

# Methodologic Issues when Estimating Risks in Pharmacoepidemiology

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## Abstract

**Purpose of Review** Risk is an important parameter to describe the occurrence of health outcomes over time. However, many outcomes of interest in healthcare settings, such as disease incidence, treatment initiation, and cause-specific mortality, may be precluded from occurring by other events, often referred to as competing events. Here, we review straightforward approaches to estimate risk in the presence of competing events. **Recent Findings** We illustrate the application of these methods using timely examples in pharmacoepidemiologic research and compare results to those obtained using analytic simplifications commonly used to handle competing events. **Summary** These examples demonstrate how the analytic methods used to account for competing events affect the interpretation of results from pharmacoepidemiologic studies.

**Keywords** Pharmacoepidemiology · Epidemiologic methods · Survival analysis · Bias (epidemiology)

## Introduction

Health sciences research, including pharmacoepidemiology, seeks to inform healthcare decisions and policy development. Descriptions of the occurrence of health outcomes can help researchers and public health practitioners understand the burden of conditions, identify high-risk groups, and plan for resource allocation. Comparisons of the occurrence of health outcomes under 2 or more policies, treatment plans, or interventions can inform decision making in public health and medicine. “Risk” is a foundational parameter to describe the occurrence of health outcomes in epidemiologic studies [1•]. In this paper, we discuss considerations in estimating risks of important outcomes in pharmacoepidemiology, such as disease incidence, medication uptake, and cause-specific mortality.

All outcomes (*events of interest*) other than all-cause mortality may require special consideration in analyses because they may be precluded from occurring by *competing events*. For example, in a study of medication uptake, participants who die before starting the medication will never be able to start the medication. In this case, death is a *competing event* which precludes the occurrence of the *event of interest*, medication initiation. In studies of cause-specific mortality, death due to causes other than the cause of interest are competing events.

Competing events are not the same as censoring events and should be treated differently in analyses. While a competing event precludes the outcome from occurring, a censoring event merely prevents us from observing the outcome. Common reasons for censoring include loss to follow-up or administrative end of follow-up before the outcome occurs. Though the distinction between competing events and censoring events has been noted in many fields of clinical research (for example, [2–9]), competing events continue to bring up methodological challenges in the estimation of risk in many settings [10].

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Here, we first summarize a modern definition of risk and then outline approaches to estimate risk in settings with competing events. Next, we discuss extensions to estimate counterfactual risks, or risks that would have occurred, under various treatment plans. Throughout the paper, we illustrate concepts using examples derived from recent pharmacoepidemiologic studies.

## Parameters and Estimators

Risk is a function describing the cumulative probability of an event of interest occurring over time since a given origin in a specific population. Risk can be reported at any specified time since the origin. The *origin* is the time at which individuals become at risk for the event under study, that is, where they have any probability of experiencing the event and having their events observed by investigators. The appropriate origin depends on both the event under study and the study question. Multiple origins may be appropriate for a given event [11], and we discuss considerations in choosing the optimal origin in the Discussion.

First, note that risk at time  $t$  is a *probability*, meaning that it is bounded by 0 (no subjects experience the outcome by time  $t$ ) and 1 (all subjects experience the outcome by time  $t$ ). Risk can be interpreted as a population average probability or as the proportion of subjects expected to experience the outcome by time  $t$  [1••]. Second, note that risk is a function of time since the origin, and as such, risks should always be reported with the time period for which they are calculated.

When no competing events are possible, such as when studying all-cause mortality, or when the follow-up time is so short that no competing events occurred, we can define risk as the cumulative distribution function for the time between the origin and the event of interest,  $F(t)$ , where

$$F(t) = P(T_i \leq t)$$

and  $T_i$  is the time from the origin to the event of interest for subject  $i$ . In this setting,  $F(t)$  can be estimated as the complement of any consistent estimator of the survival function, such as the Kaplan-Meier estimator [12].

Because competing events are nearly ubiquitous in pharmacoepidemiology, we discuss a generalization of the risk function allowing for multiple event types in the remainder of this paper. We will denote the risk function for event type  $j$  as  $F(t, j)$ , where

$$F(t, j) = P(T_i \leq t, J_i = j),$$

$T_i$  is the time from the origin to the event of interest or the competing event and  $J_i$  is the event type for subject  $i$ . This risk function is sometimes called the cumulative incidence

function [13, 14]. The risk  $F(t, j)$  may be estimated using the Aalen-Johansen estimator [15]

$$\hat{F}(t, j) = \sum_{k \leq t} \frac{d_{kj}}{n_k} \hat{S}(k-1),$$

where  $d_{kj}$  is the number of events of type  $j$  occurring at time  $k$ ,  $n_k$  is the number of subjects at risk of the event at time  $k$ ,  $d_{kj}/n_k$  is the cause-specific hazard for the event of interest at time  $k$ , and  $\hat{S}(k-1)$  an estimate of the overall survival function at the previous time point.  $\hat{S}(k-1)$  can be estimated using any consistent estimator for the survival function, such as the Kaplan-Meier estimator  $S(t) = \prod_{k \leq t} \{1 - d_k/n_k\}$ , where  $d_k$  is the total number of events of any type at time  $k$  [12].

