Environ Health Perspect

DOI: 10.1289/EHP10570

Supplemental Material

A Permutation Test-Based Approach to Strengthening Inference on the Effects of Environmental Mixtures: Comparison between Single-Index Analytic Methods

Drew B. Day, Sheela Sathyanarayana, Kaja Z. LeWinn, Catherine J. Karr, W. Alex Mason, and Adam A. Szpiro

Table of Contents

Additional Information about Bootstrap Weighted Quantile Sum Regressions (WQSBS)

TIDES Correlation Matrix

Confidence Interval Coverage Results from Simulations

Rates of WQSr Models Failing to Estimate a Coefficient in the Desired Direction

Table S1. Covariates Included in the CANDLE Models and their Times of Collection and Categorizations.

Table S2. Numbers of Failed WQS Models and Failed Internal Iterations for Iterative WQS Models by Correlation and True Mixture Coefficient Value without the “b1_constr” Constraint.

Table S3. Mixture Coefficients, Confidence Intervals, and p-values from Models Associating Prenatal Maternal Phthalate Mixtures with Female Child Age 4-6 FSIQ in the CANDLE Cohort with or without the “b1_constr” Parameter.

Table S4. Numbers of Failed WQS Models and Failed Internal Iterations for Iterative WQS Models by Correlation and True Mixture Coefficient Value with the “b1_constr” Constraint.

Figure S1. Comparing Bootstrapped b1 Values from the WQSBS_Split Model with “b1_constr” Set to True or False.

Figure S2. Pearson Correlation Coefficients between 10 Specific Gravity-Adjusted, log10-Transformed Maternal Urinary Phthalate Metabolites and 10 Covariates in the TIDES Study.

Figure S3. Pearson Correlation Coefficients between $\log_{10}$-transformed Maternal Third Trimester Urinary Phthalate Metabolites in the CANDLE Study.

Figure S4. Confidence Interval Coverage Rates for Mixture Coefficient Estimates in 500 Simulations for Nonzero or Zero Mixture Coefficients Between Correlation Conditions.

Figure S5. Model Performance Measures for Mixture Coefficient Estimates in 500 Simulations for Nonzero or Zero Mixture Coefficients Between Correlation Conditions when the “b1_constr” Constraint was Set to be True.

Figure S6. MAPE for High and Low Mixture Weight Estimates Rescaled as Component-Specific Coefficients in 500 Simulations for Nonzero Mixture Coefficients Between Correlation Conditions when the “b1_constr” Constraint was Set to be True.

Figure S7. Mixture Coefficient and Component Coefficient Results for All Models Evaluating Associations between Prenatal Maternal Phthalate Mixtures and Female Child FSIQ in the CANDLE Cohort when the “b1_constr” Constraint was Set to be True.

References

Additional Information about Bootstrap Weighted Quantile Sum Regressions (WQSBS)

Equation S1 describes in further detail the iterative, two-stage process used to perform a WQS regression, specifically using the bootstrap algorithm. For each i bootstrap iteration out of B total iterations, the rows of the quantile-transformed exposure mixture training dataset (X_{qt}) are bootstrapped to form X_{qti}. Equation S1.1 represents the linear model for which a nonlinear optimization algorithm maximizes likelihood by calculating a set of mixture weights ω_i to combine with X_{qti} to get WQS_i as shown in Equation 1.2. In the original form of the R implementation of the bootstrap WQSr (WQSBS) as encoded in the *gWQS* R package,[1] the nonlinear optimization algorithm used was the solving for nonlinear problems (SOLNP) algorithm.[2] More recent *gWQS* R package versions rely on the nonlinear optimization method "BFGS" as the default nonlinear optimization estimation algorithm.[3,4] The bootstrapped training outcome data y_{ti} are then regressed on WQS_i and bootstrapped training covariate data Z_{ti} in Equation 1.1 to get iterative coefficients for the intercept (b_{0i}), the WQS (b_{1i}), and the covariates (g_i), as well as residuals ε_i. After B bootstrap iterations, the iterations that converged and provided b_{1i} in the specified direction d, either positive or negative, are selected to get B_d usable bootstrap iterations. Final weights w for direction d are determined as a weighted average of the ω for each mixture component weighted by the t-statistic for that j iteration's mixture coefficient $tstat_{b_1 j}$ (Equation S1.3). The final weights w are then combined with the validation quantile-transformed mixture exposure matrix X_{qv} to get WQS (Equation 1.4). Finally, coefficients (β_0, β_1, and γ) are determined when the validation set of outcome data y_v is regressed on the WQS and the validation set of covariate data Z_v (Equation S1.5).

