

## Practice of Epidemiology

### Competing Risk Regression Models for Epidemiologic Data

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Competing events can preclude the event of interest from occurring in epidemiologic data and can be analyzed by using extensions of survival analysis methods. In this paper, the authors outline 3 regression approaches for estimating 2 key quantities in competing risks analysis: the cause-specific relative hazard ( $_{cs}RH$ ) and the subdistribution relative hazard ( $_{sd}RH$ ). They compare and contrast the structure of the risk sets and the interpretation of parameters obtained with these methods. They also demonstrate the use of these methods with data from the Women's Interagency HIV Study established in 1993, treating time to initiation of highly active antiretroviral therapy or to clinical disease progression as competing events. In our example, women with an injection drug use history were less likely than those without a history of injection drug use to initiate therapy prior to progression to acquired immunodeficiency syndrome or death by both measures of association ( $_{cs}RH = 0.67$ , 95% confidence interval: 0.57, 0.80 and  $_{sd}RH = 0.60$ , 95% confidence interval: 0.50, 0.71). Moreover, the relative hazards for disease progression prior to treatment were elevated ( $_{cs}RH = 1.71$ , 95% confidence interval: 1.37, 2.13 and  $_{sd}RH = 2.01$ , 95% confidence interval: 1.62, 2.51). Methods for competing risks should be used by epidemiologists, with the choice of method guided by the scientific question.

competing risks; epidemiologic methods; mixture model; proportional hazards; regression; survival analysis

Abbreviations: AIDS, acquired immunodeficiency syndrome; CIF, cumulative incidence function;  $_{cs}CIF$ , cause-specific cumulative incidence function;  $_{cs}RH$ , cause-specific relative hazard; HIV, human immunodeficiency virus;  $_{sd}CIF$ , subdistribution cumulative incidence function;  $_{sd}RH$ , subdistribution relative hazard; WIHS, Women's Interagency HIV Study.

In time-to-event analyses, the occurrence of the event of interest is often precluded by another event. The canonical example is the study predictors of cause-specific mortality, whereby a death due to the primary cause of interest (e.g., cancer-related deaths) is precluded by death due to other causes. In this competing risks setting (1–3), individuals are observed from study entry to the occurrence of the event of interest, a competing event, or censoring. Competing risks are common to epidemiologic research (4–7), and recognition dates to the 1700s when Bernoulli estimated mortality rates (1, 8, 9).

The complement of the Kaplan-Meier survival curve may not appropriately estimate the cumulative incidence when competing events are censored (10–13). Both nonparametric (2, 10, 14, 15) and regression (8, 16, 17) methods exist for analyzing data with competing events. Although the non-

parametric approaches have been well described, 2 widely used measures from regression approaches, the cause-specific relative hazard ( $_{cs}RH$ ) and the subdistribution relative hazard ( $_{sd}RH$ ), have not been well described in the epidemiology literature (18).

The purpose of this paper is 3-fold. First, we provide intuition for the  $_{cs}RH$  and  $_{sd}RH$  by considering the construction of risk sets and interpretation of the underlying hazard function. Second, we describe 3 different regression models for the analysis of epidemiologic data with competing risks. Third, we illustrate the use of these methods in an analysis that explores the association of injection drug use with the time to 2 competing outcomes in a cohort of human immunodeficiency virus (HIV)-infected women: initiation of combination antiretroviral therapy and the occurrence of acquired immunodeficiency syndrome (AIDS)

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or death prior to initiating combination antiretroviral therapy.

## MATERIALS AND METHODS

### Key measures in a competing risk framework

Five interrelated building blocks underpin standard (non-competing) survival analysis: the time scale  $t$  (e.g., age, calendar time, disease duration, or study duration); the risk set; the hazard function  $h(t)$ ; the cumulative incidence function (CIF)  $F(t)$ ; and its complement, the survival function  $S(t) = 1 - F(t)$ . In a competing risks framework, each of these components remains of central importance but modified, depending on how the competing event is handled. We consider an event of interest (event 1) and only 1 competing event (event 2), although one may extend to more events. We assume no measurement error, noninformative censoring, and no unmeasured confounding. Henceforth,  $T$  will be defined as the minimum time to either event 1 or event 2 ( $T = \min(T_1, T_2, C)$ , where  $T_1$  and  $T_2$  correspond to time to event 1 and event 2, respectively, and  $C$  corresponds to the censoring time).

### A framework for competing risk regression

The regression approaches described below focus on 2 definitions of hazard, the cause-specific and the subdistribution hazards. The corresponding  $_{cs}RH$  may be better suited for studying the etiology of diseases, whereas the  $_{sd}RH$  has use in predicting an individual's risk or allocating resources.

Consider an example. A group of diseased individuals are randomized to treatment A or treatment B, everyone is compliant to treatment protocols, and all are followed until either the disease is cured or individuals have an adverse event requiring discontinuation of treatment. The cumulative incidence for being cured may be estimated as  $1 -$  the Kaplan-Meier product limit estimator stratified by treatment. Both curves will be essentially 1.0 by the end of follow-up, as everyone is followed to 1 of the 2 events. The shift in curves represents the etiologic association between treatment type and being cured, in that it reflects the relative change in the underlying hazard. However, one would not predict that the probability of being cured was 1.0 for either treatment by the end of follow-up, as we know that some individuals have the adverse event and must discontinue therapy. For prediction, one may require a curve that reflects the proportion cured by the end of follow-up. Additionally, if the  $_{cs}RH_{adverse} > _{cs}RH_{cure} \geq 1.0$  comparing treatment A versus treatment B, then the adverse event is occurring at a greater hazard rate in treatment group A. Thus, the proportion of individuals being cured would be different by treatment status by the end of follow-up even if the cure rates are the same. Therefore, the shift in these observed cumulative incidence curves should represent not only the etiologic association of treatment with being cured but also the influence of having a reduced number of individuals remaining at risk for being cured in group A due to a greater number of adverse events. The lower observed number of individuals being cured because of a greater proportion of

adverse events may actually overpower the etiologic association, such that the observed cumulative incidence of being cured is no longer different between treatment groups. The nonparametric estimator for competing risks accounts for these issues. Similarly, the cause-specific and subdistribution hazard approaches reflect these 2 different kinds of comparison.

### The cause-specific hazard

The manner in which risk sets are defined in standard survival analyses may be modified to allow for competing events. In standard survival analysis, the *risk set* is defined as the group of individuals that have not experienced the outcome and therefore are at risk for the event of interest at time  $t$ . Individuals who have a competing event can be removed from all later risk sets for the event of interest. Figure 1 illustrates this approach in discrete time. At time 0, there are 30 individuals at risk. At time 1, 1 individual has event 1, and another individual has event 2, such that the risk set for time 2 is now  $28 = 30 - 1_{\text{event 1}} - 1_{\text{event 2}}$ . Thus, individuals with an event 1 or event 2 prior to time  $t$  are excluded from the risk set at time  $t$ .