Several ad hoc simplifications exist to estimate quantities related to risk in the presence of competing events. These simplifications include censoring the competing events and using composite endpoints. Using these simplifications changes the interpretation of the results in many settings. In the following sections, we discuss each of these simplifications and compare risk estimated using the Aalen-Johansen estimator to risk estimated by censoring the competing events (example 1) and using a composite endpoint (example 2).

## Simplification 1: Censor Competing Events

Sometimes, epidemiologists simply censor records at the time subjects experience a competing event. Rather than acknowledging that a competing event precludes the event of interest, censoring a competing event is equivalent to assuming that the event of interest occurs at some time point after the competing event. The measure that results from censoring competing events is the *conditional* risk or the risk that would be observed if all competing events in the cohort were prevented from occurring without altering the hazard of the event of interest [16–18]. However, it is difficult to imagine the intervention that would completely eliminate competing events, much less the intervention that would completely eliminate competing events without also changing the risk of the event of interest. The assumptions necessary for interpreting conditional risks limit the utility of such estimates for measuring public health impact.

Estimates of conditional risk, obtained by censoring competing events, are always greater than or equal to estimates of risk obtained using the Aalen-Johansen estimator. This is because each censored observation up-weights events observed after the censoring time [19]. To see why, consider that an analysis that censors the competing events scales the cause-specific hazard by the

cause-specific survival function  $S(k-1, j)$  rather than the overall survival function  $S(k-1)$ . The resulting estimator is

$$\hat{F}_{cs}(t, j) = \sum_{k \leq t} \frac{d_{kj}}{n_k} S(k-1, j).$$

Note that the cause-specific survival function  $S(t, j)$  will always be greater than or equal to the overall survival function  $S(t)$  if there are any competing events. In the setting where competing events are censored, the cause-specific hazard will be scaled by a larger value, resulting in inflated estimates of risk. The degree of inflation will be proportional to the incidence of the competing event. In settings where competing events are rare,  $S(t, j) \approx S(t)$  and censoring the competing events will have little impact on the estimated risk for event type  $j$ . However, when competing events are common or the event of interest is rare, censoring the competing events can dramatically distort estimates of risk.

### Simplification 2: Use a Composite Endpoint

A second common simplification in analyses with competing risks is to estimate the risk of a composite endpoint. That is, the outcome is defined as the first of several possible endpoints (e.g., AIDS or death prior to an AIDS diagnosis). Specifying a composite endpoint is useful in many settings, particularly when all of the event types are of interest or when the number of occurrences of a single event type is small [20–22]. If all competing event types are included in the composite endpoint, the risk function collapses to  $F(t)$ . However, combining multiple event types may obscure important relationships between exposures and the event type of interest, particularly if the event type of interest is rare compared to all other event types. In addition, combining a beneficial outcome (e.g., cancer remission or hospital discharge) with a negative outcome like death may render a composite endpoint difficult to interpret. Approaches to weight the types of competing events in a composite endpoint or to assign a utility function to the types of competing events may offer a way forward in these settings [1•, 23].

## Part 1. Risk under no Intervention on Treatment Plan

We refer to risk estimated under no intervention on the conditions, treatments, exposures, or policies that occurred during the study as risk under the “natural

course.” Estimating risk under the natural course is an important tool to understand specific target populations [24]. For example, describing the risk of a given disease, uptake of a new drug, or the risk of death after contracting a disease (or starting a drug) in a given population requires estimation of risk under the natural course. Risks at specific points in time from the origin (e.g., at 5 years after treatment initiation) can be compared between subsets of study participants using risk ratios or risk differences.

To estimate the risk under the natural course, we must assume that (1) the event time is measured without error, (2) the event type is measured without error, and (3) that subjects under observation are exchangeable with subjects not under observation at time  $t$  [25, 26•, 27]. Methods to relax each of these assumptions are explored in the Discussion.

