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*Flexible marginal structural models for estimating cumulative effect of time-varying treatment on the hazard*

Many longitudinal studies deal with both time-dependent (TD) exposures or treatments and TD confounders. When a TD confounder acts also as a mediating variable, marginal structural Cox models (Cox MSM) can be used to consistently estimate the causal effect of the TD exposure. On the other hand, modeling of the effect of a TD exposure requires specifying the relationship between the hazard at time  $t$  and the entire past exposure history, up to time  $t$ . Flexible modeling of the weighted cumulative exposure (WCE) has been proposed to address this challenge. However, the existing WCE models do not permit accurate adjustment for TD confounding/mediating variables, while the existing MSMs do not incorporate flexible estimation of the cumulative effects of TD exposures.

In this study, we propose a flexible marginal structural Cox model with weighted cumulative exposure modeling (WCE MSM), which combines the Cox MSM and WCE approaches, thereby simultaneously addressing the two aforementioned analytical challenges. Specifically, by controlling for confounders using the inverse-probability-of-treatment weights and estimating the WCE with cubic regression splines, the new WCE MSM can estimate the total causal treatment effect, that accounts for both direct cumulative effects of past treatments and their 'indirect effects', mediated by the TD mediators.

Simulation results confirm that the proposed WCE MSM yields accurate estimates of the causal treatment effect under settings of complex exposure effects and time-varying confounding. The new method was applied to the Swiss HIV Cohort Study data to reassess the association between antiretroviral treatment abacavir (ABC) and cardiovascular risk.