

Cumulative effects of time-varying risk factors in survival analyses: Flexible modeling and applications

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Longitudinal studies of disease progression and treatment increasingly involve time-varying risk factors and exposures $X(t)$. Many such exposures have cumulative effects, where the risk of the outcome does depend not only on the current or most recent exposure but also on the history of the past values treatment. One important analytical challenge in such studies concerns the need to specify an ‘etiologically correct exposure metric’ that summarizes the impact of treatment/exposure history on the current hazard (1). To address this challenge, we propose flexible modeling of a weighted cumulative exposure (WCE), where the exposure metric is defined as a weighted sum of past values of $X(t)$. To assess the cumulative effect of the past exposures, we use cubic regression splines to model the weight function, which estimates the relative importance weights assigned to the past exposures, depending on the time elapsed since the exposure (2). More recently, we have extended the WCE model to Marginal Structural Model (MSM), with inverse-probability of treatment (IPT) weights (3), and to competing risks modeling (4). I will introduce these new, flexible WCE models and validate them in simulations. Finally, in real-life applications, I will use the WCE methodology to re-assess the safety or effectiveness of different medications, in large population-based cohort and nested case-control studies.

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