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Bias due to confounders for the exposure-competing risk relationship

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Abstract

Background—Epidemiologic studies that aim to estimate a causal effect of an exposure on a particular event of interest may be complicated by the existence of competing events that preclude the occurrence of the primary event. Recently, many articles have been published in the epidemiologic literature demonstrating the need for appropriate models to accommodate competing risks when they are present. However, there has been little attention to variable selection for confounder control in competing risk analyses.

Methods—We employ simulation to demonstrate the bias in two variable selection strategies: include covariates that are associated with the exposure and 1) which change the cause-specific hazard of any of the outcomes; or 2) which change the cause-specific hazard of the specific event of interest.

Results—We demonstrated minimal to no bias in estimators adjusted for confounders of exposure and either the event of interest or the competing event, but bias of varying magnitude in almost all estimators adjusted only for confounders of exposure and the primary outcome.

Discussion—When estimating causal effects for which there are competing risks, the analysis should control for confounders of both the exposure–primary outcome effect and of the exposure–competing outcome effect.

In many epidemiologic studies, the event of interest may be precluded by another event, termed a competing risk. The majority of the epidemiologic literature on competing risk has focused on explaining why and how competing risks should be incorporated into epidemiologic analyses,[1–5] prediction,[6] inference when the cause of failure is misclassified or incompletely recorded.[7] However, there has been little attention given to estimation of causal effects in the presence of competing risks, and in particular to variable selection for confounder control.

Recent work on model specification in the presence of competing risks has focused on the development of stepwise variable selection procedures based on information criterion,[8] score statistics,[9] or various penalized likelihoods.[10,11] However, the field of epidemiology has largely moved away from automated variable selection procedures,[12–15] in favor of the use

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of background knowledge encoded in directed acyclic graphs (DAGs) to identify a set of variables sufficient for confounder control.[15–17] Our objective was to show that estimation of the cumulative incidence function will be biased when a confounder of the effect of exposure on a *competing* event is ignored. Furthermore, estimands based upon the cumulative incidence function, including the subdistribution proportional hazard ratio will also be biased.[18] We illustrate the bias with a simulation.

METHODS

Motivating example

Imagine an observational study of a hypothetical drug that alleviates symptoms of chronic obstructive pulmonary disease (COPD) but also increases mortality. A standard analysis might censor individuals when they die or report the incidence of a composite outcome. However, censoring individuals who die will overestimate the probability of chronic obstructive pulmonary disease (COPD) remission when deaths are not rare. Furthermore, it does not make sense to combine remission (a desirable outcome) with death (an undesirable outcome). Even when both outcomes are desirable or undesirable, analyzing a composite outcome results in a loss of information.[19] An analysis that explicitly incorporates competing risks (e.g., one that employs the Fine and Gray subdistribution hazard model[18] or that estimates the cumulative incidence function non-parametrically[1]) accounts for both the "direct" effect of the drug on the probability of COPD remission (because treated individuals have a higher hazard of COPD remission), and the "indirect" effect (because individuals who die are no longer at risk for COPD remission).

In the presence of competing risks, there are at least as many causal estimands as there are competing events. For example, denote the difference in the cumulative incidence of remission due to drug, $P(T_{a=1}<t,\ J_{a=1}=1) - P(T_{a=0}<t,\ J_{a=0}=1)$ and the difference in the cumulative incidence of death due to drug, $P(T_{a=1}<t,\ J_{a=1}=2) - P(T_{a=0}<t,\ J_{a=0}=2)$. Here, $P(\cdot)$ denotes probability; T is the composite event time; A denotes treatment type; and J distinguishes event types. T_a and J_a denote composite event time and event type that we would have seen under treatment a (that is, potential outcomes). Following convention, we denote random variables with capital letters and possible realizations of random variables with lower case letters. We borrow potential outcomes notation from Cole et al (2015).[1] In eAppendix A, we present an extension of potential outcomes notation that combines an event indicator with an event type indicator at a particular point in time, which allows incorporation of Greenland's causal response types to the competing risk setting.[20]

Brief introduction to competing risk

Complete introductions to competing risks have previously been published.[1,2,21] Nevertheless we reiterate some concepts for completeness. We limit discussion to two competing events; however, methods are easily extended to settings with more than two competing events.