An estimate of the hazard for event 1 can be described in the discrete time setting as the number of individuals who experience the event divided by the number at risk at time  $t$ . For example, at time 3, this would be  $3/26 = 0.12$ , which estimates the *cause-specific hazard*, which is formally defined as  $h_j(t) = P(T = t, J = j | T \geq t)$ , where  $J = j$  indicates whether event 1 ( $j = 1$ ) or event 2 ( $j = 2$ ) is being estimated.

The cause-specific hazard can be extended to continuous time (8, 19):

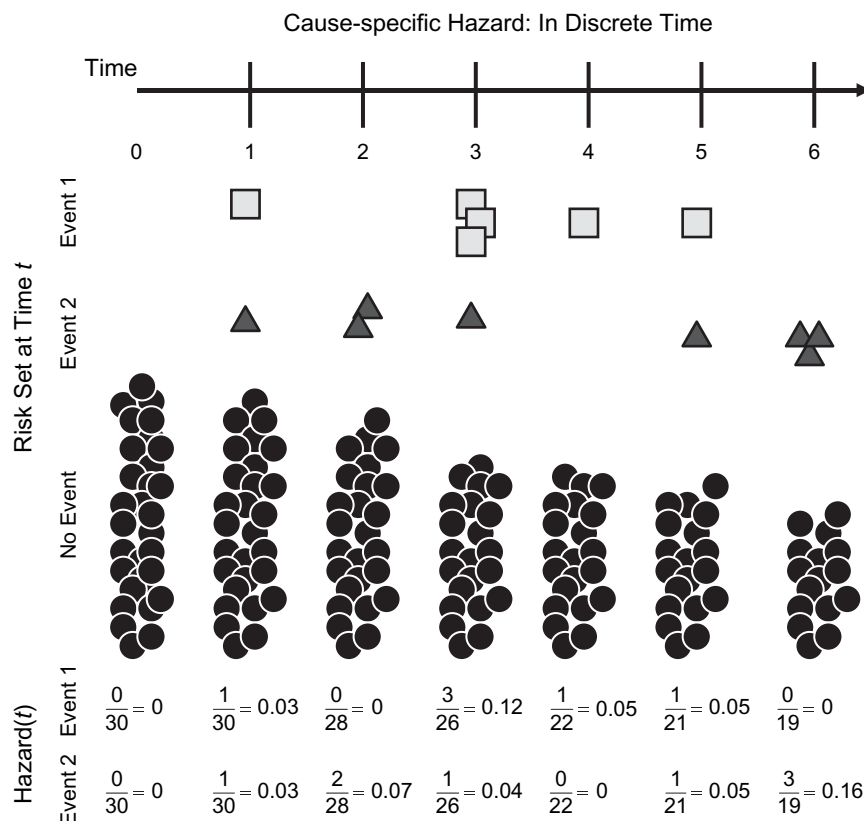
$$h_j(t) = \lim_{\Delta t \rightarrow 0} \left\{ \frac{P(t < T \leq t + \Delta t, J = j | T > t)}{\Delta t} \right\} = \frac{f_j^*(t)}{S(t)}, \quad (1)$$

where  $f_j^*(t) = P(T = t, J = j)$  is a "sub"-density function ("\*" indicates an improper, i.e., "sub"-density function that integrates to  $< 1$ ), and  $S(t)$  reflects the net survival function of both events 1 and 2, that is,  $S(t) = P(T > t) = \exp[-\int_0^t \sum_{j=1}^2 h_j(u) du] = \exp[-\int_0^t h(u) du]$ , where  $h(t)$  is the net hazard for having either event 1 or event 2 (8).

As described in the Web supplement posted on the *Journal's* website (<http://aje.oxfordjournals.org/>), a likelihood function can be constructed from the cause-specific hazards, whereby individuals who experienced a competing event are treated as censored (8). Consequently, a proportional hazards model can be constructed for the cause-specific hazard:

$$h_j(t|z) = h_{0j}(t) \exp(z^T \beta_j) \quad j = 1, 2, \quad (2)$$

where  $h_{0j}$  is the arbitrary baseline cause-specific hazard, and  $\beta_j$ ,  $j = 1, 2$  are the corresponding regression coefficients, where  $\exp(\beta_j) = _{cs}RH_j$  is interpretable as the relative change in the cause-specific hazard for the  $j$ th event corresponding to a 1-unit increase in the corresponding covariate.



**Figure 1.** Cause-specific hazard schematic. The risk set starts with 30 individuals (solid circles). Over time, individuals have either event 1 (square) or event 2 (triangle). As individuals have either event, they are removed from the remaining risk sets. The calculation for the cause-specific hazard is given at the bottom of the figure.

No assumptions of the relation between the competing outcomes are needed for estimation (2, 8). Estimation may be accomplished by using standard software. A proportional hazards model is constructed separately for each event type in which individuals who experience the competing event are treated as censored observations. Because the likelihood may be written such that the competing event is treated as a censored event, this proportional hazards model is exactly the same as what some investigators model when “ignoring” competing events. Alternatively, rather than separate models, a joint model could be used (20) (refer to Web supplement).

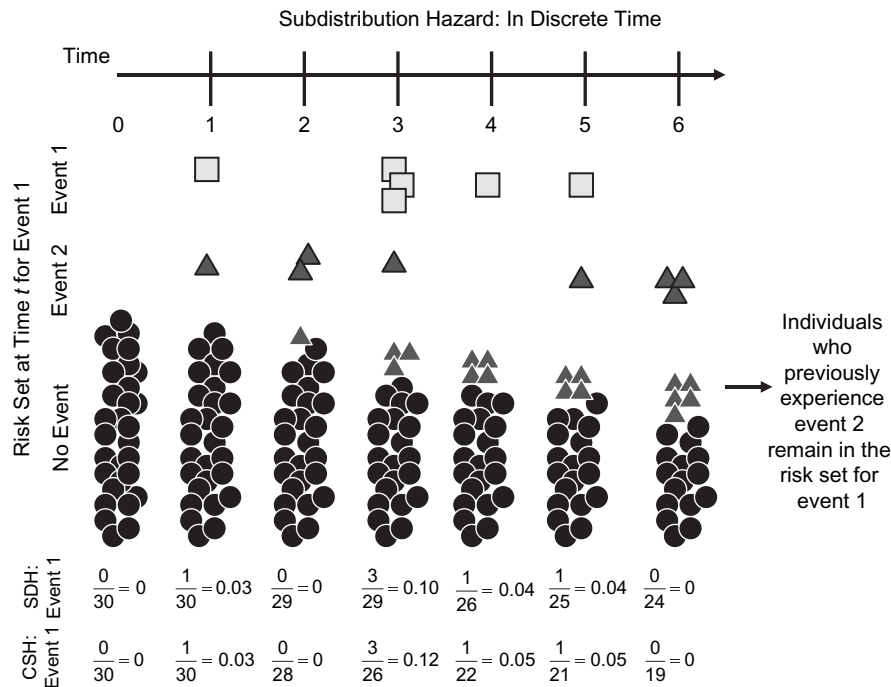
A Breslow estimator (21, 22) of the cumulative incidence proportion can be calculated by using the cause-specific hazard under the (untestable) assumption that the competing events are independent of each other (3, 18, 23–25). Models linking covariates to cause-specific hazards as measured by  ${}_{cs}RH_{j=1}$  provide a summary of how a covariate directly impacts the incidence without considering the effect of the competing event. Much has been written about how inferences from this approach need to be evaluated cautiously (8, 26), because the assumption of independent competing events is strongly needed to underpin the inference that the cause-specific hazard and corresponding cumulative inci-

