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

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We thank Dr. Gennings for taking interest in our research. Here we respond to Dr. Gennings' letter (Gennings 2021; hereafter referred to as "the letter"), which raises several points relating to our assessment of weighted quantile sum regression (WQSR) and a method we described called quantile g-computation (QGC) (Keil et al. 2020b). Namely, the letter states, first, that our assessment of impacts of exposure correlation is inadequate; second, that overall effects are at odds with the joint action of exposures; and third, that we mischaracterize the target parameter of WQSR.

Regarding the first point, it is not clear why the letter states that our approach to simulating highly correlated exposures is inadequate. Whereas the method cited in the letter simulates continuous, correlated exposures, we simulated discrete, correlated exposures. Both WQSR and QGC discretize exposures during fitting, so we know of no reason why our results would change under a different simulation approach.

Regarding the second point, it helps to note that QGC is a special case of g-computation and was motivated by our work in settings of complex exposure settings (Keil et al. 2020a, 2018a, 2018b, 2014; Keil and Richardson 2017). These methods are grounded in theory and applied examples (e.g., Taubman et al. 2009) that support their use for estimating joint effects of multiple exposures. Notably, these effects are clearly interpreted as what we would estimate in an experiment in which we could increase all exposures by one quantile in the study population. Those actions can have unintended consequences if exposures act in different directions, an idea that joint effects inherently incorporate.

Regarding the third point, we did not intuit that WQSR is biased for all estimands, merely the one we assessed: a joint effect of simultaneously increasing all exposures simultaneously by one quantile. Our initial insight into QGC and WQSR was our large sample simulation that showed that WQSR and QGC converge to the same estimated effect when *a*) all mixture components have linear effects in the same direction and *b*) the sample size is large enough that random error is negligible. Under such limited circumstances we showed that WQSR and QGC estimate the same interpretable parameter with essentially no bias. We designed our simulations to assess whether bias existed in more realistic settings.

The "mixture effect" of the letter is not precisely defined, but we interpret it as the joint effect of all exposures with true linear effects in the same direction. Thus, the "mixture" and "overall" effects coincide in scenario 4 of our paper, where QGC was unbiased and WQSR was biased (except in very large samples). Thus, at least in this setting, WQSR is also biased for the mixture effect. Bias patterns in WQSR under positive effect constraints were similar to those under negative effect constraints and offered no unique insights, so we did not report it.

We agree with Dr. Gennings that individual exposures can have small, clinically negligible effects, yet the joint effect can be larger and clinically relevant. Our simulations demonstrated that QGC reliably estimated a joint effect of many exposures with small effects (up to 14 in our scenario 4).

Ultimately, a parameter of interest is chosen by the analyst, and not the method. Our approach has spurred several dialogs and exchanges of simulation results with other researchers who sought to answer different questions. No approach will be best for every question, so we enthusiastically agree with the spirit of Dr. Gennings' letter that a clear scientific question should drive the approach underlying any analysis.

References

Gennings C. 2021. Comment on "a quantile-based g-computation approach to addressing the effects of exposure mixtures." Environ Health Perspect 129:xxx, https://doi.org/10.1289/EHP8739.

Keil AP, Buckley JP, Kalkbrenner AK. 2020a. Bayesian g-computation to estimate impacts of interventions on exposure mixtures: Demonstration with metals from coal-fired power plants and birthweight. Am J Epidemiol, https://doi.org/10.1093/aje/kwab053 [in press].

Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. 2020b. A quantile-based g-computation approach to addressing the effects of exposure mixtures. Environ Health Perspect 128(4):47004, PMID: 32255670, https://doi.org/10.1289/EHP5838.

Keil AP, Daza EJ, Engel SM, Buckley JP, Edwards JK. 2018a. A Bayesian approach to the g-formula. Stat Methods Med Res 27(10):3183–3204, PMID: 29298607, https://doi.org/10.1177/0962280217694665.

Keil AP, Edwards JK, Richardson DR, Naimi AI, Cole SR. 2014. The parametric g-formula for time-to-event data: intuition with a worked example. Epidemiology 25(6):889–897, PMID: 25140837, https://doi.org/10.1097/EDE.0000000000000160.

Keil AP, Richardson DB. 2017. Reassessing the link between airborne arsenic exposure among Anaconda copper smelter workers and multiple causes of death using the parametric g-formula. Environ Health Perspect 125(4):608–614, PMID: 27539918, https://doi.org/10.1289/EHP438.

Keil AP, Richardson DB, Westreich D, Steenland K. 2018b. Estimating the impact of changes to occupational standards for silica exposure on lung cancer mortality. Epidemiology 29(5):658–665, PMID: 29870429, https://doi.org/10.1097/EDE.0000000000000867.

Taubman SL, Robins JM, Mittleman MA, Hernán MA. 2009. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. Int J Epidemiol 38(6):1599–1611, PMID: 19389875, https://doi.org/10.1093/ije/dyp192.

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