### Example: Estimating the Risk of Cancer-Related Mortality by Comorbidity Status under the “Natural Course”

In the example below, we estimate 5-year cancer-related mortality risks using a large claims database linked with cancer registry data. First, we use the Aalen-Johansen estimator,  $\hat{F}(t, j)$ , to account for competing events in cancer-related risk estimates and illustrate graphical approaches to display risks of competing event types. Then, we compare risk estimated using  $\hat{F}(t, j)$  with conditional risk estimated by censoring the competing events  $\hat{F}_{cs}(t, j)$ .

We compare 5-year cancer-related mortality risk between patients with and without each of 3 common comorbidities at the time of their cancer diagnosis: diabetes, congestive heart failure (CHF), and chronic obstructive pulmonary disease (COPD). The analysis included patients aged  $\geq 65$  years diagnosed with non-Hodgkin lymphoma (NHL) from 2007 to 2009 who resided in any of 18 Surveillance, Epidemiology, and End Results (SEER) cancer registry areas at diagnosis and had linked US Medicare health insurance claims. All patients were required to have 12 months of continuous enrollment in Medicare before NHL diagnosis so that prevalent diabetes, CHF, or COPD could be identified using validated ICD-9 diagnosis and procedure codes in claims data [28]. We followed patients from NHL diagnosis until death from any cause or administrative censoring at 5 years or on December 31, 2012. Deaths were ascertained from US death certificate data collected and maintained by the National Center for Health Statistics. The National Cancer Institute’s algorithm [29] was used to identify deaths due to cancer ( $j=1$ ),

and deaths not meeting the cancer classification were considered non-cancer deaths ( $j=2$ ).

Because older patients have a high probability of dying from non-cancer conditions before they die of cancer, censoring patients when they experience a competing non-cancer death will overestimate cancer-related mortality risk. We estimated 5-year risks and conditional risks of cancer-related and non-cancer mortality using the Aalen-Johansen estimator  $\hat{F}(t, j)$  and the estimator in which competing events were censored  $\hat{F}_{cs}(t, j)$ , respectively. We contrasted risks and conditional risks between groups with and without diabetes, CHF, and COPD using risk ratios. Confidence intervals were estimated as the 2.5th and 97.5th percentiles of point estimates obtained from 1000 bootstrap samples of the data [30]. SAS code to estimate the risk functions is provided in Appendix 1.

Among the 5192 NHL patients included in the analysis, 1284 (25 %) had prevalent diabetes, 620 (12 %) had CHF, and 810 (16 %) had COPD. Over the study period, there were 2514 deaths, for a 5-year all-cause mortality risk of 56 %. Of these deaths, 1600 were cancer-related deaths and 914 were related to other causes. The 5-year risks of cancer and non-cancer related mortality were higher for patients with each comorbidity than without each comorbidity (Table 1). Figure 1 presents a graphical depiction of  $\hat{F}(t, 1)$  and  $\hat{F}(t, 2)$  showing the relationship between the risk functions for the two competing event types [31].

Conditional risks, estimated by  $\hat{F}_{cs}(t, j)$ , were greater than risks estimated by  $\hat{F}(t, j)$  for all groups (Table 1). For example, estimates of conditional risk  $\hat{F}_{cs}(5, 1)$  and  $\hat{F}_{cs}(5, 2)$  in the overall study sample (not stratifying on comorbidity) were 33 and 34 %, respectively, while estimates of risk  $\hat{F}(5, 1)$  and  $\hat{F}(5, 2)$  were 31 and 25 %, respectively. Furthermore, because the risk of non-

cancer mortality was higher among patients with each of the three comorbidities under study, conditional cancer-related mortality risks estimated using  $\hat{F}_{cs}(5, 1)$  were more inflated for patients with each comorbidity than for patients without, and thus, conditional risk ratios comparing  $\hat{F}_{cs}(5, 1)$  between persons with versus without comorbidities were higher than risk ratios calculated by comparing  $\hat{F}(5, 1)$  between groups. The inflation in the risk ratio was greatest for CHF, which had the highest non-cancer mortality. The risk ratio comparing 5-year cancer-related mortality for patients with CHF versus those without CHF when non-cancer deaths were censored was 1.52 (95 % confidence interval (CI): 1.36, 1.69), while the risk ratio was 1.35 (95 % CI: 1.21, 1.50) when competing events were taken into account using the Aalen-Johansen estimator.