The cumulative incidence function is perhaps the most natural estimand in the presence of competing risks and is defined:

$$F_j^*=P(T \leq t, J=j) \quad \text{Equation 1}$$

where F_j^* is used to denote the cumulative incidence function for the j^{th} event type, $j = 1, \ldots, J$; T and J are defined as above; and the asterisk distinguishes the cumulative incidence function from the conditional risk function estimated in standard survival analyses (e.g., complement of a Kaplan-Meier curve). Causal estimates can be generated by estimating the cumulative incidence function for each level of exposure, then taking a difference or ratio of those estimates, e.g., $F_{j,a=1}^* - F_{j,a=0}^*$. Contrast the cumulative incidence function with the conditional risk (where competing events are censored):

$$F_j=P(T' \leq t) \quad \text{Equation 2}$$

In (2), T' denotes time to event j. We explicitly embrace the term *conditional* risk function[22] to highlight the assumption embedded in the risk function when competing events are censored; the conditional risk function is the risk of the outcome in a world in which *all competing risks have been eliminated*, (without changing the cause-specific hazard of the event of interest). Imagining an intervention that would result in such a world is typically difficult, if not impossible. This assumption is also inherent in our definition of T'. T' does not exist for people who get the competing event; estimators of the conditional risk impute T' for people with the competing risk when they are treated as censored, despite the fact that by definition experiencing a competing event precludes the occurrence of event j. Therefore the conditional risk is rarely of interest because of its lack of grounding in reality.

Furthermore, in the presence of competing risks, $\sum_{j=1}^{J} F_j$ may exceed 1, violating the rule of coherence.[23]

The cumulative incidence function is a function of the cause-specific hazards:[24,25]

$$\begin{aligned} F_j^*(t) &= \int_0^t S(u-) h_j(u)\, du \\ &= \int_0^t \exp\left(-\int_0^{u-} \sum_{j=1}^{J} h_j(x)\, dx\right) h_j(u)\, du \end{aligned} \quad \text{Equation 3}$$

where $S(u-)$ is the survival function from all events (i.e., from the composite outcome) as it approaches u from the left and $h_j(t)$ denotes the cause-specific hazard for outcome j at time t:

$$h_j(t)= \lim_{\Delta t \to 0} \left\{ \frac{P(t<T \leq t+\Delta t,\ J=j | T>t)}{\Delta t} \right\} \quad \text{Equation 4}$$

The cause-specific hazard includes individuals who have survived from all events to time *t* in the risk set. Informally, (3) shows that the cumulative incidence function for event *j* is obtained by partitioning the cumulative incidence function for the composite event according to the relative magnitude of the cause-specific hazards. Importantly, one can see that the cumulative incidence function relies on the survival function, which is itself a function of the sum of the cause-specific hazards for both the primary event of interest and the competing event(s).

Because there is not a one-to-one relationship between the cause-specific hazard ratios and the relative cumulative incidence functions, Fine and Gray introduced the subdistribution hazards model. The risk set for the subdistribution hazard includes individuals who have survived until time *t* and those who failed due to the competing event prior to *t*.[18] The subdistribution hazard is defined:[18]

$$\lambda_j(t)=\lim_{\Delta t\to 0}\left\{\frac{P[t<T\leq t+\Delta t,\, J=j|T>t\cup(T<t\cap J\neq j)]}{\Delta t}\right\} \quad \text{Equation 5}$$

The cumulative incidence function is directly estimable from the subdistribution hazards:[18]

$$F_j^*(t)=1-\exp\left(-\int_0^t\lambda_j(u)\,du\right) \quad \text{Equation 6}$$

In the presence of confounding, the cumulative incidence functions for each level of exposure can be estimated nonparametrically (or semiparametrically, depending on the formulation of the weights) by estimating cause-specific or subdistribution hazards and applying (3) or (6) above, weighting each observation by the inverse probability of exposure.[26] CIFsCumulative incidence functions could also be estimated parametrically.[27–29] Interpretation of the these functions should be complemented by examination of the cause-specific hazards for *all* events.[3] If the exposure effects on the cause-specific hazard ratios are in the same direction for competing events, the exposure effects on the cumulative incidence functions are less predictable.[30]

