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Supplemental Material

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

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Additional File- Supplemental Code and Data Files

Supplementary material for: A quantile-based g-computation approach to addressing the effects of exposure mixtures

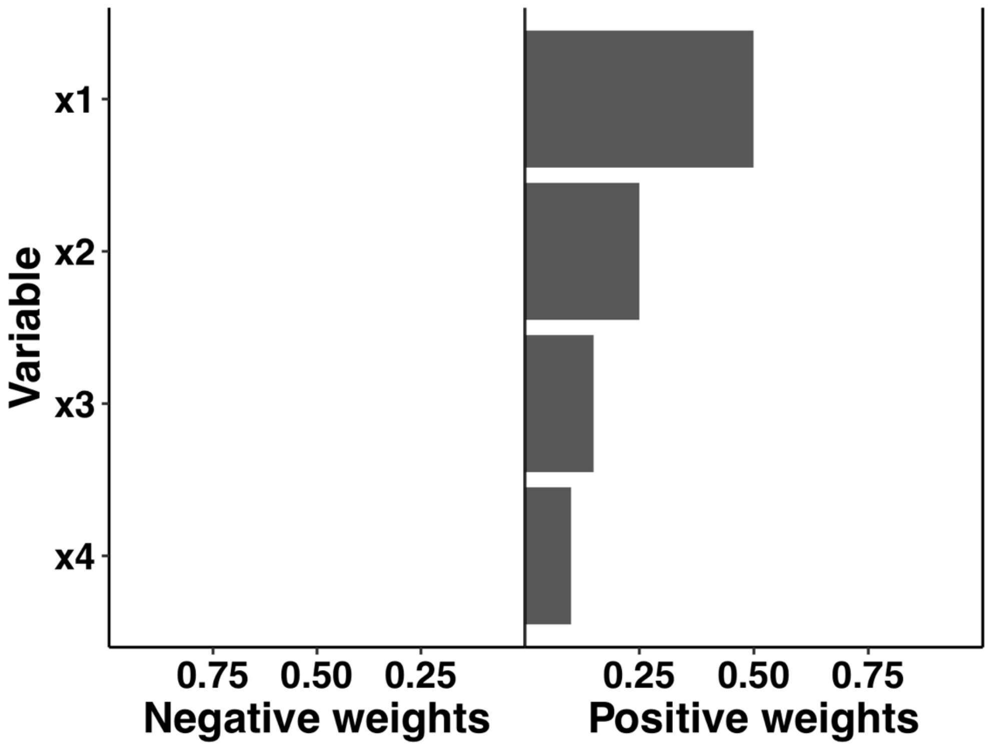


Figure S1: Large sample simulation results demonstrating the default graphical output of the "qgcomp" R package showing the point estimates of the exposure weights in quantile g-computation (when weights are estimable in a linear/additive model). Under a linear model when effects of exposures are all in the same direction, the weights correspond to the proportion of the total mixture effect that is due to each exposure.