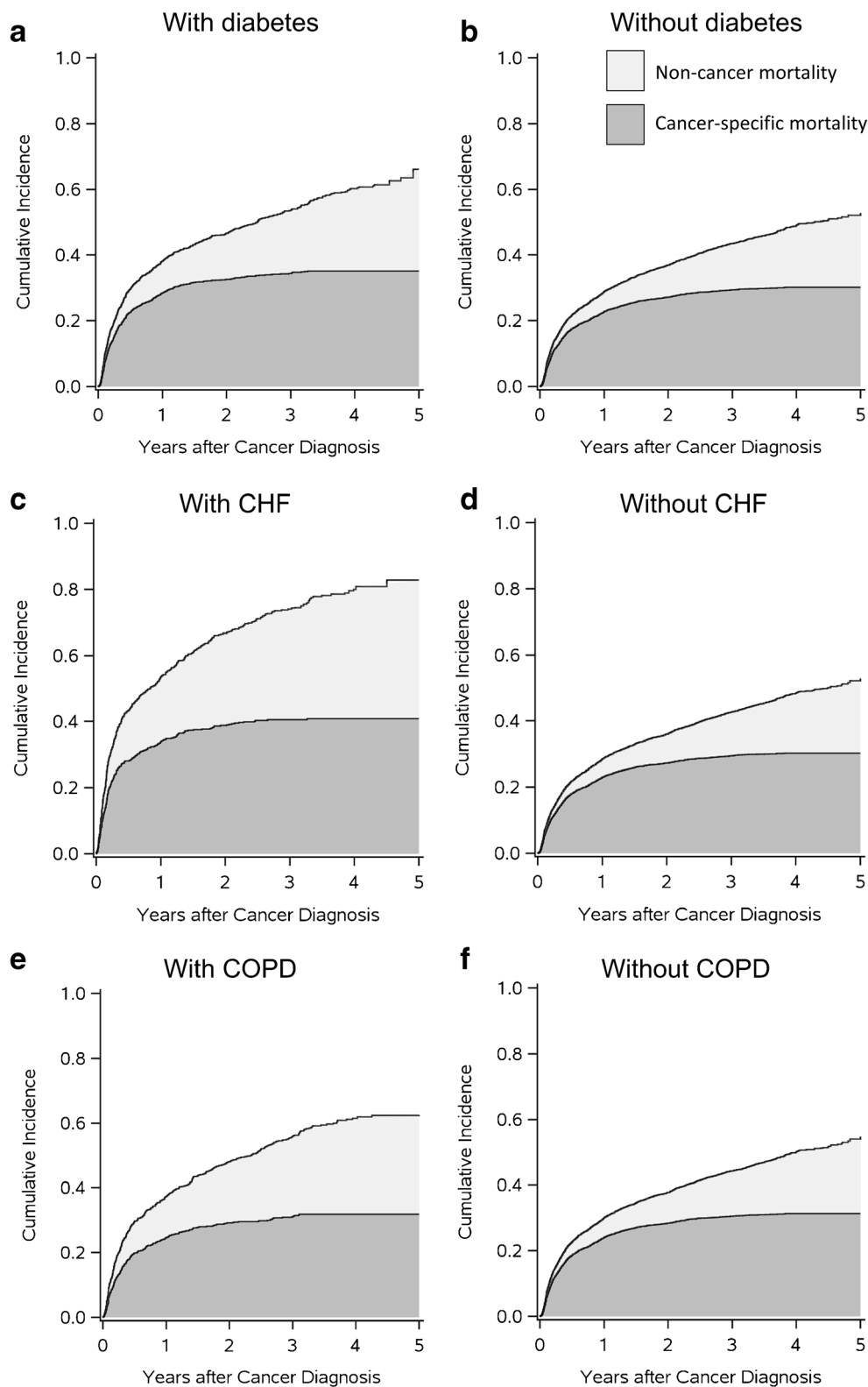
## Part 2. Counterfactual Risk under Treatment Plan $a$

Sometimes, rather than compare outcomes between 2 groups of patients, we wish to compare the outcomes that would have occurred in the same group of patients under 2 or more treatment strategies. The risk that would have occurred under treatment plan  $a$  is known as the *counterfactual risk* under treatment plan  $a$ , and will be denoted  $F^a(t, j) = P(T^a \leq t, J^a = j)$ , where  $T^a$  is the time from the origin to the event and  $J^a$  is the event type under treatment plan  $a$ . The counterfactual risk is the proportion of subjects we would expect to experience event  $j$  by time  $t$  if all subjects were observed from origin to event *and all subjects received treatment plan  $a$* . Counterfactual risks are particularly important for pharmacoepidemiology due to their role in comparative effectiveness studies [32–34].