The cause-specific hazards can be estimated from a Cox proportional hazards model, censoring individuals who fail with the competing event:

$$h_j(t|z)=h_{0j}(t)\exp(z^T\boldsymbol{\beta}_j) \quad \text{Equation 7}$$

where $h_{0j}(t)$ is the unspecified baseline cause-specific hazard, **z** a vector of covariates, and $\boldsymbol{\beta}_j$ the corresponding vector of regression coefficients such that $\exp(\boldsymbol{\beta}_j)$ are cause-specific hazard ratios associated with **z**. In the subdistribution proportional hazards model individuals who experience the competing event remain in the risk set until the end of follow-up and censored individuals are partitioned across the cumulative incidence functions for all the event types:

$$\lambda_j(t|z)=\lambda_{0j}(t)\exp(z^T\phi_j) \quad \text{Equation 8}$$

where λ_{0j} is the unspecified baseline subdistribution hazard and $\boldsymbol{\phi_j}$ the corresponding vector of regression coefficients such that exp($\boldsymbol{\phi_j}$) are subdistribution hazard ratios associated with **z**. Confounders can be included in either model, resulting in a covariate conditional hazard ratio due to exposure, or confounding can be controlled with inverse probability exposure weights, resulting in a marginal hazard ratio due to exposure. The covariate conditional and marginal hazard ratios may not be equal because the hazard ratio is a non-collapsible estimator.[31]

Variable selection strategies

When etiologic or interventional parameters are of interest, the purpose of variable selection is to block non-causal pathways between the exposure and outcome under study,[14–16,32] rather than to maximize a model's predictive ability. Strategies put forward for variable selection for confounder control, include identifying a minimally sufficient set of covariates for d-separation between exposure and outcome on a directed acyclic graph[17] (considered in more detail in the Discussion) and identifying confounders based on a set of criteria. One set of criteria for identifying confounders includes: confounders must be 1) associated with exposure, 2) either a true cause or a surrogate of a true cause of the outcome, and 3) not affected by exposure.[33,34] Another set of criteria states that if any set of covariates suffice to control confounding, selecting all pretreatment variables that cause exposure or cause the outcome will also control confounding.[32] However, existing strategies only reference the relationship between covariates and one outcome; to our knowledge, there is no guidance on how to handle covariates associated with exposure and competing outcomes. One strategy for selecting covariates for confounder control would be to include confounders of only the outcome of interest. A second, more inclusive strategy would be to also include confounders of the competing event.

Simulation

We simulated 1,000 cohorts of 1,000 individuals each, in which we estimated the effect of a dichotomous exposure, A on an outcome of interest, $j = 1$, in the presence of a competing event, $j = 2$, and two dichotomous confounders: Z_1, a confounder of the cause-specific hazard ratio for A on $j = 1$, and Z_2, a confounder of the cause-specific hazard ratio for A on $j = 2$ (henceforth, a confounder of A on $j = 1$and a confounder of A on $j = 2$, respectively). Discussions of confounders are typically not specific as to the estimand of interest, but previous work has shown that presence of confounding can depend on the outcome parameter of interest.[35] In this paper we generate confounding by simulating variables that change the odds of the exposure log-linearly and that change the cause-specific hazard of one of the two simulated events (but not the other) log-linearly. Details of the simulated data structure are provided in eAppendix B.

To establish values for the truth for each estimand, we generated deterministic potential outcomes for the 1,000,000 individuals across all simulations and cohorts, then calculated

the value of each estimand using the 2,000,000 potential outcomes (one for each of the two treatments).[36] Because the hazard ratio is non-collapsible,[31,35] we calculated true marginal and covariate conditional hazard ratios to contrast with inverse probability exposure weighted and covariate conditional estimators, by including only exposure, or exposure and covariates, respectively, in models fitted on the simulated potential outcomes. To calculate cause-specific hazard ratios, we fit Cox proportional hazards models[37] and censored individuals experiencing the competing event. To calculate subdistribution hazard ratios, we fit Cox proportional hazards models and set follow-up time to the end of follow-up for individuals experiencing the competing event; this is the subdistribution proportional hazards model in the absence of censoring.[18] We assumed no censoring in our simulation, as it would have complicated calculations without changing any conclusions. We calculated the true conditional risk functions and cumulative incidence function nonparametrically using the simulated potential outcomes.