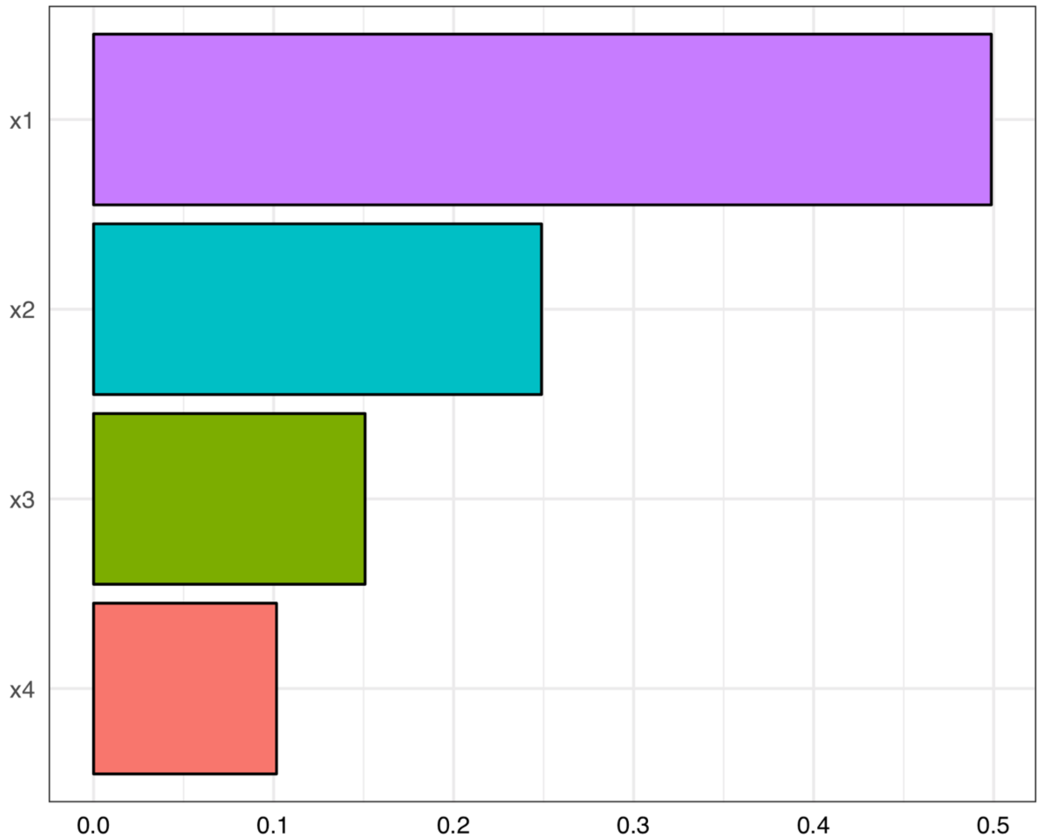


Figure S2: Large sample simulation results demonstrating the default graphical output of the "gWQS" R package showing the point estimates of the exposures weights in WQS regression. Under a linear model when effects of exposures are all in the same direction, the weights correspond to the proportion of the total mixture effect that is due to each exposure.