dence functions quantify the risk of the event in hypothetical populations where competing events are eliminated (8). Therefore, caution must be used in interpreting  ${}_{cs}RH$  as an increase (decrease) in apparent risk; it is, however, valid to interpret it as a relative change in the cause-specific hazard rate.

### The subdistribution hazard

In light of the strong assumption of independence between events to allow interpretation of the cause-specific cumulative incidence function ( ${}_{cs}CIF$ ), the competing risk literature has focused on an alternative measure of risk: the subdistribution cumulative incidence function ( ${}_{sd}CIF$ ). This function is defined as the joint probability of an event prior to time  $t$  and that the event is of type  $j$ :  $F_j^*(t) = P(T < t, J = j)$ . Although the  ${}_{sd}CIF$  may be estimated from the  ${}_{cs}RH_{j=1}$ , extra steps are required as the  ${}_{sd}CIF$  is a function of the net survivor function and therefore directly impacted by the competing event (27, 28). The  ${}_{sd}CIF$  may be modeled directly.

Interpretation of this measure can be understood by returning to the construction of risk sets and hazard functions. In contrast to the construction of risk sets that eliminate



**Figure 2.** Subdistribution hazard schematic. The risk set starts with 30 individuals (solid circles). Over time, individuals have either event 1 (square) or event 2 (triangle). As individuals have the competing event (event 2, triangle), they are maintained in the risk set as triangles. Thus, over time, a greater proportion of the risk set becomes full of triangles that are individuals who have had the competing event prior to that time. The subdistribution hazard (SDH) for event 1 is given near the bottom of the figure along with the cause-specific hazard (CSH) for event 1 for comparison. Note that, because individuals are maintained in the risk set, the SDH tends to be lower than the CSH.

individuals who have the competing cause, risk sets were constructed so that they include both individuals without any event and those who have had the competing event. It may be counterintuitive to maintain individuals who had a competing event in the risk set. However, one can think of these individuals as a “placeholder” for the proportion of the population that cannot have the event of interest and place a constraint on this hazard function definition (16). Figure 2 illustrates this construction with the same population as in Figure 1. For example, one individual had the competing event at time 1 and is therefore maintained in the subsequent risk sets. Therefore, at  $t = 2$ , the risk set comprised 29 individuals; at  $t = 3$ , a total of 3 individuals by this time have previously experienced event 2 and are maintained in the risk set. With increasing  $t$ , the risk set comprised an increasing proportion of individuals who have had event 2.

With this structure, a different hazard function is defined as the probability of the event given that an individual has survived up to time  $t$  without any event or has had the competing event prior to time  $t$ . This is the *subdistribution hazard* (16). For example at  $t = 3$ , the subdistribution hazard is  $3/29 = 0.103$ , which is smaller than the cause-specific hazard of 0.12 because of the larger risk set.

For the discrete time setting, the subdistribution hazard is  $\lambda_j(t) = P(T = t, J = j | T \geq t \text{ or } (T < t \text{ and } J \neq j))$ . In continuous time, the subdistribution hazard is the following (16):

$$\lambda_j(t) = \lim_{\Delta t \rightarrow 0} \left\{ \frac{P[t < T \leq t + \Delta t, J = j | T > t \cup (T < t \cap J \neq j)]}{\Delta t} \right\} = \frac{f_j^*(t)}{1 - F_j^*(t)} = \frac{f_j^*(t)}{P(J \neq j) + S_j^*(t)}, \quad (3)$$

where  $F_j^*(t) = P(T < t, J = j)$ ,  $S_j^*(t) = P(T > t, J = j)$ , and  $f_j^*(t) = \frac{\partial F_j^*(t)}{\partial t}$  are the subdistribution cumulative incidence, subsurvivor, and subdensity functions (note that  $P(J = j) = S_j^*(t) + F_j^*(t)$ ).

An alternative proportional hazards model may be constructed from the subdistribution hazard, which is useful because the cause-specific hazard approach does not necessarily reflect what occurs with the *sd*CIFs (16). This occurs because the *sd*CIF is a function of the cause-specific hazards for both events 1 and 2 (29, 30) (Web supplement). The proportional subdistribution hazards model is then:

$$\lambda_j(t | z) = \lambda_{0j}(t) \exp(z^T \phi_j), \quad (4)$$

where  $\lambda_{0j}$  is the unspecified baseline subdistribution hazard. The proportionality assumption may be assessed by plotting the  $\log(-\log(1 - F_j^*(t)))$  against  $\log(\text{time})$  stratified by the covariate, where  $F_j^*(t)$  can be estimated from a nonparametric estimator for competing risks (2, 10, 14, 15). In the presence of noninformative censoring, it has been recommended to use a weighted score function to obtain an

**Table 1.** Assumptions, Uses, and Advantages of 3 Different Regression Approaches to Modeling Competing Risks

	Approach		
	Cause-specific Proportional Hazards Model	Subdistribution Proportional Hazards Model	Parametric Mixture Model
Model assumption	Assumes proportionality of the cause-specific hazard, as this model is exactly the same as conducting a regular proportional hazards model in which individuals with the competing event are censored at that time point.	Assumes that the subdistribution hazards are proportional <sup>a</sup>	Assumes that the investigator has correctly specified both the distribution for the event of interest and the competing event
Are these assumptions reasonable?	As with all proportional hazards models, the analyst should evaluate whether the proportionality assumption is met. In practice, this assumption is often violated.	The assumption that the subdistribution is proportional should be assessed.	Correctly specifying the distribution of events is difficult for any parametric model.
	Nevertheless, the investigator should acknowledge that there was some indication of nonproportionality and report the $_{cs}RH$ as this is the weighted average over follow-up.	This can be done by assessing the residuals that are returned by the “crr” function in R against the unique failure times (16). This is analogous to examining the Schoenfeld residuals from a regular proportional hazards model.	The correct specification of the distribution may be made more tenable by utilizing a flexible distribution that can accommodate various shapes of the hazard function.
	Alternatively, violation of the proportional hazards assumption may be mitigated by including an interaction between variables and time to allow the $_{cs}RH$ to vary over time.	Alternatively, proportionality may be assessed by evaluating the log(–log) transformation of the nonparametric cumulative incidence function estimators (2, 10, 14, 15) stratified by exposure variable. The step function curves should be separated by a constant difference.  Nevertheless, the investigator should acknowledge that there was some indication of nonproportionality and report the $_{sd}RH$ as this is the weighted average over follow-up.  When the proportionality assumption is violated, this may be mitigated by including an interaction between variables and time.	A generalized gamma distribution is an example of a flexible distribution that can accommodate increasing, decreasing, arc-shaped- (increasing then decreasing), and bathtub-shaped (decreasing then increasing) hazard functions.