In each simulated cohorts, we estimated the cause-specific hazard ratio and subdistribution hazard ratio from a Cox model and Fine and Gray model, respectively. We controlled for different sets of confounders using covariate adjustment and inverse probability exposure weights.[38] The conditional risk function and cumulative incidence function were estimated using inverse probability exposure weights,[26] and incidence was read off of those curves at t = 200 to estimate risk differences. Calculated risk differences at other times yielded substantively similar results; we present risk differences at only one time point (the end of follow-up) to simplify results. Within-simulation standard error for the inverse probability exposure weighted estimator (for calculating 95% confidence interval coverage) of the cause-specific and subdistribution hazard ratios was estimated using the robust variance. Within-simulation standard error for risk differences were estimated using the standard deviation of estimates from 200 bootstrap samples, sampled with replacement within each simulated cohort. We report the bias and percent bias averaged across all 1000 simulations, the average within-simulation standard error of the 1000 estimates, the average mean squared error (MSE) which we calculated as $[Bias(\hat{\theta},\theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance, and the percent coverage averaged across all 1000 simulations.

RESULTS

We present estimates from the simulation for in tables 1–6. For all parameter values we investigated, there was minimal to no bias in any estimators when we adjusted for both Z_1 and Z_2. There were, however, varying degrees of bias in the covariate-adjusted subdistribution hazard ratios for J = 1 when we adjusted only for Z_1. The percent bias was −14.8% in the base case (table 1; odds ratios for association between Zs and A, and cause-specific hazard ratio for association between Zs and T = 2.0). Percent bias increased to −19.2 when the odds ratios for association between Zs and A increased from 2.0 to 4.0 (table 2) and increased to −29.6 when the cause-specific hazard ratio for association between Zs and T increased from 2.0 to 4.0 (table 3). The bias remained when the cause-specific hazard ratio for A on T was set to 1.0 (null; table 4) and when the cause-specific hazard ratio for A on T was increased to 4.0 (table 5). Finally, in table 6, we present results from a simulation with strong associations between covariates Z_1 and Z_2 and A and the cause-specific hazard

ratios for T, to show that (although the set-up may be more extreme) there is bias in almost all the estimators adjusting only for Z_1 (i.e. adjusting only for confounders specific to the event under study and ignoring confounders of the competing event). In table 6, the percent bias in the subdistribution hazard ratio jumped to −44.3, while it was 11.0 and 9.5 for the inverse probability of exposure weighted estimator of the subdistribution hazard ratio and cumulative incidence difference, respectively.

All estimators related to the subdistribution hazards (the covariate-adjusted subdistribution hazard ratio, inverse probability exposure weighted subdistribution hazard ratio, and the cumulative incidence function) were biased when the confounder of the effect of exposure on the competing event was omitted, although by far the most clinically meaningful bias was in the covariate-adjusted subdistribution hazard ratio.

DISCUSSION

Others have suggested that all the pertinent statistical estimands in the presence of competing risks (cumulative incidence function, subdistribution hazards and subdistribution hazard ratio) are derived from the cause-specific hazards.[30] Therefore, given that the cumulative incidence function (and therefore the subdistribution hazards) are a function of all events (Equation 3), an imbalance in a covariate related to the exposure and a competing event would distort the difference in the cumulative incidence between exposed and unexposed groups. It is fairly straightforward to show mathematically that an unbiased estimator for any of the statistical estimands for a competing risks analysis requires adjustment for confounders of the effect of exposure on the competing event, in addition to the confounders of the effect of exposure on the event of interest. The reader may be disturbed by our demonstration that the competing risk estimands are biased when the cause-specific hazard ratios are not, but previous work has shown that confounding can depend on the outcome parameter of interest.[35] Furthermore, the cause-specific hazard ratios in our simulation were unbiased because the correct models were fit; in practice, correct model specification will never be assured. In a competing risk setting, the exposure may be associated with the probability of a particular event because (1) the exposure only directly causes or prevents the event of interest, (2) the exposure only causes or prevents the competing event, which subsequently indirectly permits or prevents the event of interest, or (3) the exposure both directly and indirectly causes or prevents the occurrence of the event of interest.