**Table 1** Five-year cancer-related and non-cancer mortality risks and risk ratios for 5192 patients diagnosed with non-Hodgkin between 2007 and 2009 in a US Medicare population

Group	Deaths			Risk: accounting for competing events				Conditional risk: censoring competing events			
	Total	Cancer	Non-cancer	Cancer-related 5-year mortality	Risk %	RR (95 % CI)	Non-cancer 5-year mortality	Risk %	RR (95 % CI)	Cancer-related 5-year mortality	Non-cancer 5-year mortality
Overall	5192	1600	914	31.4	–	–	24.6	–	–	33.4	33.7
Diabetes											
No	3908	1154	634	30.2	1	–	22.4	1	–	31.9	30.3
Yes	1284	446	280	35.2	1.16 (1.10, 1.24)	–	30.9	1.38 (1.26, 1.50)	–	38.0	44.9
CHF											
No	4572	1353	699	30.3	1	–	22.6	1	–	31.8	31.0
Yes	620	247	215	40.9	1.35 (1.21, 1.50)	–	43.0	1.90 (1.69, 2.10)	–	48.5	65.6
COPD											
No	4382	1341	693	31.3	1	–	23.4	1	–	33.0	32.2
Yes	810	259	221	31.9	1.02 (0.92, 1.12)	–	31.1	1.33 (1.18, 1.50)	–	35.8	42.1

**Fig. 1** Cancer-related (*dark gray*) and non-cancer (*light gray*) mortality risks a (stacked) after diagnosis with non-Hodgkin lymphoma (NHL) among Medicare patients aged over age 65 who have or do not have diabetes (**a** and **b**), CHF (**c** and **d**), and COPD (**e** and **f**) at NHL diagnosis. Cancer-related and non-cancer mortality risks are estimated using the Aalen Johansen estimator. In this figure, cancer-related mortality risks and non-cancer mortality risks are stacked, such that the top line of the two stacked curves represents all-cause mortality risk. Stacked plots like these allow the depiction of risk for all event types in a single plot

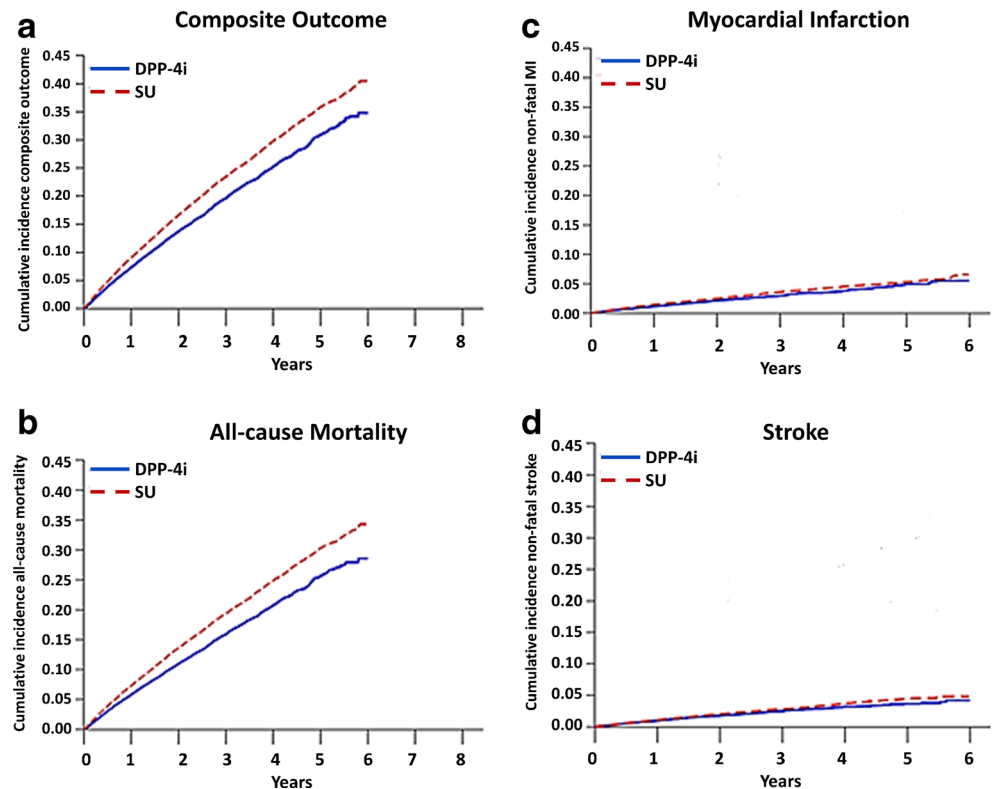


Counterfactual risks can be estimated under the assumptions outlined to estimate risk under the natural course in part 1, plus the additional assumption that subjects

receiving treatment plan *a* are exchangeable with subjects not receiving treatment plan *a* at time *t*. Exchangeability implies that the counterfactual risk, or the risk that *would*



