, minor events, this approach may be sub-optimal if the treatment effects vary across individual events.[34,35] Indeed, a recent meta-analysis suggested that TD effects may differ between CHD events versus stroke.[54]

Our analyses used data from MarketScan, a large medical claims US database. In this retrospective cohort study, we used the Truven Health MarketScan® Research Databases (2011–2014) that contain claims data for privately insured patients, including information on the dates, doses, and duration of all drug prescriptions. The detailed criteria and steps used to select the final cohort of 9896 male TD users are described in Section 8 of the Supplementary Material. The date of the first TD prescription was defined as the cohort entry (t_0) according to the new-users design.[55] Each subject was followed from the date of the first TD prescription t_0 until the earliest of the dates of (a) either event of primary interest, or (b) administrative censoring on 31 December 2014 or (c) loss of coverage, or (d) first switch to another anti-hypertensive drug. The latter censoring criterion helped to avoid complications related to possible carry-over effects of previously used drugs, patients' follow-up was censored at the time of their first switch to another anti-hypertensive drug.

5.2 Exposure

The time-varying covariate representing the daily dose of any TD drug was reconstructed based on the MarketScan records of the total doses and durations of each prescription. We converted doses of all other TD drugs into pharmacologically equivalent dose of hydrochlorothiazide, the most frequently used TD drug.[56]

In the case of two overlapping prescriptions for TD drug, we assumed that the corresponding doses were not taken simultaneously but, instead, the subject started using the ''excess'' pills, generated by the later prescription, only after the end of the earlier one. This implied that, when creating the time-varying covariate *daily dose,* the effective period of exposure was extended beyond the end date of the later prescription.[57]

An additional binary time-varying covariate was created to indicate the periods when a patient had overlapping prescriptions between a TD drug and another antihypertensive drug.

5.3 Statistical methods

To estimate the cumulative impact of past TD exposures on the current hazards of either CHD events or stroke, we relied on the competing risks WCE model, proposed in Section 2.2. In the main analysis, we assumed that the weight functions for the two competing events will be different, consistent with equation (7). We analyzed the data with both the right-constrained and the unconstrained WCE models, and fit each model with 1–3 interior knots, uniformly distributed within the pre-selected time window. We considered four different windows of potentially etiologically relevant exposure: 30, 60, 90, and 180 days. The best-fitting of the aforementioned WCE models was selected using the minimum AIC. Then, we used the procedure described in Section 2.4 to test if the two weight functions might (i) be identical (ii) have the same shape but different strength, or (iii) have different shapes. We also estimated a simpler "parametric" competing risks extension of the Cox model, where the time-varying exposure was defined as the current daily dose. Similar to the WCE analyses, the current-dose was fitted using the data augmentation approach[41] with spline-based estimation of two event-specific baseline hazards.[42] Each model adjusted the TD exposure for two *a priori* selected potential confounders: age at the cohort entry and a time-varying binary indicator of current use of another anti-hypertensive treatment. The 95% pointwise confidence bands around the weight functions from the best-fitting final WCE model were estimated using the Monte-Carlo procedure described in Section 6 of the Supplementary Material.

Studies of cardiovascular risks should account for the competing risks of non-cardiovascular mortality.[58] However, the main limitation of the MarketScan database is that only inpatients deaths are reported.[59,60] Therefore, in order to both (i) illustrate how a more accurate analysis should be performed and (ii) assess the robustness of our results, we conducted a sensitivity analysis, in which a plausible number of non-cardiovascular deaths were imputed, and then added as a third competing event (details of imputation are described in Section 9.1 of the Supplementary Materials).

5.4 Results

A total of 979 subjects, 9.89% of the study sample, experienced an event during up to four years of follow-up, including 440 coronary heart events and 539 strokes. The overall incidence rates were 4.03/100 person-years (py) for CHD and 4.94/100 py for stroke. On average, subjects were exposed to TD for two-thirds of their follow-up. During the periods of TD use, the median dose, across all subjects, was 25 mg per week (interquartile range (IQR): 12.5 to 25 mg).

For both constrained and unconstrained WCE models, the best fit was obtained using one knot for the estimated weight functions for both CHD events and stroke (data not shown). This finding was consistent regardless of the time window considered, but the 60 days time window yielded the best fit. Furthermore, the LRT tests indicated a lack of a significant improvement in model's deviance using the unconstrained model, compared to the more parsimonious constrained model (p value $= 0.98$). Finally, the LRT proposed to compare the weight functions for the two events indicated that the "Model 3" (Section 2.4: equation (10)), which allowed the two weights functions to have different shapes, fit the data significantly better than either of the two simpler models ($p = 0.026$ and $p = 0.047$ for comparisons with, respectively, Model 1 with two identical functions, and Model 2 with the two functions proportional to each other). Therefore, in this section we show only the results of the final WCE model, corresponding to the constrained model, with 60 days window and one interior knot placed at 30 days and with two different event-specific weight functions.