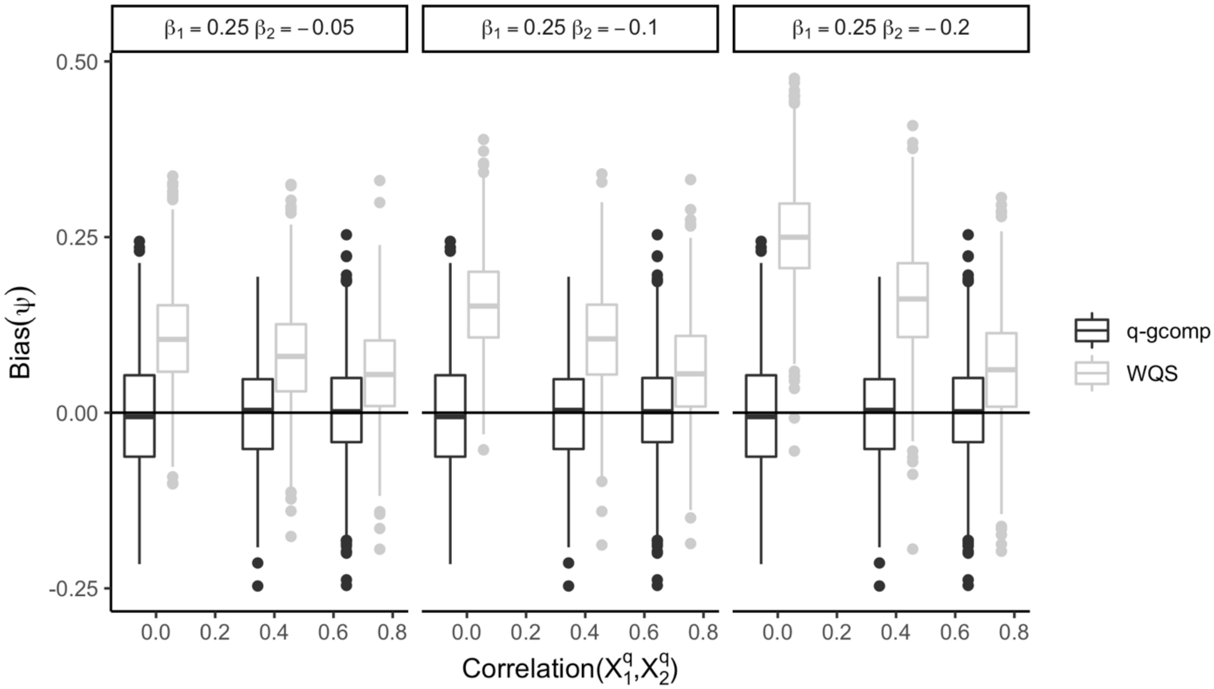


Figure S3. Scenario 5: Impact of co-pollutant confounding on the bias of the overall exposure effect estimate (N=500, d=4) for quantile g-computation (q-gcomp) and WQS regression (WQS) at exposure correlations ($\rho_{X_1X_2}$ of 0.0, 0.4, and 0.75) and varying total effect sizes ($\psi = \beta_1 + \beta_2 \in 0.2, 0.15, 0.05$). Boxes represent the median (center line) and interquartile range (outer lines of box) and outliers (points outside of the 1.5*IQR length whiskers) across 1,000 simulations.