Cause-specific hazards interplay with one another and may produce unexpected results in the cumulative incidence function. In the simulation presented in this paper, we simulated cause-specific hazard ratios that were in opposite directions. However, if cause-specific hazard ratios are in the same direction for both the event of interest and the competing event, it is possible that the effect of exposure on the cumulative incidence function may be in the opposite direction.[30] It is impossible to accurately predict the effect of an exposure on the cumulative incidence function based on a single cause-specific hazard ratio alone. Both cause-specific hazard ratios and cumulative incidence functions should be investigated in the presence of a competing risk.[3]

In presenting results from our simulation, we have chosen to present the conditional risk curves and conditional risk differences. We have done this because it is not uncommon for analyses that include competing risks to ignore them and treat individuals who get the competing risk as censored. However, as stated earlier, interpretation of a conditional risk functions requires the assumption that somehow all the competing events could prevented without affecting the risk of the event of interest; in nearly every scenario, this assumption is unrealistic. We reiterate that estimating conditional risks is not appropriate or meaningful when competing risks are present.

To our knowledge, this is the first paper to address variable selection for competing risk analyses when causal inference is the goal of the inquiry. We have demonstrated that in order to have unbiased estimators in a competing risk analysis, the analysis should control for confounders of both the effect of exposure on the primary event and of the effect of exposure on the competing event. However, we have not addressed how to identify confounders of either or both relationships. In the Methods section we recalled criteria for confounder selection and briefly mentioned directed acyclic graphs (DAGs) as an aid favored by epidemiologists for confounder identification. DAGs are a representation of the researcher's hypothesis about the causal relationships between exposure, the outcome of interest, and all of their common causes. Using graphical criteria to analyze the DAG leads to identification of a minimally sufficient set of variables to block all non-causal paths between exposure and the *primary* outcome of interest.[17] While the extension of this strategy to a competing risk situation may seem trivial, there are no established rules for representing competing risks on a DAG. To illustrate bias in the presence of competing risks, several authors have drawn DAGs with two outcome nodes, one for the event of interest and one for the competing event, with a box around the competing event indicating that a typical cause-specific analysis is restricted to those who do not experience the competing event.[39,40] An analysis that censors individuals who experience the competing event and estimates conditional risks might be represented by drawing a box around the competing event. However, it is unclear how to alter the DAG when conducting a competing risk analysis. Indeed, including separate nodes for the event of interest and the competing event may cause researchers to forget that the two nodes cannot be separated because they are often two halves of the same coin.[19,41] On such a DAG, one may be tempted to remove the box around the competing event, but then the DAG appears to indicate that $Z_2 \perp Y, J{=}1$, which we demonstrated *not* to be the case in our simulation. Perhaps researchers would do better to include a node on the DAG that is the composite outcome, because that would generally lead us to the correct conclusion about what covariates are confounders (all covariates that are confounders of any exposure-outcome cause-specific effect). A complete discourse on DAGs in the presence of competing risks is beyond the scope of this paper.

Both the cumulative incidence functions and the cause-specific hazard ratios provide insight into the mechanisms at work in the presence of competing risks, and both should be estimated. When the goal of an investigation is causal inference, and there is a competing event that may preclude occurrence of the event of interest, we have demonstrated that confounders of the effect of the exposure on both the primary event and the competing event must be controlled. The resultant bias from failing to account for confounders of the

exposure effect on the competing event is likely to increase with increasing incidence of the competing event, although the direction of the bias is generally unpredictable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Simulation results, estimands for event of type $J = 1$, true cause-specific $HR_{J=2} = 2.0$, true association between Z_1 and A OR= 2.0, true association between Z_2 and A OR=2.0, true cause-specific HR = 2.0 for associations between Z_1 and event $J = 1$ and between Z_2 and event $J = 2$

	Truth		Avg. Bias		Avg. Pct. Bias		Avg. Std. Error		MSE[a]		95% Coverage	
	Conditional on…[b]		Controlling for…		Controlling for…		Controlling for…		Controlling for…		Controlling for…	
Parameter	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**
Cause-specific log(HR)												
Covariate adjusted	−0.692	−0.692	−0.006	−0.005	0.8	0.8	0.128	0.126	0.019	0.019	96.7	96.3
IPEW estimator[c]	−0.679		−0.004	−0.004	0.6	0.6	0.128	0.126	0.022	0.051	97.1	97.1
RD, [d] conditional risk[c]	−0.168		−0.000	−0.000	0.1	0.2	0.031	0.030	0.001	0.001	96.9	96.8
Subdistribution log(HR)[e]												
Covariate adjusted	−0.746	−0.733	−0.007	0.109	1.0	−14.8	0.128	0.126	0.015	0.027	96.1	87.5
IPEW estimator[c]	−0.733		−0.005	−0.016	0.7	2.2	0.128	0.126	0.015	0.015	96.6	96.9
RD,[d] CIF[c]	−0.170		−0.001	−0.003	0.3	1.8	0.029	0.020	0.001	0.000	96.4	96.6