Equation S1: $(1)\ y_{ti} = \ b_{0i} + WQS_i \cdot b_{1i} + \ Z_{ti} \cdot g_i + \varepsilon_i$

$$(2)\ WQS_i = X_{qti} \cdot \omega_i$$

$$(3)\ w = \frac{\sum_{j=1}^{B_d} \omega_j * tstat_{b_1 j}}{\sum_{j=1}^{B_d} tstat_{b_1 j}}$$

$$(4)\ WQS = X_{qv} \cdot w$$

$$(5)\ y_v = \ \beta_0 + WQS \cdot \beta_1 + \ Z_v \cdot \gamma + \varepsilon$$

For the *gWQS* package, the specified direction d is chosen with the input "b1_pos", which also sets the initial value of the first bootstrapped b_1 in the first stage to either positive or negative $1\text{x}10^{-4}$. An additional parameter related to directionality is the constraint parameter "b1_constr", which when set to be true constrains the initial value for each bootstrapped b_1 to be in the specified positive or negative direction, thereby increasing the number of bootstrapped b_1 in the specified direction, though not entirely eliminating the possibility of b_1 being sampled in the opposite direction.

An illustration of this is shown in Figure S1, which plots histograms of bootstrapped b_1 from 5 iterations of the positive direction WQSBS_Split model using the uncorrelated and true zero β_1 simulation conditions used in the broader analysis. The darker grey histograms show when the "b1_constr" argument is set to be false and the light grey are when the argument is true, with medium grey bins showing overlap between the two conditions. Zero is marked with a solid black vertical line. The seeds used as well as the eventual β_1 values chosen by the "b1_constr = FALSE" and "b1_constr = TRUE" models are shown in the strip labels at the top of the plot. There are many more negative bootstrapped b_1 when "b1_constr" is set to be false, though there are still some when "b1_constr" is set to be true too. Since these negative b_1 are omitted from the subsequent second stage of the model, the estimates for the final mixture coefficient β_1 are extremely close in value no matter the setting for "b1_constr".

TIDES Correlation Matrix

Figure S2 shows the example Pearson correlation matrix used as a template for the multivariate unit normally-distributed mixture components and covariates in the simulations. Phthalate metabolites were specific gravity-adjusted and $\log_{10}$-transformed prior to correlation analysis. All phthalate metabolites were measured in urine collected from participating mothers in early pregnancy, and additional methodological details have been published.[6] Monocarboxyoctyl phthalate (MCOP) was not included in the referenced analysis due to a higher number of values that were missing, but it was included in this correlation table in order to bring the number of phthalate metabolites up to 10. Covariates included in this example correlation matrix include the continuous covariates maternal and child age, pre-pregnancy BMI ("PrepregBMI"), and gestational age at urine collection ("GestAge_U"). In addition, the categorical variables of race and any reported cigarette smoking ("Cigarettes") or alcohol use ("Alcohol") during pregnancy were converted into dummy variables with numeric values of zero or one. The race variable has "Asian" as the referent level, and there are three additional levels ("Black", "Other", and "White") included in this correlation matrix as dummy variables.

Confidence Interval Coverage Results from Simulations

Figure S4 shows mixture coefficient confidence interval (CI) coverage results from the simulations. Coverage was defined as having the true mixture coefficient estimate fall within the confidence interval. WQSr models that failed to return estimates were said to have no coverage for that simulation iteration. As can be seen from this figure, only QGC models consistently have coverages around 95%, suggesting that only the ψ parameter CIs from those models accurately reflect 95% CIs. All other models appear to have improper CI estimates. PT models were omitted from Figure S4 because the permutation test only returns a new p-value for the mixture coefficient and does not provide any CIs.

