Joint flexible estimation of cumulative effects and non-linear dose-response relationships for time-varying exposures in survival analyses

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Many exposures and risk factors evaluated in prospective cohort epidemiological studies show important variation over time in their intensity. We focus on 2 challenges that need to be addressed to ensure accurate testing and modeling of the potential cumulative effects of such time-varying exposures[1]. (i) Firstly, while the etiological relevance of an exposure may vary considerably depending on how long ago it occurred, little is known about relative importance of exposures that occurred in different intervals in the past[2]. (ii) Secondly, the form of the dose-response relationship, describing the impact of increasing exposure intensity at a fixed point in time on the hazard, is typically unknown. For example, (i) cardiovascular (CVD) risk factors, such as serum cholesterol or blood pressure, change considerably over the person's lifetime, with different individual showing different patterns of change[3], and there is a continuing debate about the relative impact of their recent vs much earlier values on the current CVD risks[3, 4]. On the other hand, (ii) several CVD risk factors have non-linear relationships with the logit or log-hazard of CVD risk, and the form of the dose-response curve varies depending on the risk factor[5]. Whereas there is vast statistical literature on flexible modeling of dose-response curves, the only published method for flexible modeling of the function assigning relative importance weights to past exposures is limited to logistic regression analyses of case-control studies[6]. Most importantly, no currently available method handles flexible modeling of both (i) weight function for cumulative effects modeling, and (ii) non-linear dose response curve. We propose the following model to estimate the weighed cumulative exposure (WCE) effect at time τ, as a function of the past exposure history, described by the time-dependent exposure intensity x(t), at 0<t< τ: WCE(τ|x(t), t< τ) = ∑w(τ –t)*s[x(t)], where w(τ –t) assigns importance weights to past exposures as the function of the time elapsed since the exposure, while s[x(t)] represents a smooth dose-response curve describing the relationship between exposure intensity (dose) at a given point in time and the logarithm of the hazard. The estimated WCE is then included as a time-dependent covariate in the Cox's proportional hazards model. Both w(τ –t) and s[x(t)] are modeled using low-dimension cubic regression splines[7]. Quasi-parametric likelihood ratio tests are[8] are used to test the non-linearity of s[x(t)], and to compare w(τ –t) against the standard un-weighted cumulative dose, as well as to test the Ho of no association between exposure and time-to-event. w(τ –t)*s[x(t)]. We use simulations to assess the accuracy of the proposed estimates and tests, and to compare the efficiency of alternative methods for estimating the proposed model. To illustrate a real-life application, we use a large long-term cohort study with repeated measures of cholesterol and blood pressure, to re-assess their effects on CVD mortality and morbidity.

Reference List

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