Figure 3(a) and 3(b) shows the weights functions, respectively, for CHD events and stroke, with 95% Monte Carlo pointwise confidence bands, estimated through the final WCE competing risks model. The bold curve in Figure 3(b) suggests a protective effect of recent TD exposures against the stroke, for which the weight function has negative values for doses taken up to 25 days ago while doses taken more than 25 ago have no effect on the current hazard of stroke. In contrast, for CHD events, the estimated weight function (bold curve in Figure 3(a)) suggests a lack of a consistent effect, with positive weights for doses taken in the window between 5 and 25 days ago, and negative weight values for exposures on both sides of this window. The above conclusions were confirmed by LRT comparing the deviances of (a) the final WCE model versus (b) simplified models that assumed no TD effect on one of the two competing events. The results indicated a marginally significant effect of recent TD doses on the hazard of stroke ($p = 0.058$) but a completely non-significant effect for CHD events ($p = 0.318$). Section 9.2

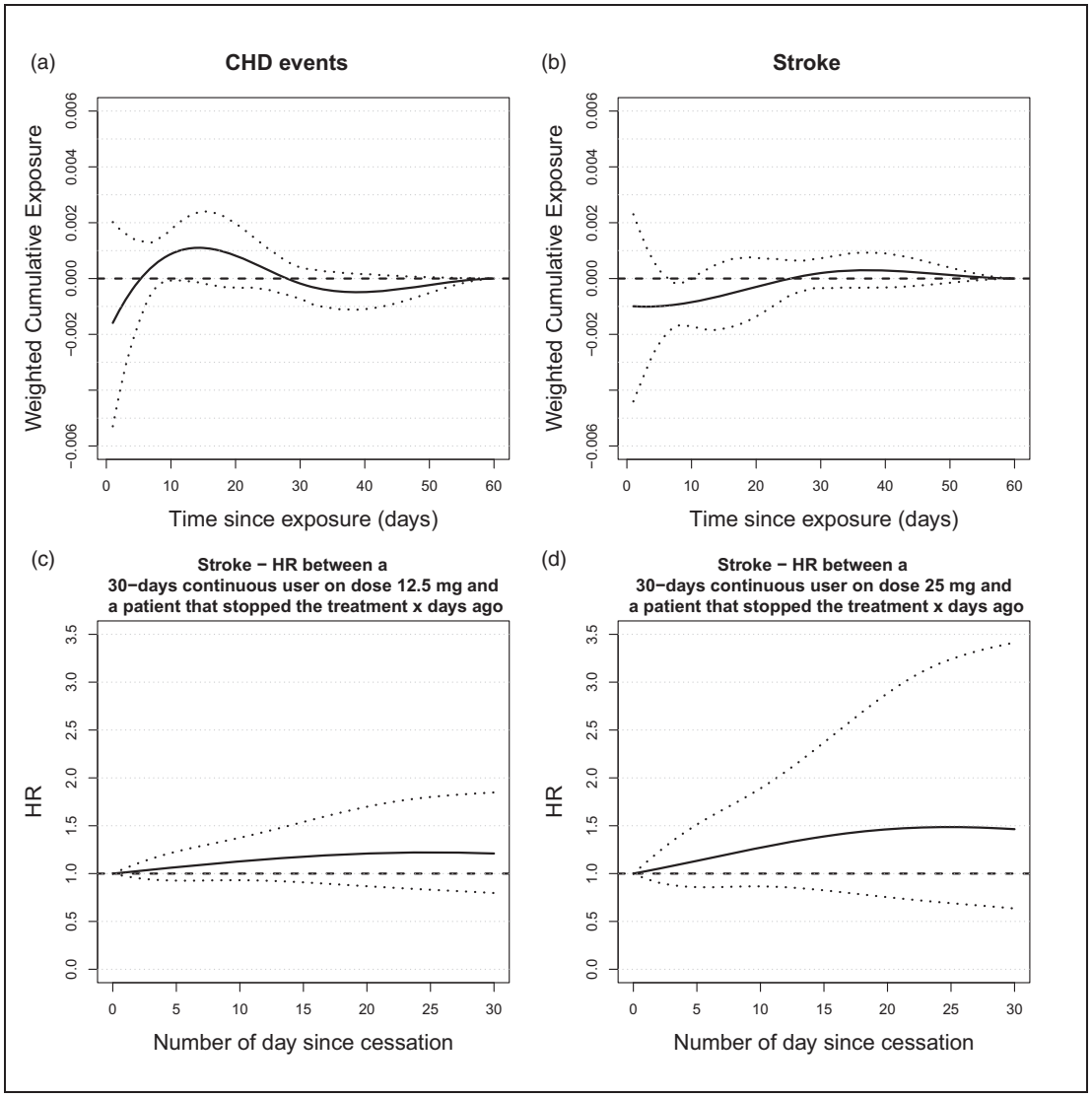

Figure 3. Estimated weight functions for both events and pointwise 95% bootstrap confidence intervals for the associations between exposure to TD drugs and (a) coronary heart events (CHD) and (b) stroke. The estimated HRs for stroke over time since TD treatment discontinuation, relative to a continuous user, prescribed the same daily dose, are depicted in (c) and (d).

of the Supplementary Material shows that, for both CHD events and stroke, very similar results were obtained in sensitivity analyses, where imputed non-cardiovascular deaths were considered as the third competing event. However, no inference can be made concerning the effect of the TD treatment on the hazard of non-cardiovascular death since the latter events are artificially imputed.

Overall, the results of the flexible WCE model for stroke are qualitatively similar to those of the conventional ''current dose'' model (Table S4 and Section 10 of the Supplementary Material) in that both models indicate that higher recent TD doses are associated with reduced risk of stroke. These findings are consistent with the Cochrane review of the randomized controlled trials, in which higher doses of TDs were also associated with a significant reduction in the risk of stroke.[54] For CHD events, both the WCE and the conventional models suggest a trend toward a possible minor risk increase associated with higher recent TD doses (Table S4), which would be similar to the Cochrane review findings,[54] but the results for CHD events are statistically non-significant in both models. However, it should be emphasized that the conventional ''current dose'' estimate implicitly pools together the relative risks associated with different exposure histories (in terms of duration, timing and/or doses of past exposures), across all subjects currently prescribed a given dose. In contrast, the flexible WCE model accounts also for all other aspects of the recent exposure history. Indeed, as discussed in detail in Section 10 of