**Fig. 2** Counterfactual risk functions for **a** a composite endpoint (MI, stroke and all-cause mortality), **b** all-cause mortality, **c** myocardial infarction (MI), and **d** stroke under initiation of dipeptidyl-peptidase 4 inhibitors (DPP-4i) and sulfonylureas (SU) among US Medicare recipients, 2007–2013, *dashed line* sulfonylureas, *solid line* dipeptidyl peptidase 4 inhibitor



have occurred under treatment plan  $a$ , is the same for patients who actually received treatment plan  $a$  as for patients who received other treatment plans. We can relax the exchangeability assumption to be conditional on a vector of covariates  $Z$  using inverse probability of treatment weights [35–37], as will be demonstrated in the next example. Other methods are possible, including the parametric g-formula [38–40] and targeted maximum likelihood estimation [41]. Relaxing the exchangeability assumption to be conditional on  $Z$  additionally requires the assumptions of positivity [42] (that is, that participants in all strata of  $Z$  have nonzero probability of being exposed to treatment plan  $a$ ) and correct specification of parametric models.

Inverse probability weights are a particularly appealing tool to estimate counterfactual risks [36, 43, 44]. As described by Cole et al. [45•], the weighted Aalen-Johansen estimator takes the form

$$\hat{F}^a(t, j) = \sum_{k \leq t} \frac{d_{kj}^w}{n_k^w} \prod_{h < k} \left\{ 1 - \frac{d_h^w}{n_h^w} \right\},$$

where  $d_{kj}^w$  is the weighted number of events of type  $j$  at time  $k$ ,  $n_k^w$  is the weighted number of subjects in the

risk set at time  $k$ , and  $d_h^w$  is the weighted number of all events at time  $h$  regardless of event type. The weights for each subject may take the form  $W_i = f\{A\}/f\{A|Z\}$ , where  $Z$  is a vector of covariates needed to satisfy the conditional exchangeability assumption and  $f\{A\}$  represents the conditional density function for  $A$  evaluated at the observed value. Other forms of the weights are possible when, for example, treatment plan is time-varying [37] or depends on subject-specific covariates [46]. When competing events may occur,  $Z$  must include all covariates needed to satisfy the assumption of conditional exchangeability between the treatment plan and both the event of interest and the competing events [47•]. If censoring is informative, an additional set of weights,  $W_i^C(t)$  may be used to account for differences between participants lost to follow-up and participants remaining in the study. Existing work provides technical details on censoring weights [48], intuition behind when and why such weights are needed [25], and practical details on when and how to implement censoring weights [26•]. The final weight for each subject is the product of the treatment and censoring weights. For a practical example of exposure and censoring weights in a setting with competing events, see [45•].

### Example: Comparative Risks of Cardiovascular Events under 2 Antidiabetic Drugs

In the following section, we compare counterfactual risk of CVD events under 2 alternative treatment strategies. Full details are available in work by Gokhale [49]. Briefly, this example compares risk of myocardial infarction (MI) and stroke among Medicare enrollees under initiation of 2 second-line antidiabetic drugs, dipeptidyl peptidase 4 inhibitors (DPP-4i) and sulfonylureas (SU), between 2007 and 2013. In this example, death is a common competing event. As in example 1, censoring patients who die may lead to overestimation of individual risks of MI or stroke. Instead, here we compare the two treatments using risk differences for MI and stroke (estimated using the Aalen-Johansen estimator) with risk differences for a composite endpoint of MI, stroke, or death.

This study included Medicare enrollees over age 65 who initiated DPP-4i ( $n=44,771$ ) or SU ( $n=119,436$ ) and had not used either of these drugs during the 6 months before drug initiation. To increase the probability that patients were actually started on treatment (reduce potential for secondary non-adherence), patients were required to fill a second prescription of the same drug class in the 180 days after initiation. Patients were followed from the date of their second prescription to the earliest of MI, stroke, death, treatment changes (stopping, switching or augmenting), end of Medicare enrollment or end of the administrative follow-up in December 2013. We compared risk at multiple time points using risk differences. Confidence intervals were obtained from the 2.5th and 97.5th percentiles of the point estimates from 1000 bootstrap resamples of the data [30].

This new-user active comparator design is analogous to a head-to-head randomized controlled clinical trial that answers the question of “which second-line treatment to initiate” rather than “whether to initiate a second-line treatment or not” [50]. Using an active comparator design balances the treatment groups with respect to many baseline patient characteristics and minimizes confounding by indication and confounding by frailty or functional status [51•, 52•]. We minimized remaining differences in a set of measured covariates between exposure groups using inverse probability of treatment weights [36, 43, 44].