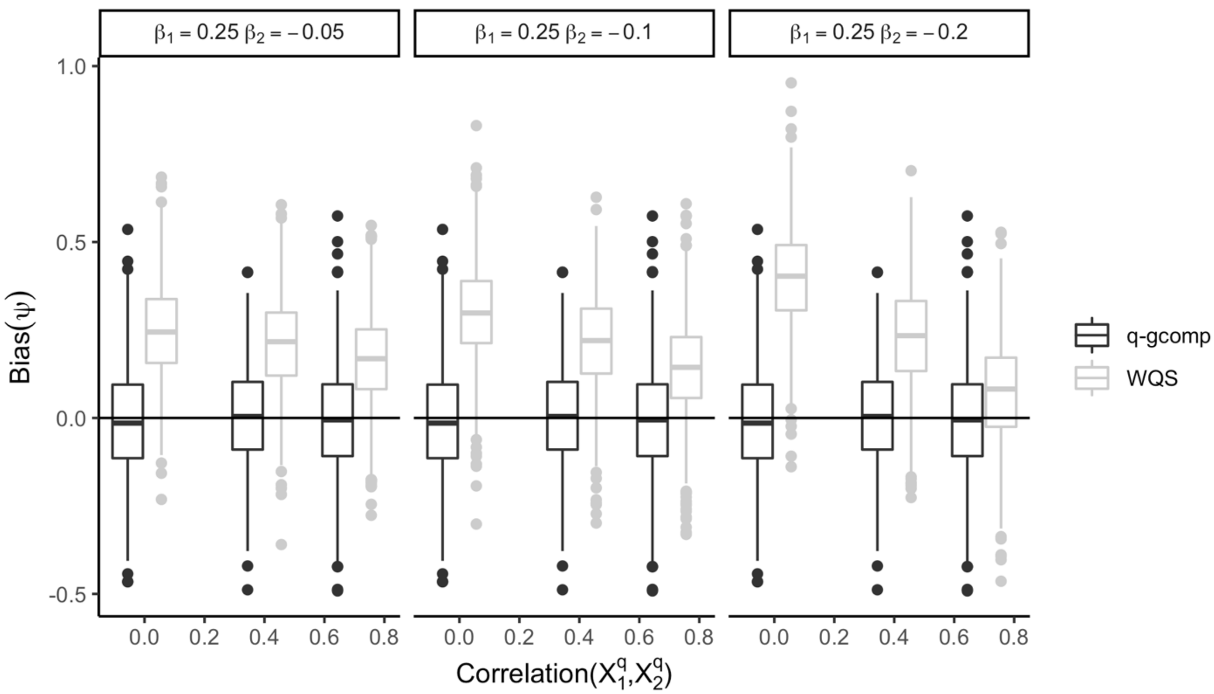
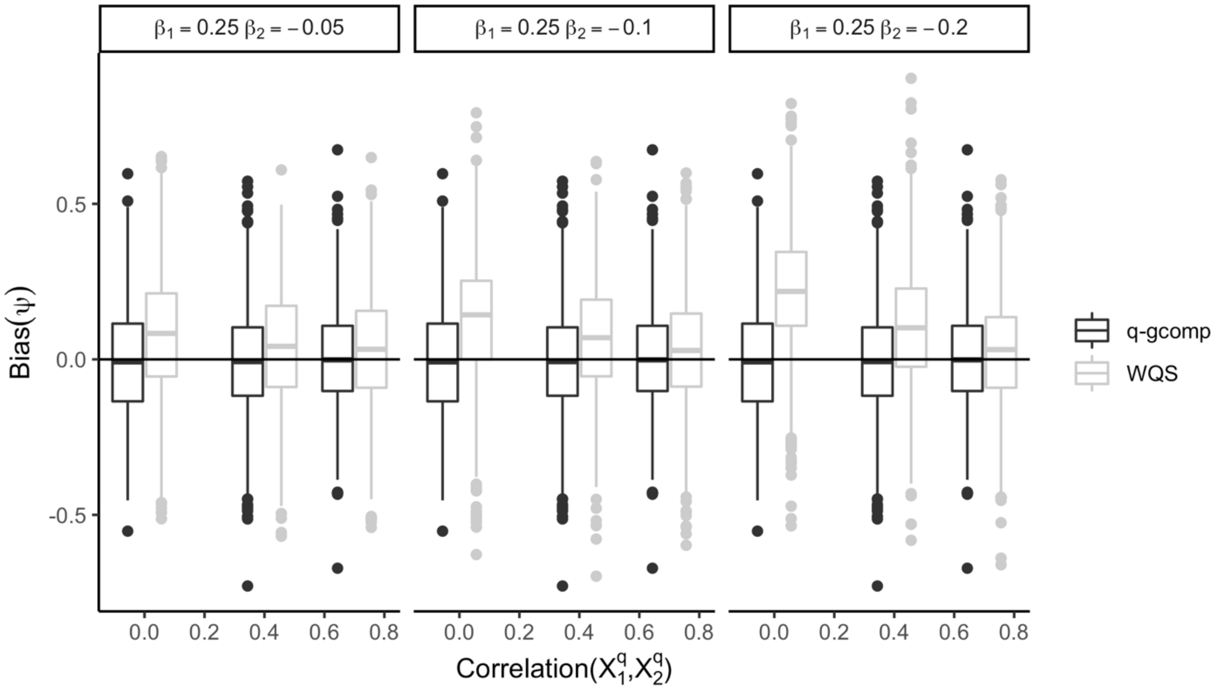


Figure S4. Scenario 5: Impact of co-pollutant confounding on the bias of the overall exposure effect estimate (N=500, d=14) for quantile g-computation (q-gcomp) and WQS regression (WQS) at exposure correlations ($\rho_{X_1X_2}$ of 0.0, 0.4, and 0.75) and varying total effect sizes ($\psi = \beta_1 + \beta_2 \in 0.2, 0.15, 0.05$). Boxes represent the median (center line) and interquartile range (outer lines of box) and outliers (points outside of the 1.5*IQR length whiskers) across 1,000 simulations.