Supplementary Material, the WCE estimates in Table S4 show important differences between the hazards ratios for current users with different patterns of TD dose and treatment duration relative to non users.

Consistent with the new users design,[55] our study population is limited to people who were initially prescribed anti-hypertensive TD drugs and who should likely continue their treatment. Thus, it could be of interest to assess the impact of the cessation of the TD treatment. Figure 3(c) and 3(d) show how, for two hypothetical past TD users with different daily doses, the estimated HRs for stroke change with increasing time since TD treatment discontinuation, relative to a continuous user, prescribed the same daily dose. The graphs show that both HRs increase gradually during about first 20 days after treatment cessation and then stabilize, and that the impact of treatment discontinuation is more important for patient prescribed higher doses. These estimates may help illustrating the importance of continuous adherence to anti-hypertensive treatment.

6 Discussion

We propose and validate a new method that permits assessing and comparing the separate associations of a time-dependent exposure with the hazards of different, mutually exclusive competing events. To this end, we combine flexible modeling of cumulative effects of time-varying exposures,[26] which incorporates several simpler time-varying exposure metrics as special cases,[12] with the competing risks modeling of separate event-specific hazards.[4,36–38] Our new competing risks model allows flexible estimation of (i) the baseline hazards and (ii) the separate cumulative effects of the time-varying exposure or prognostic factor on the hazard of each of the competing events. The essential components of the proposed competing risks WCE model are the separate event-specific weight functions, each of which describes how the effects of past exposures on the current hazard of a specific event cumulate over time. To allow comparisons of the effects of the same exposure on the hazards of competing events, we proposed three different LRTs.

Simulations demonstrated that the proposed method yields accurate estimates of both the event-specific weight functions, of different shapes, and of the strength of the cumulative effects of past exposures on the hazards of each of the competing events. Furthermore, the LRTs, proposed to test if the event-specific weight functions are the same or not, have type I error rates reasonably close to the nominal and good power to detect different strengths and/or patterns of event-specific cumulative effects.