Table continues

unbiased estimating equation from the partial likelihood (Web supplement) (16). This has been implemented in the CMPSRK library in the R statistical program.

The interpretation of  $_{sd}RH_j = \exp(\varphi_j)$  is the relative change in the subdistribution hazard for a 1-unit increase in the corresponding covariate. The  $_{sd}RH_j$  is directly interpretable as a measure of association for the  $j$ th  $_{sd}CIF$ , and it is straightforward to estimate the subdistribution cumulative incidence by using a Breslow-type estimator to obtain the cumulative subdistribution hazard and evaluate  $1 - \exp(\text{cumulative subdistribution hazard})$  (16).

### Comparisons between $_{cs}RH$ and $_{sd}RH$

The relation between the  $_{cs}RH_{j=1}$  and  $_{sd}RH_{j=1}$  is a function of the  $_{cs}RH$  for the competing event ( $_{cs}RH_{j=2}$ ), the

unspecified baseline cause-specific hazard for both events ( $h_{01}(t)$  and  $h_{02}(t)$ ), and time (refer to Appendix):

$$_{cs}RH_{j=1}(t) = \frac{\left(1 + \frac{F_{12}^*(t)}{S(t|X=1)}\right)}{\left(1 + \frac{F_{02}^*(t)}{S(t|X=0)}\right)} \times _{sd}RH_{j=1}(t). \quad (5)$$

Therefore, a situation in which the  $_{cs}RH_{j=1} = _{sd}RH_{j=1}$  is when  $h_{02} = 0$ . This also suggests that the  $_{cs}RH_{j=1}$  will be similar to  $_{sd}RH_{j=1}$  when  $h_{02}$  is small but that generally  $_{cs}RH_j \neq _{sd}RH_j$ . When  $_{cs}RH_{j=2} \neq 1$ , the risk sets for the event of interest among exposed and unexposed individuals are modified differentially. When  $_{cs}RH_{j=2} > 1$ , a larger proportion of the risk set (for event  $J = 1$ ) for exposed compared with unexposed individuals have had the competing event (and vice versa for  $_{cs}RH_{j=2} < 1$ ). Consequently, the ratio between the



Table 1. Continued

	Approach		
	Cause-specific Proportional Hazards Model	Subdistribution Proportional Hazards Model	Parametric Mixture Model
What is the model useful for?			
Measuring the association?	Yes, the $_{cs}RH$ is a measure of association. It implies that, among any individuals who survive all events up to some unspecified time $t$ , those with the exposure have a cause-specific hazard rate of $_{cs}RH \times$ the cause-specific hazard rate of those who do not have the exposure.	Yes, the $_{sd}RH$ is a measure of association. However, it is a measure of association that is due to both the association of the exposure at the event of interest and the possibly differential impact of competing events on the risk set for exposed and unexposed individuals.	Yes, both the $_{cs}RH$ and $_{sd}RH$ are estimable.
Evaluating the risk of the event?	No, the $_{cs}RH$ by itself cannot be used to predict whether the event will be observed. Whether the event will be observed is a function of both the $_{cs}RH$ associated with the event of interest and the $_{cs}RH$ associated with the competing event.  $_{cs}RH > 1$ does <i>not</i> necessarily imply that the $_{sd}CIF_{exposed} >$ the $_{sd}CIF_{unexposed}$ and vice versa.	Yes, because the $_{sd}RH$ intrinsically accounts for the competing event by modifying the risk set at time $t$ , a $_{sd}RH > 1$ indicates that those with exposure will be seen to have a quicker time to event in the study population. Similarly, a $_{sd}RH < 1$ indicates a longer time to event for those exposed.  $_{sd}RH > 1$ does imply that the $_{sd}CIF_{exposed} >$ the $_{sd}CIF_{unexposed}$ and vice versa.	Yes, in addition to the $_{sd}RH$ , the $_{sd}CIF$ is directly estimable.
What is the model's advantage?	It measures the association of an exposure on the corresponding event in which the competing event contributes only by passively removing individuals from the risk set.  The model does not have to correctly specify the unspecified baseline cause-specific hazard function.	It measures the association of an exposure to the corresponding event in which the competing event actively contributes to the risk set.  The model does not have to correctly specify the unspecified baseline subdistribution hazard function.	The model can obtain the $_{cs}RH$ , the $_{sd}RH$ , and the subdistribution cumulative incidence, as well as the cause-specific hazard and subdistribution hazards all as functions of time.  The model does not require the assumption of proportional hazards over time.  When correctly specified, parametric models generally tend to have more power than semi- or nonparametric models.

Abbreviations:  $_{cs}RH$ , cause-specific relative hazard;  $_{sd}CIF$ , subdistribution of the cumulative incidence function;  $_{sd}RH$ , subdistribution relative hazard.

<sup>a</sup> The subdistribution proportional hazards model assumes that the transformation of the subdistribution cumulative incidence functions as  $\log(-\log)$  transformation results in a constant difference between curves (16).

subdistribution hazards for exposed and unexposed individuals for the event of interest will not be equivalent to the  $_{cs}RH$ .

Given that the  $_{cs}RH_j$  and  $_{sd}RH_j$  are generally different, how do we use these measures (Table 1)? In noncompeting risk settings, the impact of a high (low) relative hazard will directly translate to an increase (decrease) in cumulative incidence of the event for the exposed individuals as compared with unexposed individuals. In a competing risk framework, this is not necessarily true for the  $_{cs}RH_j$ . The  $_{cs}RH$  is a measure of association that does not necessarily directly translate into a measure of risk without the assumption of independence between the competing events. Without the assumption of independence or conducting extra steps to obtain the  $_{sd}CIF$  (Web supplement), the  $_{cs}RH$  does not allow comparison of the cumulative incidence of the event in exposed versus unexposed individuals. Rather, the  $_{cs}RH$  is a valid measure of the apparent effect of a covariate

on the relative instantaneous hazard rate given that individuals have survived both events until time  $t$ . However, in that same instant, individuals may have a stronger (or weaker) relative hazard rate for the competing event.

