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Statistical methods for identifying time windows of susceptibility to early life exposures of chemical mixtures

Shelley Liu

Department of Population Health Science and Policy
Icahn School of Medicine at Mount Sinai
New York, NY

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Abstract: The impact of neurotoxic chemical mixtures on children's health is a critical public health concern. It is well known that during early life, toxic exposures may impact cognitive function during critical time intervals of increased vulnerability, known as windows of susceptibility. There are several statistical challenges in estimating the health effects of time-varying exposures to multi-pollutant mixtures, such as multi-collinearity among the exposures both within time points and across time points, and complex exposure-response relationships. To address these concerns, we develop a flexible statistical method, called lagged kernel machine regression (LKMR). LKMR identifies critical exposure windows of chemical mixtures, and accounts for complex nonlinear and non-additive effects of the mixture at any given exposure window. LKMR estimates how the effects of a mixture of exposures change with the exposure time window using a Bayesian formulation of a grouped, fused lasso penalty within a kernel machine regression framework. A simulation study demonstrates the performance of LKMR under realistic exposure-response scenarios, and demonstrates large gains over approaches that consider each time window separately, particularly when serial correlation among the time-varying exposures is high. We apply LKMR to estimate associations between neurodevelopment and metal mixtures in ELEMENT, a prospective cohort study of child health in Mexico City. Because LKMR inference by Markov chain Monte Carlo methods (MCMC-LKMR) is computationally burdensome and time intensive for large datasets, we also describe a mean field variational Bayesian inference procedure for LKMR (MFVB-LKMR). MFVB-LKMR is designed to reduce computation time without loss of analytical precision. MFVB-LKMR was applied first in a simulation dataset and then to a real life study using PROGRESS, a prospective cohort study of children's environmental health in Mexico City.

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