Rates of WQSr Models Failing to Estimate a Coefficient in the Desired Direction

WQSr models at times can fail to detect any bootstrapped mixture coefficients (b_1) in the specified direction (e.g., positive) if there is little to no signal in that direction, which we have treated in our simulation analysis as equivalent to returning a mixture coefficient of zero in the specified direction. This can happen for an overall model (e.g., WQSBS_Split) or internally for iterative processes, namely the permutation test. Permutation test WQSr models could only fail for the overall model if the Nosplit WQSr that precedes that step failed to return any b_1 in the specified direction. Table S2 summarizes the number of times WQSr models failed to return any estimates for overall models ("N Failed Models"), as well as how many internal iterations of the permutation test algorithms failed to return estimates ("N Failed Iter"). Given the default 100 bootstraps used in these simulations, the WQSBS_Nosplit and WQSBS_Split models would fail in the positive direction 0.2-2% of the time if the true mixture coefficient was zero and never if the true mixture coefficient was 0.2 or 0.3. When the true mixture coefficient was zero and model predictors were uncorrelated, the WQSRS_Nosplit and WQSRS_Split models would fail at a similar rate (0.4-0.8%), but the number of failures rose dramatically when the TIDES predictor correlation structure was introduced (11-13.6%). The repeated holdout versions of the WQS regressions most frequently failed at the overall model level, with WQSBS_RH and WQSRS_RH models failing only once when the mixture coefficient was nonzero and predictor variables were uncorrelated but each failing numerous times when the mixture coefficient was zero (WQSBS_RH: 35%, WQSRS_RH: 26-85.8%). For the permutation test models, WQSBS_PT models had 0-4% failed internal iterations (1% on average) for all simulated conditions. WQSRS_PT models had similar numbers of failed internal iterations when predictors were uncorrelated (0-3%), but with correlated predictors the WQSRS_PT had 5-19% failed internal iterations (11-12% on average).

TABLES

Table S1: Covariates Included in the CANDLE Models and their Times of Collection and Categorizations

Covariate	**Visit of Collection**	**Categorization**
Study site	Pregnancy	Two categories: 1. general community or 2. medical group clinics
Maternal age	Pregnancy	Continuous, linear
Maternal race	Pregnancy	Two categories: 1. Black or 2. non-Black
Maternal education	Pregnancy	Five categories: 1. <high school, 2. high school/GED, 3. technical school, 4. college, or 5. graduate or professional degree
Marital status	Pregnancy	Three categories: 1. married, 2. living with a partner or 3. never married/separated/divorced/widowed
Medical insurance	Pregnancy	Two categories: 1. no insurance/Medicaid or Medicare only or 2. Medicaid/Medicare and private insurance/Private insurance only
Pre-pregnancy BMI	Pregnancy	Four categories: 1. underweight, 2. normal weight, 3. overweight, or 4. obese
Parity	Pregnancy	Two categories: 1. primiparous or 2. multiparous
Maternal tobacco smoking during pregnancy	Pregnancy	Two categories: 1. never or 2. ever
Household adjusted income	Pregnancy	Continuous, linear
Maternal psychopathology score (Brief Symptoms Inventory)	Pregnancy	Continuous, linear

Maternal childcare knowledge score (Knowledge of Infant Development Inventory)	Pregnancy	Continuous, linear
Child Opportunity Index (COI) educational score	Pregnancy	Continuous, 3-degree of freedom cublic spline
COI health and environment score	Pregnancy	Continuous, 3-degree of freedom cublic spline
COI social and economic score	Pregnancy	Continuous, 3-degree of freedom cublic spline
Year of birth	Birth	Five categories: 1. 2007, 2. 2008, 3. 2009, 4. 2010, or 5. 2011
Maternal IQ (Weschler Abbreviated Scales of Intelligence)	Age 4-6	Continuous, linear
Child age	Age 4-6	Continuous, linear
Breastfeeding history	Age 4-6	Two categories: 1. never or 2. ever