In contrast, the  $_{sd}RH$  is useful for comparing the cumulative incidence for those with and without exposure because of the direct modeling of the  $_{sd}CIF$ . For instance, a situation could arise where the  $_{cs}RH_{j=1} = 1$ , suggesting no difference in the cause-specific hazard rate comparing exposed versus unexposed individuals. However, because the exposed individuals are more likely to have the competing event ( $_{cs}RH_{j=2} > 1$ ), the  $_{sd}RH_{j=1}$  will be  $< 1$  (Table 2) because of the differential modification of the risk sets as caused by the association between exposure and the competing event. This drives the subdistribution hazard lower for those with exposure relative to unexposed individuals, causing  $_{sd}RH_{j=1} < 1$ . While  $_{cs}RH_{j=1} = 1$  suggests no

association, exposed individuals will be less likely to have the event because of the association of the exposure with the competing event. Therefore, the  ${}_{cs}RH_{j=1}$  directly measures the association of an exposure on event 1 as the competing event contributes only passively by removing individuals from the risk set, whereas the  ${}_{sd}RH_{j=1}$  is a measure of association that reflects both the association of exposure with event 1 and the contribution of event 2 by actively maintaining individuals in the risk sets for exposed and unexposed individuals. Should the association of the exposure with event 1 be in direct opposition with the contribution of event 2, the  ${}_{sd}RH$  may be quite different from the  ${}_{cs}RH$  (Table 2).

A caveat when applying the  ${}_{sd}CIF$  to other populations is that the transportability of the estimate may be questionable if the distribution of the competing events differs from the original population. This is because the risk sets for exposed and unexposed individuals will be impacted differently by a change in the distribution of competing events.

### A unified regression approach

The 2 primary models developed for estimating  ${}_{cs}RH$  and  ${}_{sd}RH$  depend upon proportional hazard assumptions. Because equations 1 and 3 are not equivalent, a proportional cause-specific hazards model does not necessarily imply a proportional subdistribution hazards model (29, 30). Although time interactions could be included in the model to account for nonproportionality, this can complicate interpretation.

An alternative approach is to consider more general models that do not constrain any of the hazard functions to be proportional. A mixture of distributions for competing risks was proposed by Cox in 1959 (31) and was later expanded through decomposing the  ${}_{sd}CIF$  as follows (17):

$$\begin{aligned} F_j^*(t) &= P(T \leq t, J = j) \\ &= P(T \leq t | J = j) P(J = j) \\ &= F(t | J = j) P(J = j) \end{aligned} \quad (6)$$

and constructing likelihood contributions for the  $i$ th individual:

$$\begin{aligned} L_i &= [\pi_i f_1(t_i)]^{\gamma_i} \times [(1 - \pi_i) f_2(t_i)]^{\theta_i} \\ &\times [\pi_i S_1(t_i) + (1 - \pi_i) S_2(t_i)]^{(1 - \gamma_i - \theta_i)}, \end{aligned} \quad (7)$$

where  $f_j^*(t) = \frac{\partial F_j^*(t)}{\partial t}$  for  $j = 1, 2$  corresponds to a probability density function to model the  $j$ th event,  $S_j(t)$  is the corresponding survivor function  $P(T > t | J = j)$ ,  $\pi_i$  is the mixture probability  $P(J = 1)$ , and  $\gamma_i$  and  $\theta_i$  are indicator functions for  $J = 1$  and  $J = 2$ , respectively.

Under this formulation, parametric distributions can be utilized to impose structure for  $f$  and  $\pi$  with parameters that can be linked to covariates. To model  $f$  (and  $S$ ), a flexible parametric distribution, such as the generalized gamma distribution, can accommodate various shapes of the hazard function (32). A binary model can be constructed for the  $P(J = j)$  term to describe the occurrence for 2 events. Re-

gression analysis can proceed by linking covariates to the parameters of these distributions (Web supplement).

This mixture model approach has a distinct advantage over other models: Both the cause-specific and subdistribution relative hazards  ${}_{cs}RH_j$  and  ${}_{sd}RH_j$  may be derived and are not constrained to be constant over time. If a summary (over time) measure is desired, a time-weighted estimate can be constructed with confidence intervals obtained by bootstrap (33). Another advantage of the mixture model is that it is relatively easy to compare the subdistribution CIF, cause-specific hazards, or subdistribution hazards stratified by exposure and over time (34). Estimation of the parameters for the mixture model can be performed in SAS software by using the NLMIXED procedure and the log-likelihood function from equation 7.

### Application

Prior studies have shown that HIV-infected individuals with past injection drug use are less likely to initiate effective therapy than those without (35–38) and are more likely to die in the era of highly active antiretroviral therapy (5, 38, 39). Yet, the comparison of treatment initiation by history of injection drug use when it has the potential to be the most effective (prior to AIDS or death) has not been undertaken.

### Study population

The Women's Interagency HIV Study (WIHS) was established in August 1993 to investigate the impact of HIV infection on US women at 6 sites in New York (2 sites); Washington, DC; Los Angeles and San Francisco, California; and Chicago, Illinois. Details are provided elsewhere (40–43). In 1994–1995, 2,054 HIV-positive and 569 HIV-negative women were enrolled. Follow-up visits occur at 6-month intervals in which data are collected by structured interviews, physical examinations, and laboratory testing.

The study sample consisted of 1,164 women enrolled in WIHS, who were alive, infected with HIV, and free of clinical AIDS on December 6, 1995 (baseline), when the first protease inhibitor (saquinavir mesylate) was approved by the Federal Drug Administration. Women were followed until the first of the following: treatment initiation, AIDS diagnosis, death, or administrative censoring (September 28, 2006). Covariates included history of injection drug use at WIHS enrollment, whether an individual was African American, age, and CD4 nadir prior to baseline.

### RESULTS

Individuals with and without an injection drug use history had similar nadir CD4 counts prior to baseline (Table 3). Women with an injection drug use history were more likely to be African American and older than those without an injection drug use history. Although the majority of women initiated treatment prior to clinical AIDS or death, this proportion was lower among those with a history of injection drug use. The proportion with AIDS or death prior to treatment was higher among those with injection drug use.