Our application of the proposed method to re-assess the potential effectiveness of TD antihypertensive drugs against serious cardiovascular events, using population-based observational data, mostly confirmed the results of a meta-analysis of clinical trials.[54] Specifically, we replicated the findings of both: (i) a protective effect of recent high-dose TD use against stroke and (ii) lack of a systematic association between TD use and hazard of CHD events.[54] Our competing risks WCE model helps address the challenges of this application, which required accounting for both (1) different effects of TD exposure on the hazards of each of the two competing events and (2) the cumulative effects of the TD doses taken in the last three weeks for stroke. Compared to the current dose model, our flexible WCE model yielded new insights regarding the possible mechanisms linking the history of time-varying TD exposure with the risk of CHD and stroke since it takes into account also the duration and the recency of the treatment. The results allowed us also to assess the negative impact of treatment discontinuation on the increased risk of stroke.

Recent reviews of the methodological issues in longitudinal studies of the safety or effectiveness of medications emphasized the need to account for all competing risks, in order to provide a full assessment of the risks and benefits associated with the use of a given drug.[3–5,58] One important advantage of the competing risks approach, relevant for both clinical trials and observational pharmaco-epidemiological cohort studies, is that it permits avoiding the limitations related to the use of "composite outcomes"[3] such as, for instance, cardiovascular events, all-cause mortality or all emergency room visits. Clinical research, including both observational studies and randomized trials, tends to often pool together such heterogeneous events, with different etiology and/or clinical importance, even if it may be inappropriate in terms of both interpretation of results and risk prediction.[34,35] From this perspective, our new competing risks WCE model builds on these recent recommendations and extends the existing hazards-based competing risks methods to flexible modeling of the cumulative effects of time-varying drug exposures.

Our method may be especially useful for the competing risks analyses of post-marketing pharmaco-epidemiological studies of real-life safety or effectiveness of drugs. In clinical trials, a complete competing risks analysis should involve estimation, and comparison of the trial arms with respect to both (i) the event-specific hazards and (ii) the cumulative incidence functions, that quantify the probability of the occurrence of adverse events in the presence of competing risks.[4,5] However, the analyses of observational (non-randomized) studies need

to account for considerable heterogeneity in (i) individual patterns of time-varying drug use[2,3] and (ii) baseline risks, due to different covariate vectors, both of which complicate comparisons of the cumulative incidence. Thus, our competing risks analyses are limited to modeling hazards associated with different exposure patterns, separately for each of the competing events. As illustrated in the real-life application, our hazard-based competing risks model yields estimates that can be interpretable in familiar terms of HRs,[4] and allow the end-users to comprehensively assess the relative risks or benefits associated with different treatment regimes or treatment discontinuation.

Our study has some limitations, similar to other pharmaco-epidemiology database studies, where (i) exposure measurement errors and (ii) unmeasured confounding are major threats to the accuracy of results and validity of conclusions.[1,3] Concerning the exposure measurement, large administrative health databases typically reflect only the dispensing of medications and not their actual use, which can lead to biased estimates and spurious conclusions.[61] It will be helpful, therefore, to find the way to adapt the generic SIMEX methodology[62] to specific measurement error structure, most relevant for pharmaco-epidemiology, where the main source of the errors is the treatment non-adherence.[3] To address concerns about potential biases due to several patient characteristics, related, e.g. to lifestyle, clinical variables and laboratory test results, not recorded in large health databases, future research should attempt to combine our flexible competing risks model with methods specifically designed to reduce the impact of unmeasured confounding in observational studies of medication effects. This work may focus on adapting the instrumental variables (IV) approach that relies on physicians' subjective prescribing preferences as proposed by Brookhart et al.,[63] and possibly building on the recent extension of the IV methodology to time-to-event analyses.[64]

In conclusion, pharmaco-epidemiological studies of drug safety or effectiveness should involve full assessment of the risks of all relevant competing events[3–5,58] and, at the same time, account for possible cumulative effects of time-varying exposures.[12] Based on encouraging results of our simulations and a real-life application, we believe that our flexible model can offer an useful tool to address these analytical challenges, which may ultimately enhance the benefit/risk assessment of different drugs and help optimizing prescribing practice.[10]

Acknowledgements

The authors thank Dr Cristiano Moura for helpful advice regarding the use of the MarketScan data, Dr Rebecca Burne for a revision of an earlier draft of the manuscript, and Dr Adrian Levy for comments regarding the disadvantages of composite endpoints.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: the Canadian Institutes of Health Research (CIHR) grant # PJT-148946 and Natural Sciences and Engineering Research Council (NSERC) of Canada # 228203. Coraline Danieli was supported by the post-doctoral fellowship from the CAN-AIM team grant of the Drug Safety and Effectiveness Network (DSEN) of CIHR.

Supplemental material

Supplemental material is available for this article online.

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