Abbreviations: Avg., average; CIF, cumulative incidence function; HR, hazard ratio; IPEW, inverse probability of exposure weighted; MSE, mean squared error; OR, odds ratio; Pct., percent; RD, risk difference

[a] Mean Squared Error. $MSE(\hat{\theta}) = [Bias(\hat{\theta}, \theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance

[b] Truth varies according to variables included in the model for the HR because it is a non-collapsible measure.

[c] Truth is marginal (not conditional on any covariates)

[d] Difference in cumulative incidence functions or conditional risk functions estimated at $t = 200$.

[e] Because cause-specific hazards were simulated to be proportional, subdistribution hazards are not proportional. Truth here is a time-averaged subdistribution hazard ratio.

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Table 2

Simulation results, estimands for event of type $J = 1$, true cause-specific $HR_{J=2} = 2.0$, true association between Z_1 and A OR = **4.0**, true association between Z_2 and A OR = **4.0**, true cause-specific HR = 2.0 for associations between Z_1 and event $J = 1$ and between Z_2 and event $J = 2$

	Truth		Avg. Bias		Avg. Pct. Bias		Avg. Std. Error		MSE[a]		95% Coverage	
	Conditional on…[b]		Controlling for…		Controlling for…		Controlling for…		Controlling for…		Controlling for…	
Parameter	Z_1 & Z_2	Z_1 only	Z_1 & Z_2	Z_1 only	Z_1 & Z_2	Z_1 only	Z_1 & Z_2	Z_1 only	Z_1 & Z_2	Z_1 only	Z_1 & Z_2	Z_1 only
Cause-specific log(HR)												
Covariate adjusted	−0.692	−0.692	−0.008	−0.007	1.1	1.1	0.138	0.129	0.017	0.016	95.4	95.7
IPEW estimator[c]	−0.679		−0.008	−0.006	1.2	0.9	0.139	0.129	0.018	0.015	96.0	96.2
RD, [d] conditional risk[c]	−0.168		−0.001	−0.001	0.8	0.6	0.033	0.031	0.001	0.001	95.7	96.1
Subdistribution log(HR)[e]												
Covariate adjusted	−0.746	−0.733	−0.010	0.214	1.3	−19.2	0.136	0.129	0.018	0.062	95.6	61.1
IPEW estimator[c]	−0.733		−0.009	−0.028	1.3	3.9	0.139	0.129	0.018	0.016	96.1	95.9
RD,[d] CIF[c]	−0.171		−0.001	−0.006	0.9	3.5	0.031	0.029	0.001	0.001	95.7	95.7

Abbreviations: Avg., average; CIF, cumulative incidence function; HR, hazard ratio; IPEW, inverse probability of exposure weighted; MSE, mean squared error; OR, odds ratio; Pct., percent; RD, risk difference

[a] Mean Squared Error. $MSE(\hat{\theta}) = [Bias(\hat{\theta}, \theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance

[b] Truth varies according to variables included in the model for the HR because it is a non-collapsible measure.

[c] Truth is marginal (not conditional on any covariates)

[d] Difference in cumulative incidence functions or conditional risk functions estimated at $t = 200$

[e] Because cause-specific hazards were simulated to be proportional, subdistribution hazards are not proportional. Truth here is a time-averaged subdistribution hazard ratio.

Table 3

Simulation results, estimands for event of type $J = 1$, true cause-specific $HR_{J=2} = 2.0$, true association between Z_1 and A OR = 2.0, true association between Z_2 and A OR = 2.0, true cause-specific HR = **4.0** for associations between Z_1 and event $J = 1$and between Z_2 and event $J = 2$