**Table 2.** General Direction of the Time-averaged Subdistribution Relative Hazard for a Given Direction of the Time-averaged Cause-specific Relative Hazards for Both Events 1 and 2<sup>a</sup>

$_{cs}RH_1$	$_{cs}RH_2$	$_{sd}RH_1^b$	$_{cs}RH_1$ Interpretation <sup>c</sup>	$_{sd}RH_1$ Interpretation <sup>d</sup>
<1	<1	$>_{cs}RH_1$	Exposure associated with a decreased cause-specific hazard rate for event	Because exposure is associated with a decreased cause-specific hazard rate for the competing event, the $_{sd}RH_1$ is greater than what one would expect if the exposure were not associated with the competing event (e.g., $_{cs}RH_2 = 1$ ), and therefore $_{sd}RH_1 >_{cs}RH_1$ . <sup>e</sup>
<1	>1	$<_{cs}RH_1$	Exposure associated with a decreased cause-specific hazard rate for event	Because the exposure is associated with an increased cause-specific hazard rate for the competing event, the $_{sd}RH_1$ is less than what one would expect if the exposure were not associated with the competing event (e.g., $_{cs}RH_2 = 1$ ), and therefore $_{sd}RH_1 <_{cs}RH_1$ .
>1	<1	$>_{cs}RH_1$	Exposure associated with an increased cause-specific hazard rate for event	Because exposure is associated with a decreased cause-specific hazard rate for the competing event, the $_{sd}RH_1$ is greater than what one would expect if the exposure were not associated with the competing event (e.g., $_{cs}RH_2 = 1$ ), and therefore $_{sd}RH_1 >_{cs}RH_1$ .
>1	>1	$<_{cs}RH_1$	Exposure associated with an increased cause-specific hazard rate for event	Because the exposure is associated with an increased cause-specific hazard rate for the competing event, the $_{sd}RH_1$ is less than what one would expect if the exposure were not associated with the competing event (e.g., $_{cs}RH_2 = 1$ ), and therefore $_{sd}RH_1 <_{cs}RH_1$ . <sup>f</sup>

Abbreviations:  $_{cs}RH_1$ , cause-specific relative hazard for event 1;  $_{cs}RH_2$ , cause-specific relative hazard for event 2;  $_{sd}RH_1$ , subdistribution relative hazard for event 1.

<sup>a</sup> We refer to the time-averaged relative hazards, as proportionality of the cause-specific hazards does not imply proportionality of the subdistribution hazards and vice versa. Refer to Latouche et al. (47) and Beyersmann and Schumacher (30) for further details.

<sup>b</sup> The exact magnitude of the difference between  $_{cs}RH_1$  and  $_{sd}RH_1$  depends on the level of  $_{cs}RH_1$  and  $_{cs}RH_2$  and the baseline cause-specific hazard rate,  $h_{01}(t)$ , and  $h_{02}(t)$ .

<sup>c</sup> The  $_{cs}RH_1$  is whether or not the exposure has an association with the event of interest. It cannot be used to make inferences about the cumulative incidence in the presence of competing risks (e.g.,  $P(T < t, J = j)$ ) without additional information regarding the  $_{cs}RH_2$  and the magnitude of the baseline cause-specific hazard rate for the competing event.

<sup>d</sup> The  $_{sd}RH_1$  reflects how the exposure is associated with the event of interest by incorporating both the association between the exposure and the event of interest and the association of the exposure with the competing event (which influences the risk set).

<sup>e</sup> Note that the  $_{sd}RH_1$  could be  $>1$  if both the association of the exposure with the competing event ( $_{cs}RH_2$ ) was strong enough and the baseline cause-specific hazard rate for the competing event is of great enough magnitude.

<sup>f</sup> Note that the  $_{sd}RH_1$  could be  $<1$  if both the association of the exposure with the competing event ( $_{cs}RH_2$ ) was strong enough and the baseline cause-specific hazard rate for the competing event is of great enough magnitude.

Figure 3 shows both the estimated cause-specific and subdistribution cumulative incidences by outcome and injection drug use status. To illustrate the difference between the cause-specific and  $_{sd}CIF$ s, we estimated the  $_{cs}CIF$  directly from the  $_{cs}RH$  under the assumption of independence

between events (Figure 3, A and C). However, the  $_{sd}CIF$  (Figure 3, B and D) can be estimated from the cause-specific proportional hazards model by taking extra steps (Web supplement) (27, 28). In addition, a nonparametric estimation of the subdistribution CIF was obtained by using

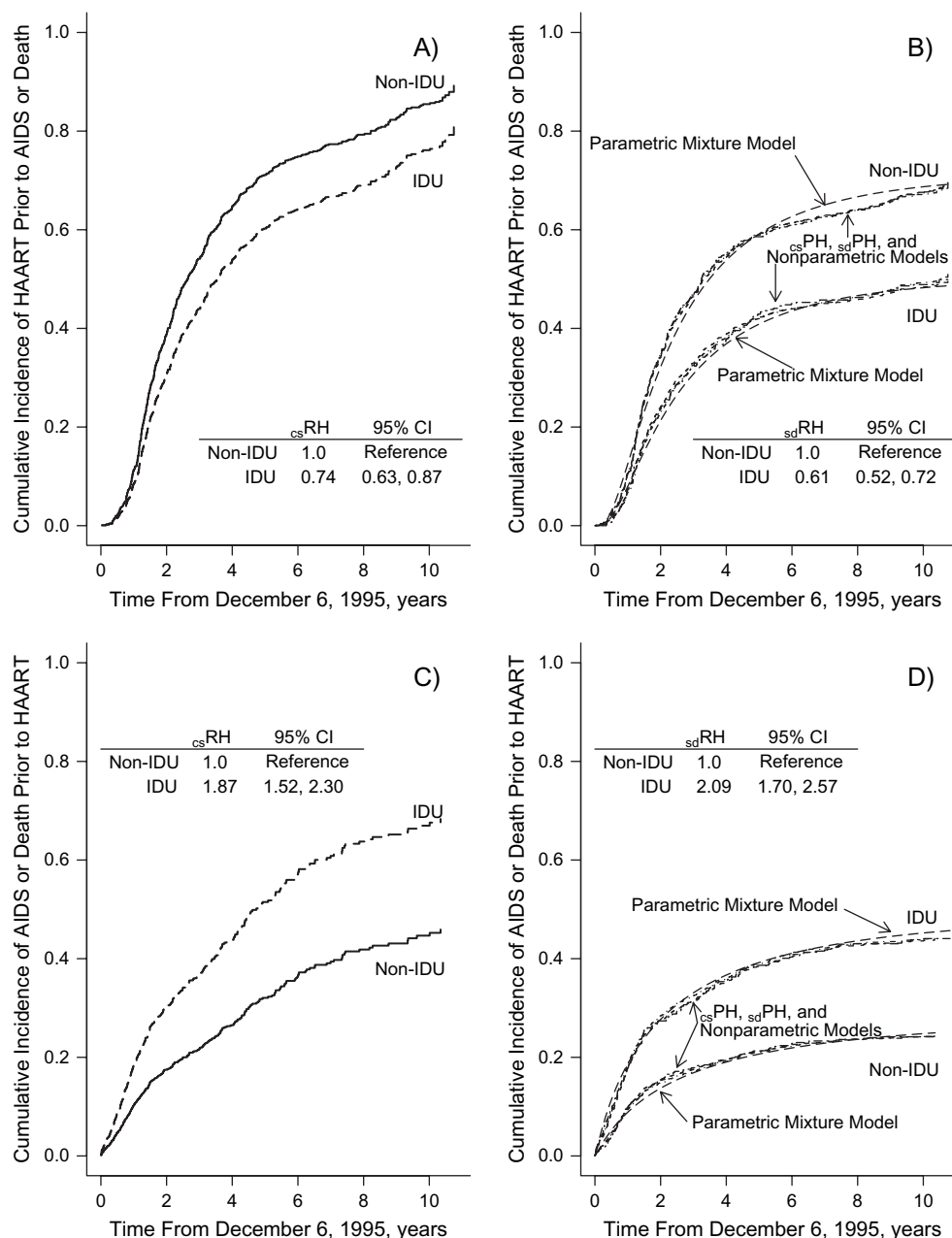
**Table 3.** Characteristics for Women Enrolled in the Women's Interagency HIV Study on December 6, 1995, and Followed Through September 2006, United States