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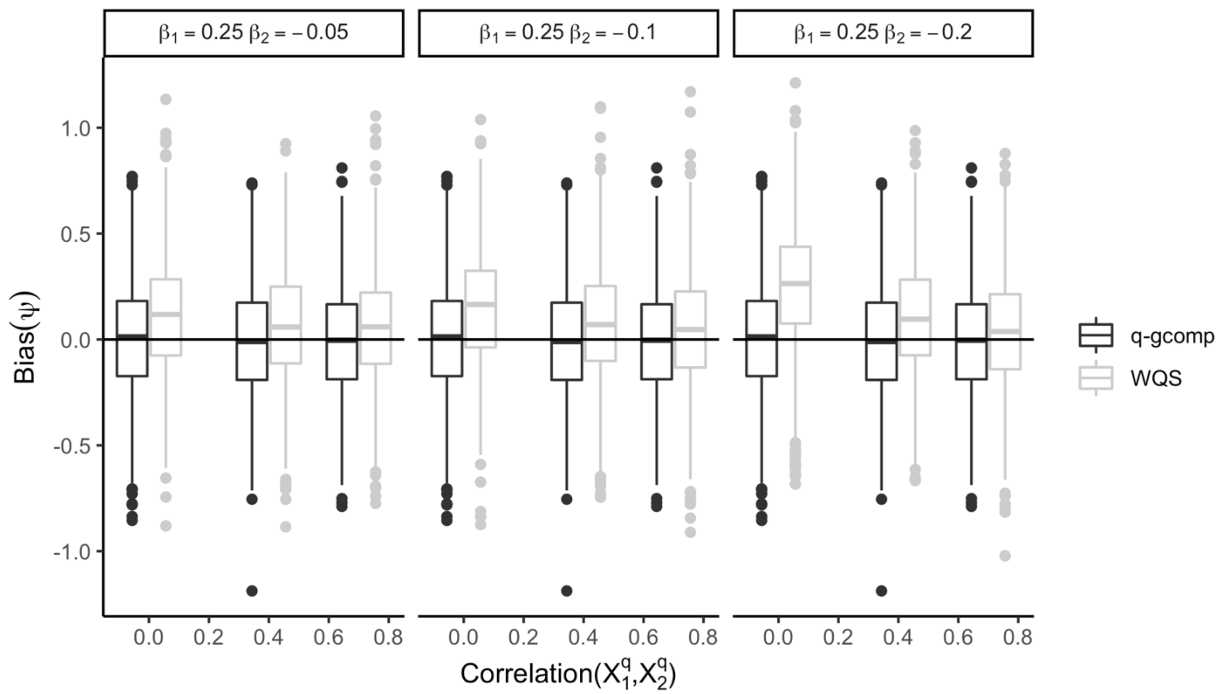