	Truth		Avg. Bias		Avg. Pct. Bias		Avg. Std. Error		MSE[a]		95% Coverage	
	Conditional on…[b]		Controlling for…		Controlling for…		Controlling for…		Controlling for…		Controlling for…	
Parameter	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**
Cause-specific log(HR)												
Covariate adjusted	−0.692	−0.692	−0.002	−0.002	0.3	0.3	0.110	0.109	0.013	0.013	95.0	95.1
IPEW estimator[c]	−0.621		−0.001	0.000	0.1	0.1	0.110	0.108	0.010	0.010	96.4	96.5
RD, [d] conditional risk[c]	−0.191		0.000	0.000	−0.2	−0.2	0.030	0.030	0.001	0.001	96.2	96.6
Subdistribution log(HR)[e]												
Covariate adjusted	−0.768	−0.704	−0.005	0.208	0.6	−29.6	0.111	0.109	0.013	0.056	95.1	51.7
IPEW estimator[c]	−0.704		−0.002	−0.035	0.3	5.0	0.110	0.108	0.011	0.012	96.2	94.9
RD,[d] CIF[c]	−0.200		0.000	−0.009	0.0	4.7	0.030	0.030	0.001	0.001	96.1	94.6

Abbreviations: Avg., average; CIF, cumulative incidence function; HR, hazard ratio; IPEW, inverse probability of exposure weighted; MSE, mean squared error; OR, odds ratio; Pct., percent; RD, risk difference

[a] Mean Squared Error. $MSE(\hat{\theta}) = [Bias(\hat{\theta}, \theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance

[b] Truth varies according to variables included in the model for the HR because it is a non-collapsible measure.

[c] Truth is marginal (not conditional on any covariates)

[d] Difference in cumulative incidence functions or conditional risk functions estimated at $t = 200$

[e] Because cause-specific hazards were simulated to be proportional, subdistribution hazards are not proportional. Truth here is a time-averaged subdistribution hazard ratio.

Table 4

Simulation results, estimands for event of type $J = 1$, true cause-specific $HR_{J=2}$ = **1.0**, true association between Z_1 and A OR = 2.0, true association between Z_2 and A OR = 2.0, true csHR = 2.0 for associations between Z_1 and event $J = 1$ and between Z_2 and event $J = 2$

	Truth		Avg. Bias		Avg. Pct. Bias		Avg. Std. Error		MSE[a]		95% Coverage	
	Conditional on…[b]		Controlling for…		Controlling for…		Controlling for…		Controlling for…		Controlling for…	
Parameter	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**
Cause-specific log(HR)												
Covariate adjusted	−0.691	−0.691	−0.001	0.000	0.1	−0.1	0.125	0.124	0.017	0.017	94.7	93.9
IPEW estimator[c]	−0.677		0.001	0.002	−0.2	−0.3	0.125	0.123	0.016	0.016	94.6	93.9
RD, [d] conditional risk[c]	−0.168		0.001	0.001	−0.5	−0.6	0.030	0.030	0.001	0.001	94.5	93.8
Subdistribution log(HR)[e]												
Covariate adjusted	−0.683	−0.670	−0.002	0.114	0.3	−17.0	0.125	0.123	0.017	0.030	94.2	83.3
IPEW estimator[c]	−0.670		0.000	−0.007	0.0	1.0	0.125	0.123	0.016	0.016	94.4	94.3
RD,[d] CIF[c]	−0.159		0.000	−0.001	−0.3	0.8	0.030	0.028	0.001	0.001	93.6	93.6

Abbreviations: Avg., average; CIF, cumulative incidence function; HR, hazard ratio; IPEW, inverse probability of exposure weighted; MSE, mean squared error; OR, odds ratio; Pct., percent; RD, risk difference

[a] Mean Squared Error. $MSE(\hat{\theta}) = [Bias(\hat{\theta}, \theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance

[b] Truth varies according to variables included in the model for the HR because it is a non-collapsible measure.

[c] Truth is marginal (not conditional on any covariates)

[d] Difference in cumulative incidence functions or conditional risk functions estimated at $t = 50$

[e] Because cause-specific hazards were simulated to be proportional, subdistribution hazards are not proportional. Truth here is a time-averaged subdistribution hazard ratio.