	No History of Injection Drug Use ( <i>n</i> = 725)		History of Injection Drug Use ( <i>n</i> = 439)		Overall ( <i>N</i> = 1,164)	
	Median	Interquartile Range	Median	Interquartile Range	Median	Interquartile Range
Nadir CD4 count, no.	348	216–505	352	209–522	349	213–516
Age on December 6, 1995, years	33	29–39	40*	35–44	36	31–41
	No.	%	No.	%	No.	%
African American	399	55	273**	62	672	58
Initiated treatment prior to AIDS or death	469	65	210	48	679	58
AIDS or death prior to treatment	169	23	190	43	359	31

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

\* $P < 0.001$ ; \*\* $P = 0.017$  for comparing those with and without a history of injection drug use.





**Figure 3.** Cumulative incidence of treatment initiation prior to acquired immunodeficiency syndrome (AIDS) or death (A and B) and the cumulative incidence of AIDS or death prior to treatment (C and D) by injection drug use status and type of cumulative incidence (cause-specific, A and C; subdistribution, B and D;  $_{cs}PH$ , from proportional cause-specific hazards model;  $_{sd}PH$ , from proportional subdistribution hazards model). The mixture model comprised a lognormal distribution for initiation of treatment and a generalized-gamma distribution for the time to AIDS or death prior to treatment initiation. CI, confidence interval;  $_{cs}RH$ , cause-specific relative hazard; HAART, highly active antiretroviral therapy; IDU, injection drug use;  $_{sd}RH$ , subdistribution relative hazard.

an extension of the Kaplan-Meier methods to competing risks (2, 44). Regardless of the method (cause-specific proportional hazards model, subdistribution proportional hazards model, or mixture model) used for obtaining the subdistribution CIF, the estimated subdistributions were essentially equivalent to the extended Kaplan-Meier method

for competing risks ( $P < 0.001$  for both events comparing those with past injection drug use vs. those without) (2, 44).

The estimates of the  $_{cs}RH$  and  $_{sd}RH$  from the semiparametric and parametric approaches are shown in Table 4 stratified by competing events. The parametric mixture model provided inferences essentially identical to the

**Table 4.** Effect of History of Injection Drug Use on the Proportion and Timing of Incident HIV Treatment Use and Incident AIDS or Death Among Women Within the Women's Interagency HIV Study, 1995–2006, United States<sup>a</sup>

	History of Injection Drug Use Cause-specific Relative Hazard		History of Injection Drug Use Subdistribution Relative Hazard	
	Estimate	95% Confidence Interval	Estimate	95% Confidence Interval
Time to treatment initiation prior to AIDS/death				
Semiparametric proportional hazards model <sup>b</sup>	0.67	0.57, 0.80	0.60	0.50, 0.71
Parametric mixture model <sup>c</sup>	0.71	0.59, 0.85	0.60	0.50, 0.71
Time to AIDS or death prior to treatment initiation				
Semiparametric proportional hazards model <sup>b</sup>	1.71	1.37, 2.13	2.01	1.62, 2.51
Parametric mixture model <sup>c</sup>	1.77	1.40, 2.27	2.02	1.62, 2.59

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

<sup>a</sup> Models are adjusted for age at study entry, race, and CD4 nadir prior to study entry; the CD4 nadir was included in the model to adjust for stage of disease in order to be able to appropriately compare those with and without a history of injection drug use.

<sup>b</sup> Some indication of proportional hazards assumption may not hold; however, these differences were quantitative rather than qualitative (i.e., hazards do not cross).

<sup>c</sup> A lognormal (for treatment) and generalized gamma (for AIDS/death) distribution was used for the parametric mixture model.

proportional hazards models. The  $_{sd}RH$  had a stronger association than the  $_{cs}RH$  for both events. The  $_{cs}RH_{treatment}$  was equal to 0.67; however, the  $_{cs}RH_{AIDS/death}$  was 1.7. Therefore, as the subdistribution hazard maintains individuals who develop the competing event in the risk set (equation 3), this implies that individuals with an injection drug use history are maintained in the risk set in a greater proportion than those without a history of injection drug use. Thus, a greater relative change between the cause-specific and subdistribution hazards would be expected for those with an injection drug use history than for those without (i.e., a larger denominator among the injection drug use group because of a higher AIDS/death hazard rate). Therefore, the  $_{sd}RH_{treatment}$  should be less than the  $_{cs}RH_{treatment}$ , which was observed (Table 4).

## DISCUSSION

In this paper, we have discussed the 2 common methods for handling competing risks and their applications to regression settings. The  $_{cs}RH$  and the  $_{cs}CIF$  are familiar quantities because they reflect measures that are estimated when individuals with the competing event are censored. However, we have illustrated the utility of the subdistribution hazard and CIF as complementary measures of risk.

Should the  $_{cs}RH_{AIDS/death}$  have been greater (e.g., 3.0), the arbitrary baseline hazard for AIDS/death  $> 0.2$  (e.g., a constant 1.1) per year, and the observed  $_{cs}RH_{treatment} = 0.67$ , then the  $_{sd}RH_{treatment}$  would have been lower than the 0.67. This would imply that, despite a direct association between injection drug use status and treatment initiation ( $_{cs}RH_{treatment} = 0.67$ ), individuals with an injection drug use (IDU) history were less likely to initiate treatment before disease progression ( $_{sd}CIF_{IDU} < _{sd}CIF_{not-IDU}$  as indi-

cated by  $_{sd}RH_{treatment} < 1.0$ ) and more likely to have HIV disease progression before therapy. However, the  $_{cs}RH_{treatment} = 0.67$  and the  $_{cs}RH_{AIDS/death} = 1.71$ , which suggests that AIDS/death should contribute to an even lower  $_{sd}RH_{treatment}$  because those with past injection drug use had a higher cause-specific hazard rate for AIDS/death. The similarity of the  $_{cs}RH_{treatment}$  and  $_{sd}RH_{treatment}$  implies that disease progression to AIDS/death did not greatly contribute to a further reduction in the association between injection drug use history and treatment initiation. This was due to the relatively low baseline hazard rate for AIDS/death;  $h_{02}(t)$  ranged from 0.157 to 0.224 per year. Thus, the  $_{sd}RH_{treatment}$  is only slightly stronger than that from the cause-specific proportional hazards model (0.60 vs. 0.67, respectively). Beyersmann et al. (29) recently provide an alternative example where the difference between  $_{cs}RH$  and  $_{sd}RH$  is large and they are in opposite directions.