Table S2: Numbers of Failed WQS Models and Failed Internal Iterations for Iterative WQS Models by Correlation and True Mixture Coefficient Value without the "b1_constr" Constraint

Correlation	True Mix Coef	Model	N Failed Models (%)	Mean N Failed Iter (%)	Median N Failed Iter (%)	Range N Failed Iter (%)
Uncorrelated	0.3	WQSBS_Split	0 (0%)	-	-	-
		WQSBS_RH	1 (0.2%)	-	-	-
		WQSBS_Nosplit	0 (0%)	-	-	-
		WQSBS_PT	0 (0%)	1.98 (0.99%)	2 (1%)	0-7 (0-3.5%)
		WQSRS_Split	0 (0%)	-	-	-
		WQSRS_RH	1 (0.2%)	-	-	-
		WQSRS_Nosplit	0 (0%)	-	-	-
		WQSRS_PT	0 (0%)	1.26 (0.63%)	1 (0.5%)	0-6 (0-3%)
	0	WQSBS_Split	10 (2%)	-	-	-
		WQSBS_RH	175 (35%)	-	-	-
		WQSBS_Nosplit	5 (1%)	-	-	-
		WQSBS_PT	5 (1%)	2.07 (1.04%)	2 (1%)	0-6 (0-3%)
		WQSRS_Split	2 (0.4%)	-	-	-
		WQSRS_RH	130 (26%)	-	-	-

		WQSRS_Nosplit	4 (0.8%)	-	-	-
		WQSRS_PT	4 (0.8%)	1.23 (0.61%)	1 (0.5%)	0-5 (0-2.5%)
Correlated	0.2	WQSBS_Split	0 (0%)	-	-	-
		WQSBS_RH	0 (0%)	-	-	-
		WQSBS_Nosplit	0 (0%)	-	-	-
		WQSBS_PT	0 (0%)	2.02 (1.01%)	2 (1%)	0-7 (0-3.5%)
		WQSRS_Split	0 (0%)	-	-	-
		WQSRS_RH	10 (2%)	-	-	-
		WQSRS_Nosplit	0 (0%)	-	-	-
		WQSRS_PT	0 (0%)	27.71 (11.36%)	22 (11%)	10-38 (5-19%)
	0	WQSBS_Split	1 (0.2%)	-	-	-
		WQSBS_RH	175 (35%)	-	-	-
		WQSBS_Nosplit	4 (0.8%)	-	-	-
		WQSBS_PT	4 (0.8%)	2.13 (1.06%)	2 (1%)	0-8 (0-4%)
		WQSRS_Split	55 (11%)	-	-	-
		WQSRS_RH	429 (85.8%)	-	-	-
		WQSRS_Nosplit	68 (13.6%)	-	-	-
		WQSRS_PT	68 (13.6%)	23.42 (11.71%)	24 (12%)	10-38 (5-19%)

Table S3: Mixture Coefficients, Confidence Intervals, and p-values from Models Associating Prenatal Maternal Phthalate Mixtures with Female Child Age 4-6 FSIQ in the CANDLE Cohort with or without the "b1_constr" Parameter

b1_constr	Direction	Model Class	Model	β_1	LCI	UCI	p-value
FALSE	Negative	WQSBS	Split	-0.425	-2.50	1.65	0.688
			RH	-0.594	-1.96	0.770	NA
			Nosplit	-1.66	-3.09	-0.235	0.023
			PT	-1.66	NA	NA	0.085
		WQSRS	Split	-0.608	-2.45	1.23	0.518
			RH	-0.53	-1.58	0.522	NA
			Nosplit	-1.52	-2.78	-0.273	0.0174
			PT	-1.52	NA	NA	0.075
	Both	QGC	Boot	-1.00	-2.69	0.686	0.245
			Noboot	-1.00	-2.63	0.62	0.227
	Positive	WQSBS	Split	1.49	-0.143	3.12	0.0751
			RH	0.400	-1.17	1.97	NA
			Nosplit	1.18	0.240	2.12	0.0143
			PT	1.18	NA	NA	0.295