In this example, 4720 composite events occurred among the DPP-4i initiators (725 MI, 593 stroke, and 3770 deaths) and 20,274 composite events occurred

among SU initiators (2765 MI, 2209 stroke, and 17,046 deaths) over the follow-up period. Deaths accounted for approximately 80 % of the events in both treatment groups indicating that a summary effect measure for the composite outcome would mainly represent the effect on death rather than the individual outcomes of MI or stroke. The risks under each treatment plan of the composite outcome and all-cause mortality indicate a protective effect of DPP-4i (Figure 2). However, risks of MI and stroke were similar under DPP-4i and SU when mortality was treated as a competing event and risk estimated with the Aalen-Johansen estimator. The adjusted risk difference for MI comparing DPP-4i versus SU ranged from  $-0.27$  % (95 % CI:  $-0.46$ ,  $-0.06$  %) at 1 year to  $-0.78$  % (95 % CI:  $-1.62$ ,  $0.12$  %) at 5 years and the adjusted risk difference for stroke ranged from  $-0.11$  % (95 % CI:  $-0.23$ ,  $0.03$  %) to  $-0.81$  % (95 % CI:  $-1.30$ ,  $-0.22$  %) at 1 and 5 years, respectively.

### Discussion

Here, we have summarized straightforward methods to estimate risk in settings with competing events. In addition, we have illustrated the application of these methods to estimate risk under the natural course and counterfactual risk using examples from pharmacoepidemiology. The examples have highlighted how competing events can inflate estimates of risk when they are inappropriately treated as censoring events and can mask or distort causal associations between treatments and outcomes when they are included as part of a composite event.

Assumptions are always required to estimate risk and counterfactual risk in scenarios with and without competing events. Methods exist to relax each of these assumptions and have been explored extensively in settings without competing events [35, 53–56]. The same methods can be applied to estimate risk in the presence of competing events. For example, in the sections above, we summarized methods to account for nonrandom treatment plan assignment (i.e., lack of exchangeability between treatment groups or confounding) and informative censoring using inverse probability weights. Appropriately relaxing assumptions in the presence of competing events may be slightly more complex than when competing events are not present; for example, the assumption of no unmeasured confounding in the presence of competing events must hold not only for

the effect of the treatment plan on the event of interest but also for the effect of the treatment plan on the competing event(s) [47••]. Extensions of the Aalen-Johansen estimator also exist to account for mismeasurement of event type [57••] and event time [58].

Risk can only be interpreted when presented as a function of time since some clearly defined origin, such as time since medication initiation or time since first treatment indication. The chosen origin should be meaningful for whomever ultimately uses the information from the study (e.g., the clinician or policy maker). The elements of the best origin for a particular analysis have been described and debated enthusiastically in the general epidemiology and pharmacoepidemiology literature [52•, 59–61]. Analyzing observational studies like hypothetical, pragmatic randomized trials can clarify decisions around the choice of origin [62]. Once choice of origin has been set, we have highlighted that risk is a function of time and as such any reported risk (or risk difference or risk ratio) must be accompanied by the time since the origin for which it was calculated. In both examples, we have also presented the full risk function such that the reader can see how risk changes as a function of time; risk ratios and risk differences could likewise be presented as a function of time [45••].

In both examples presented here, we compared risks between groups (example 1) and counterfactual risks (example 2) using risk ratios and risk differences, respectively. Alternatively, we could have compared groups or treatment plans using crude or adjusted hazard ratios from the subdistribution proportional hazards model described by Fine and Gray [63]. Such regression models are beyond the scope of this paper, but are explained clearly for the epidemiologist in work by Lau et al. [64] and Andersen et al. [65]. To illustrate how results from this approach compare with the risk ratios estimated in example 1, we have included subdistribution hazard ratios of cancer-related mortality for patients with and without each comorbidity in Appendix 2. We also compare the subdistribution hazard ratios to cause-specific hazard ratios estimated using cause-specific Cox proportional hazards models. Because comorbidities were associated with higher risk of non-cancer mortality, cause-specific hazard ratios, which censor competing events, were higher than subdistribution hazard ratios. However, the relationship between cause-specific hazard ratios and subdistribution hazard ratios is not always predictable. In settings where the effects of exposure on the event of interest and the competing event are in opposite directions, cause-specific hazard ratios and subdistribution

hazard ratios may not be on the same side of the null [66, 67•].

