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Comment on "A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures"

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In a recent paper, Keil et al. (2020) combined an analysis of mixtures of environmental chemicals with a causal inference technique. Following weighted quantile sum regression (WQSR) (Carrico et al. 2015; Curtin et al. 2019; Czarnota et al. 2015a, 2015b; Gennings et al. 2020; Tanner et al. 2019, 2020), they collapsed the environmental exposures to a weighted index. However, they mischaracterized WQSR in its intent of measuring a mixture effect and instead focused a comparison of the methods on a measure of overall effect and not on identifying chemicals of concern.

One strategy for evaluating environmental mixtures in observational studies is a focus on the concept of a mixture effect, where relevant environmental chemicals may be at exposures below an effect level but joint action of the components may produce significant effects (Silva et al. 2002). The joint action of the exposures is measured in WQSR with an empirically weighted index in the direction of the joint action, where components of concern are identified by nonnegligible weights. WQSR performs well in characterizing chemicals of concern under multiple environmentally relevant simulation studies (Bello 2014; Carrico 2015; Curtin et al. 2019; Hargarten and Wheeler 2020). In fact, we conducted simulation scenario 3 of Keil et al. (2020) where X_1 was simulated to be associated with Y. WQSR had 100% sensitivity in all three sample size cases.

In contrast, quantile g-computation defines the measure of the overall effect of the mixture as the sum of the corresponding regression coefficients, which permits a counteracting effect (i.e., positive and negative effects may zero out one another). This definition of an overall effect is contrary to the notion of "joint action" and is analogous to the logic of a drunk individual drinking coffee. The individual may be wide awake but certainly not the same as if they had not consumed either alcohol or coffee—which is what a claim of zero effect would mean. This stands in contrast to WQSR, which focuses on both a positive and negative direction sequentially (e.g., Gennings et al. 2013) and then may be combined in a final model to elucidate the response surface to improve the interpretability of the data through the two indices. This distinction has important biomedical implications given that modeling strategies should ideally be sensitive to the action of competing effects, as in WQSR. In the context of the method of Keil et al. (2020), these effects would be "canceled out."

Further, the simulation study by Keil et al. (2020) does not adequately evaluate the impact of highly correlated and environmentally relevant exposure scenarios, for example, as conducted by Curtin et al. (2019) for WQSR. In addition, their simulation framework incorrectly specifies the "truth" for WQSR (i.e., a method intended to estimate a mixture effect and not a counteracting effect). They constrained the WQSR model to be positive without also allowing the estimation in a negative direction (scenarios 2 and 5) and then characterized it as bias. Again, as per the coffee and alcohol analogy, they considered "truth" to be the canceling out of opposing effects, whereas WQSR is deliberately and appropriately intended to dissect discrete effects.

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