Table 5

Simulation results, estimands for event of type $J = 1$, true cause-specific $HR_{J=2}$ = **4.0**, true association between Z_1 and A OR = 2.0, true association between Z_2 and A OR = 2.0, true cause-specific HR = 2.0 for associations between Z_1 and event $J = 1$ and between Z_2 and event $J = 2$

	Truth		Avg. Bias		Avg. Pct. Bias		Avg. Std. Error		MSE[a]		95% Coverage	
	Conditional on…[b]		Controlling for…		Controlling for…		Controlling for…		Controlling for…		Controlling for…	
Parameter	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**
Cause-specific log(HR)												
Covariate adjusted	−0.696	−0.696	0.003	0.004	−0.4	−0.5	0.132	0.131	0.018	0.017	95.4	95.5
IPEW estimator[c]	−0.682		0.003	0.005	−0.5	−0.7	0.133	0.130	0.017	0.017	95.9	95.8
RD, [d] conditional risk[c]	−0.169		0.002	0.002	−0.9	−1.0	0.024	0.024	0.001	0.001	95.0	94.7
Subdistribution log(HR)[e]												
Covariate adjusted	−0.871	−0.857	−0.001	0.114	0.1	−13.3	0.133	0.130	0.018	0.030	94.7	85.2
IPEW estimator[c]	−0.857		0.002	−0.015	−0.2	1.7	0.133	0.131	0.017	0.017	95.8	95.9
RD,[d] CIF[c]	−0.193		0.001	−0.002	−0.6	1.1	0.028	0.028	0.001	0.001	94.9	94.7

Abbreviations: Avg., average; CIF, cumulative incidence function; HR, hazard ratio; IPEW, inverse probability of exposure weighted; MSE, mean squared error; OR, odds ratio; Pct., percent; RD, risk difference

[a] Mean Squared Error. $MSE(\hat{\theta}) = [Bias(\hat{\theta}, \theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance

[b] Truth varies according to variables included in the model for the HR because it is a non-collapsible measure.

[c] Truth is marginal (not conditional on any covariates)

[d] Difference in cumulative incidence functions or conditional risk functions estimated at $t = 50$

[e] Because cause-specific hazards were simulated to be proportional, subdistribution hazards are not proportional. Truth here is a time-averaged subdistribution hazard ratio.

Table 6

Simulation results, estimands for event of type $J = 1$, true cause-specific $HR_{J=2}$ = **4.0**, true association between Z_1 and A OR = **4.0**, true association between Z_2 and A OR = **4.0**, true cause-specific HR = **4.0** for associations between Z_1 and event $J = 1$ and between Z_2 and event $J = 2$

	Truth		Avg. Bias		Avg. Pct. Bias		Avg. Std. Error		MSE[a]		95% Coverage	
	Conditional on…[b]		Controlling for…		Controlling for…		Controlling for…		Controlling for…		Controlling for…	
Parameter	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**	**Z_1 & Z_2**	**Z_1 only**
Cause-specific log(HR)												
Covariate adjusted	−0.695	−0.695	−0.001	−0.002	0.2	0.3	0.122	0.119	0.016	0.015	94.1	93.8
IPEW estimator[c]	−0.625		0.001	0.010	−0.2	−1.6	0.127	0.118	0.014	0.013	96.4	96.4
RD, [d] conditional risk[c]	−0.192		0.001	0.003	−0.7	−1.7	0.038	0.035	0.001	0.001	95.9	96.1
Subdistribution log(HR)[e]												
Covariate adjusted	−0.962	−0.890	−0.005	0.395	0.5	−44.3	0.125	0.119	0.017	0.170	94.1	10.1
IPEW estimator[c]	−0.891		−0.001	−0.098	0.1	11.0	0.126	0.117	0.014	0.022	96.7	88.9
RD,[d] CIF[c]	−0.242		0.001	−0.023	−0.3	9.5	0.032	0.029	0.001	0.001	96.8	89.3

Abbreviations: Avg., average; CIF, cumulative incidence function; HR, hazard ratio; IPEW, inverse probability of exposure weighted; MSE, mean squared error; OR, odds ratio; Pct., percent; RD, risk difference

[a] Mean Squared Error. $MSE(\hat{\theta}) = [Bias(\hat{\theta}, \theta)]^2 + Var(\theta)$ where $Var(\theta)$ is the Monte Carlo variance

[b] Truth varies according to variables included in the model for the HR because it is a non-collapsible measure.

[c] Truth is marginal (not conditional on any covariates)

[d] Difference in cumulative incidence functions or conditional risk functions estimated at $t = 50$

[e] Because cause-specific hazards were simulated to be proportional, subdistribution hazards are not proportional. Truth here is a time-averaged subdistribution hazard ratio.