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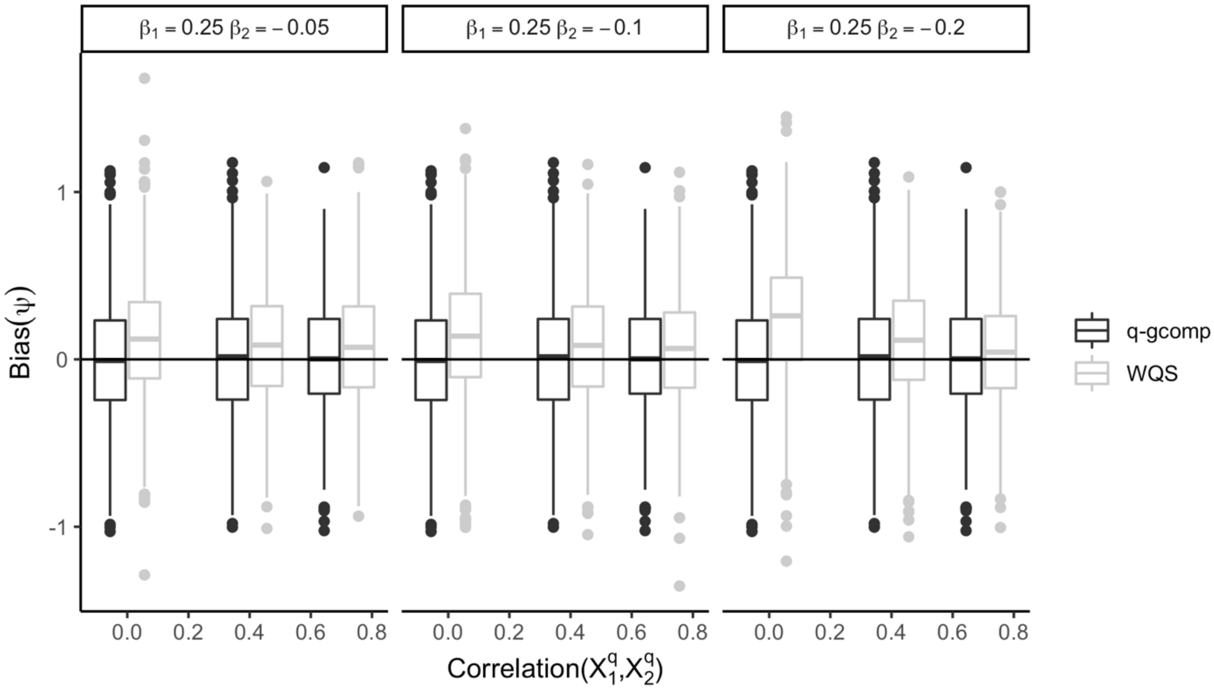

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APPENDIX TABLES

Table S1: Validity of WQS regression and quantile g-computation under the null (no exposures affect the outcome, or exposures counteract) and non-null estimates when directional homogeneity holds, 1,000 simulated samples of N=100.

Scenario	Method	d[a]	Truth[b]	Bias[c]	MCSE[d]	RMVAR[e]	Coverage[f]	Power/ Type 1 error[g]
1. Validity under the null, no exposures are causal	WQS[h]	4	0	0.00	0.19	0.20	0.95	0.05
		9	0	0.02	0.27	0.27	0.94	0.06
		14	0	0.00	0.34	0.34	0.95	0.05
	Q-gcomp[i]	4	0	0.00	0.18	0.18	0.95	0.05
		9	0	0.02	0.28	0.28	0.94	0.06
		14	0	0.00	0.36	0.36	0.95	0.05
2. Validity under the null, causal exposures counteract	WQS[h]	4	0	0.28	0.22	0.20	0.67	0.33
		9	0	0.30	0.32	0.29	0.78	0.22
		14	0	0.28	0.39	0.35	0.83	0.17
	Q-gcomp[i]	4	0	0.00	0.20	0.20	0.96	0.04
		9	0	0.01	0.30	0.30	0.95	0.05
		14	0	-0.02	0.38	0.38	0.94	0.06
3. Validity under single non-null effect	WQS[h]	4	0.25	0.04	0.21	0.19	0.92	0.37
		9	0.25	0.09	0.29	0.27	0.91	0.27
		14	0.25	0.07	0.36	0.34	0.92	0.19
	Q-gcomp[i]	4	0.25	0.00	0.18	0.18	0.95	0.29
		9	0.25	0.02	0.28	0.28	0.94	0.16
		14	0.25	0.00	0.36	0.36	0.95	0.12
4. Validity under all non-null effects with directional homogeneity	WQS[h]	4	0.25	-0.07	0.20	0.20	0.93	0.15
		9	0.25	-0.07	0.28	0.28	0.94	0.11
		14	0.25	-0.12	0.34	0.34	0.93	0.08
	Q-gcomp[i]	4	0.25	-0.01	0.18	0.18	0.95	0.26
		9	0.25	0.00	0.27	0.28	0.95	0.15
		14	0.25	0.00	0.36	0.36	0.94	0.11