The properties of the  $_{cs}RH_j$  (no interpretation to  $_{sd}CIF$  without assumption) and  $_{sd}RH_j$  (translatable to  $_{sd}CIF$ ) illustrate the circumstances in which the 2 measures of association may be most useful and therefore suggest a general guideline for use. The  $_{cs}RH$  might be more applicable for studying the etiology of diseases, whereas the  $_{sd}RH$  might be more appropriate for predicting an individual's risk for an outcome or resource allocation. For example, the use of the antiretroviral drug abacavir has recently been associated with increased risk of myocardial infarction (45). Two competing questions can be framed: 1) Is the use of abacavir directly associated with myocardial infarction, and 2) regardless of the direct association, are individuals taking abacavir more likely to experience a myocardial infarction? For the first question, the  $_{cs}RH$  may be more appropriate, as this measure will assess at any given time whether the individuals on abacavir have an increased instantaneous hazard rate for myocardial

infarction among all individuals that have survived all events to this time point.

For the second question, the  $_{sd}RH$  is a better measure of association. This can be illustrated by assuming that abacavir is not directly associated with myocardial infarction ( $_{cs}RH = 1$  for association of abacavir with myocardial infarction). It remains possible that investigators may still expect a higher probability of myocardial infarction among those taking abacavir if individuals not on abacavir were more likely to die prior to a myocardial infarction. Consequently, the  $_{sd}RH$  for myocardial infarction would be  $>1$  for those on abacavir, but it is by reducing mortality and keeping individuals alive to be able to experience a myocardial infarction. The latter knowledge may be useful in policy decisions.

We recognize that important issues such as left truncation and causality (46) as they pertain to competing risks have not been addressed here. Our goals were to describe and illustrate 2 common measures of association that may be used in the competing risk setting but that epidemiologists have avoided. The cause-specific hazard ratio and subdistribution hazard ratio are distinct, and the choice of approach should be driven by the scientific question. Future research should continue to explore the differences in approaches and expand the tools to understand and implement competing risk methods for epidemiologic data.

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## APPENDIX

This appendix further details the relation between the cause-specific hazard and the subdistribution hazard. Further details regarding the methods outlined within the main text may be found in the Web supplement data, which provide more rigorous details regarding the methods that may be useful for some readers but felt to be too technical such that the main points would be obscured to others. Additionally, the data used in the application are provided along with code to implement competing risk analyses in R or SAS.

### Relation between ${}_{cs}RH$ and ${}_{sd}RH$

Beyersmann et al. (29) noted that the  ${}_{cs}RH$  is in good agreement with the  ${}_{sd}RH$  when there is no association of exposure and the competing event. To illustrate, let  $X$  be a binary exposure variable for 2 competing events. Let the  ${}_{cs}RH(t)$  for event 1 and event 2 be equal to some constant,  ${}_{cs}RH_1$  and  ${}_{cs}RH_2$ , respectively, and thus both events have proportional hazards across exposure status. Let the arbitrary baseline cause-specific hazard (i.e., when  $X = 0$ ) for event 1 and event 2 be  $h_{01}(t)$  and  $h_{02}(t)$ , respectively. Then, the hazards for those with  $X = 1$  are  $h_{11}(t) = h_{01}(t) \exp(\beta X) = h_{01}(t) \times {}_{cs}RH_1$  and  $h_{12}(t) = h_{02}(t) \exp(\beta X) = h_{02}(t) \times {}_{cs}RH_2$  for events 1 and 2, respectively. Let  $\lambda_1(t)$  be the subdistribution hazard for event 1 and  $\lambda_{01}(t)$  and  $\lambda_{11}(t)$  be the subdistribution hazard for unexposed and exposed individuals, respectively. Beyersmann et al. (29) showed that the cause-specific hazard has the following general relation (not considering covariate  $X$ ) with the subdistribution hazard for event 1:

$$h_1(t) = \left(1 + \frac{F_2^*(t)}{S(t)}\right) \lambda_1(t), \quad (A1)$$

where  $F_2^*(t)$  is the subdistribution function for event 2, and  $S(t)$  is the net survival function. Thus, the cause-specific hazard for exposed individuals may be written as follows:

$$\begin{aligned} h_{11}(t) &= \left(1 + \frac{F_{12}^*(t)}{S(t|X=1)}\right) \lambda_{11}(t) \\ &= h_{01}(t) \times {}_{cs}RH_1 \\ &= \left(1 + \frac{F_{02}^*(t)}{S(t|X=0)}\right) \lambda_{01}(t) \times {}_{cs}RH_1 \end{aligned} \quad (A2)$$

Thus, the  ${}_{cs}RH_1$  is as follows:

$$\begin{aligned}
{}_{cs}\text{RH}_1 &= \frac{\left(1 + \frac{F_{12}^*(t)}{S(t|X=1)}\right)^{\lambda_{11}(t)}}{\left(1 + \frac{F_{02}^*(t)}{S(t|X=0)}\right)^{\lambda_{01}(t)}} \\
&= \frac{\left(1 + \frac{F_{12}^*(t)}{S(t|X=1)}\right)}{\left(1 + \frac{F_{02}^*(t)}{S(t|X=0)}\right)} \times {}_{sd}\text{RH}_1
\end{aligned} \quad (\text{A3})$$

Note that the subdistribution equals the net survival multiplied by the cause-specific hazard (i.e.,  $F_{02}(t) = \int_0^t S(u|X=0)h_{02}(u)du$  and  $F_{12}(t) = \int_0^t S(u|X=1)h_{12}(u)du$ ). Thus, when  $h_{02}(t)$  is close to 0, the fractions within the parentheses in the numerator and in the denominator both tend toward 0 and  ${}_{cs}\text{RH}_1 = {}_{sd}\text{RH}_1$ . Therefore, a low cause-specific hazard for the competing event can mitigate the effect of a large  ${}_{cs}\text{RH}_2$  that would contribute to the numerator in both the subdistribution,  $F_{12}^*(t)$  and net survival among exposed individuals,  $S(t|X=1)$ . Additionally, Latouche et al. (47) showed through simulation the  ${}_{cs}\text{RH}_1 \approx {}_{sd}\text{RH}_1$  when  ${}_{cs}\text{RH}_2 = 1$ .