## Conclusions

Competing events are ubiquitous in pharmacoepidemiologic research. Popular simplified analytic solutions to handling competing events include censoring the competing events or using a composite endpoint that combines all possible event types. The method used to account for competing risks can alter the interpretation of study results and can dramatically affect absolute and relative risk estimates, particularly when competing events are not rare. We have highlighted issues that may arise when using these analytic simplifications and illustrated the use of the Aalen-Johansen estimator obtain interpretable, policy-relevant estimates of risk in the presence of competing events.

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## Compliance with Ethical Standards

**Conflict of Interest** Mugdha Gokhale is an employee of GlaxoSmithKline.

Laure Hester, Catherine Lesko, and Jessie Edwards declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** All studies referenced in this work by Edwards, Lesko, Gokhale, and Hester involving human subjects were performed after approval by the appropriate institutional review board. When required, written informed consent was obtained from all participants.



## Appendix 1: SAS code to estimate risks of cancer-related mortality in example #1

This SAS code assumes an input dataset with at least 2 variables: (1) a time variable  $t$  indicating the time from the origin to death or censoring and (2) an event indicator  $j$  with 3 levels (0 = censoring, 1 = cancer

death, 2 = other death). This code assumes no tied event times. If ties are present, we recommend adding a very small amount of random noise to the event times so that all event times are unique. The output of this code is a dataset with estimates of cancer-related mortality risk and noncancer-related mortality risk for each event time.

```
*Step 1) Use PHREG to estimate overall survival;
PROC PHREG data=a ;
model t*j(0)= /ties=efron;
output out=overall(keep=t s j) survival=s;
run;

*Step 2) create extra records to set s=1 at t=0;
DATA dum;
    t=0; s=1;
run;
DATA CR_cuminc;
    set overall dum;
RUN;
PROC SORT data=CR_cuminc;
    by t;
RUN;

*Step 3) Calculate risks for cancer-related mortality (ci_cancerdth) and non-cancer related
mortality (ci_otherdth);
DATA CR_cuminc;
    set CR_cuminc;
    by t;
retain ci_cancerdth 0 ci_otherdth 0 olds; *olds is the survival at the previous time;
    *initialize starting values;
    if t=0 then do;
        j=0; olds=1; ci_cancerdth=0; ci_otherdth=0; eh=0; edth=0; s=1;
    end;
    *at each cancer death, add step to risk function for cancer death;
    if j=1 then do; *if there was a cancer death at the event time, then ...;
        hh=-log(s)--log(olds); *hazard=change in cumulative hazard (H(t)=-log(S(t)));
        eh=olds*hh; *step size at time t: f(t,1)=h(t1)S(t-1);
        ci_cancerdth=ci_cancerdth+eh; *F(t,1)=sum_t f(t1);
    end;
    *at each noncancer death, add step to second risk function for noncancer death;
    if j=2 then do; *if there was a noncancer death at the event time, then ...;
        hdth=-log(s)--log(olds); *hazard of noncancer death;
        edth=olds*hdth; *step size for noncancer death f(t,2)=h(t2)S(t-1);
        ci_otherdth=ci_otherdth+edth; ; *F(t,2)=sum_t f(t,2);
    end;
    *Check that the combined cancer-specific and non-cancer risk estimates add up to km estimator of
    all-cause mortality;
    combinedrisk=ci_cancerdth+ci_otherdth;
    combined_km=1-s;
    *lag survival at the end;
    olds=s;
run;
```

## Appendix 2: Subdistribution hazard ratios for example 1

**Table 2** Cancer-related cause-specific and subdistribution hazard ratios associated with prevalent diabetes, congestive heart failure (CHF), or chronic obstructive pulmonary disease (COPD) at Non-Hodgkins Lymphoma (NHL) diagnosis, among  $N = 5192$  patients over age 65 in the linked SEER-Medicare database diagnosed 2007–2009

Group (n (%))	Total	Deaths		All-cause mortality HR (95 % CI)	Cancer-related mortality	
		Cancer	Non-cancer		HR <sub>CS</sub> (95 % CI)	HR <sub>SD</sub> (95 % CI)
Diabetes	1284	446 (35)	280 (22)	1.33 (1.21, 1.46)	1.28 (1.15, 1.43)	1.23 (1.11, 1.38)
CHF	620	247 (40)	215 (35)	1.72 (1.53, 1.93)	1.83 (1.59, 2.10)	1.54 (1.34, 1.78)
COPD	810	259 (32)	221 (27)	1.21 (1.08, 1.34)	1.10 (0.96, 1.26)	1.03 (0.90, 1.18)

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