[a]Total number of exposures in the model
[b]True value of ψ, the net effect of the exposure mixture
[c]Estimate of ψ minus the true value
[d]Standard deviation of the bias across 1000 iterations
[e]Square root of the mean of the variance estimates from the 1000 simulations, should equal MCSE if the variance estimator is unbiased
[f]Proportion of simulations in which the estimated 95% confidence interval contained the truth.
[g]Power when the effect is non-null, otherwise is the type 1 error rate (false rejection of null), which should equal alpha (0.05 here) under a valid test
[h]WQS regression (R package "gWQS" defaults)
[i]Quantile g-computation (R package "qgcomp" defaults)

Table S2: Validity of WQS regression and quantile g-computation under non-null estimates when directional homogeneity holds, individual exposure effects are non-additive, and the overall exposure effect includes terms for linear (ψ_1) and squared (ψ_2) exposure (e.g. quadratic polynomial), 1,000 simulated samples of N=100.

Scenario	Method	d[a]	Bias[b]		MCSE[c]		RMVAR[d]	
			ψ_1	ψ_2	ψ_1	ψ_2	ψ_1	ψ_2
7. Validity when the true exposure effect is non-additive/non-linear	WQS[e]	4	0.13	-0.04	0.78	0.25	0.75	0.24
		9	-0.08	0.02	1.69	0.56	1.67	0.55
		14	-0.24	0.08	2.61	0.87	2.69	0.89
	Q-gcomp[f]	4	0.00	0.00	0.30	0.08	0.29	0.08
		9	0.01	0.00	0.36	0.08	0.37	0.09
		14	-0.02	0.00	0.43	0.09	0.45	0.09
8. Validity when the overall exposure effect is non-linear due to underlying non-linear effects	WQS[e]	4	-0.21	0.07	0.74	0.24	0.77	0.25
		9	-0.25	0.09	1.68	0.55	1.71	0.56
		14	-0.39	0.13	2.63	0.87	2.77	0.91
	Q-gcomp[f]	4	0.00	0.00	0.34	0.10	0.34	0.10
		9	0.00	0.00	0.41	0.10	0.41	0.10
		14	-0.01	0.00	0.46	0.11	0.49	0.11

[a]Total number of exposures in the model
[b]Estimate of ψ_1 or ψ_2 minus the true value
[c]Standard deviation of the bias across 1000 iterations
[d]Square root of the mean of the variance estimates from the 1000 simulations, should equal MCSE if the variance estimator is unbiased
[e]WQS regression (R package "gWQS" defaults, allowing for quadratic term for total exposure effect)
[f]Quantile g-computation (R package "qgcomp" defaults, including interaction term between X_1 and X_2 (scenario 7) or a term for X_1X_1 (scenario 8) as well as quadratic term for total exposure effect)

Table S3: Validity of WQS regression without sample splitting and quantile g-computation under the null (no exposures affect the outcome, 1,000 simulated samples of N=500).

Scenario	Method	df[a]	Truth[b]	Bias[c]	MCSE[d]	RMVAR[e]	Type 1 error[f]
1. Validity under the null, no exposures are causal	**WQS[g]**	4	0	0.06	0.06	0.07	0.86
		9	0	0.15	0.09	0.09	0.65
		14	0	0.25	0.10	0.11	0.38
	Q-gcomp[h]	4	0	0.00	0.08	0.08	0.06
		9	0	0.00	0.12	0.12	0.05
		14	0	-0.01	0.16	0.15	0.05

[a]Total number of exposures in the model
[b]True value of ψ, the net effect of the exposure mixture
[c]Estimate of ψ minus the true value
[d]Standard deviation of the bias across 1000 iterations
[e]Square root of the mean of the variance estimates from the 1000 simulations, should equal MCSE if the variance estimator is unbiased
[f]Type 1 error rate (false rejection of null), which should equal alpha (0.05 here) under a valid test
[g]WQS regression (R package "gWQS", validation parameter set to 0)
[h]Quantile g-computation (R package "qgcomp" defaults). Results are repeated from Table 3 in the main text for reference.