		WQSRS	Split	1.36	0.225	2.50	0.0197
			RH	NA	NA	NA	NA
			Nosplit	1.10	0.309	1.88	0.00659
			PT	1.10	NA	NA	0.365
TRUE	Negative	WQSBS	Split	-0.435	-2.50	1.63	0.681
			RH	-0.648	-1.85	0.556	NA
			Nosplit	-1.67	-3.09	-0.248	0.0218
			PT	-1.67	NA	NA	0.0850
		WQSRS	Split	-0.609	-2.46	1.24	0.519
			RH	-0.427	-1.59	0.739	NA
			Nosplit	-1.53	-2.79	-0.274	0.0174
			PT	-1.53	NA	NA	0.0650
	Both	QGC	Boot	-1.00	-2.69	0.686	0.245
			Noboot	-1.00	-2.63	0.620	0.227
	Positive	WQSBS	Split	1.35	-0.349	3.05	0.121
			RH	0.406	-1.04	1.85	NA
			Nosplit	1.17	0.275	2.06	0.0107
			PT	1.17	NA	NA	0.295
		WQSRS	Split	1.37	0.195	2.55	0.0233
			RH	NA	NA	NA	NA
			Nosplit	1.10	0.307	1.89	0.00683
			PT	1.10	NA	NA	0.380

Table S4: Numbers of Failed WQS Models and Failed Internal Iterations for Iterative WQS Models by Correlation and True Mixture Coefficient Value with the "b1_constr" Constraint

Correlation	True Mix Coef	Model	N Failed Models (%)	Mean N Failed Iter (%)	Median N Failed Iter (%)	Range N Failed Iter (%)
Uncorrelated	0.3	WQSBS_Split	0 (0%)	-	-	-
		WQSBS_RH	0 (0%)	-	-	-
		WQSBS_Nosplit	0 (0%)	-	-	-
		WQSBS_PT	0 (0%)	0 (0%)	0 (0%)	0-0 (0-0%)
		WQSRS_Split	0 (0%)	-	-	-
		WQSRS_RH	0 (0%)	-	-	-
		WQSRS_Nosplit	0 (0%)	-	-	-
		WQSRS_PT	0 (0%)	0.93 (0.46%)	1 (0.5%)	0-5 (0-2.5%)
	0	WQSBS_Split	0 (0%)	-	-	-
		WQSBS_RH	0 (0%)	-	-	-
		WQSBS_Nosplit	0 (0%)	-	-	-
		WQSBS_PT	0 (0%)	0 (0%)	0 (0%)	0-0 (0-0%)
		WQSRS_Split	1 (0.2%)	-	-	-

		WQSRS_RH	38 (7.6%)	-	-	-
		WQSRS_Nosplit	4 (0.8%)	-	-	-
		WQSRS_PT	4 (0.8%)	0.93 (0.46%)	1 (0.5%)	0-5 (0-2.5%)
Correlated	0.2	WQSBS_Split	0 (0%)	-	-	-
		WQSBS_RH	0 (0%)	-	-	-
		WQSBS_Nosplit	0 (0%)	-	-	-
		WQSBS_PT	0 (0%)	0 (0%)	0 (0%)	0-0 (0-0%)
		WQSRS_Split	0 (0%)	-	-	-
		WQSRS_RH	2 (0.4%)	-	-	-
		WQSRS_Nosplit	0 (0%)	-	-	-
		WQSRS_PT	0 (0%)	21.18 (10.59%)	21 (10.5%)	0-34 (0-17%)
	0	WQSBS_Split	0 (0%)	-	-	-
		WQSBS_RH	0 (0%)	-	-	-
		WQSBS_Nosplit	0 (0%)	-	-	-
		WQSBS_PT	0 (0%)	0 (0%)	0 (0%)	0-0 (0-0%)
		WQSRS_Split	24 (4.8%)	-	-	-
		WQSRS_RH	360 (72%)	-	-	-
		WQSRS_Nosplit	60 (12%)	-	-	-
		WQSRS_PT	60 (12%)	21.1 (10.55%)	21 (10.5%)	0-36 (0-18%)

FIGURES

Figure S1: Comparing Bootstrapped b1 Values from the WQSBS_Split Model with "b1_constr" Set to True or False

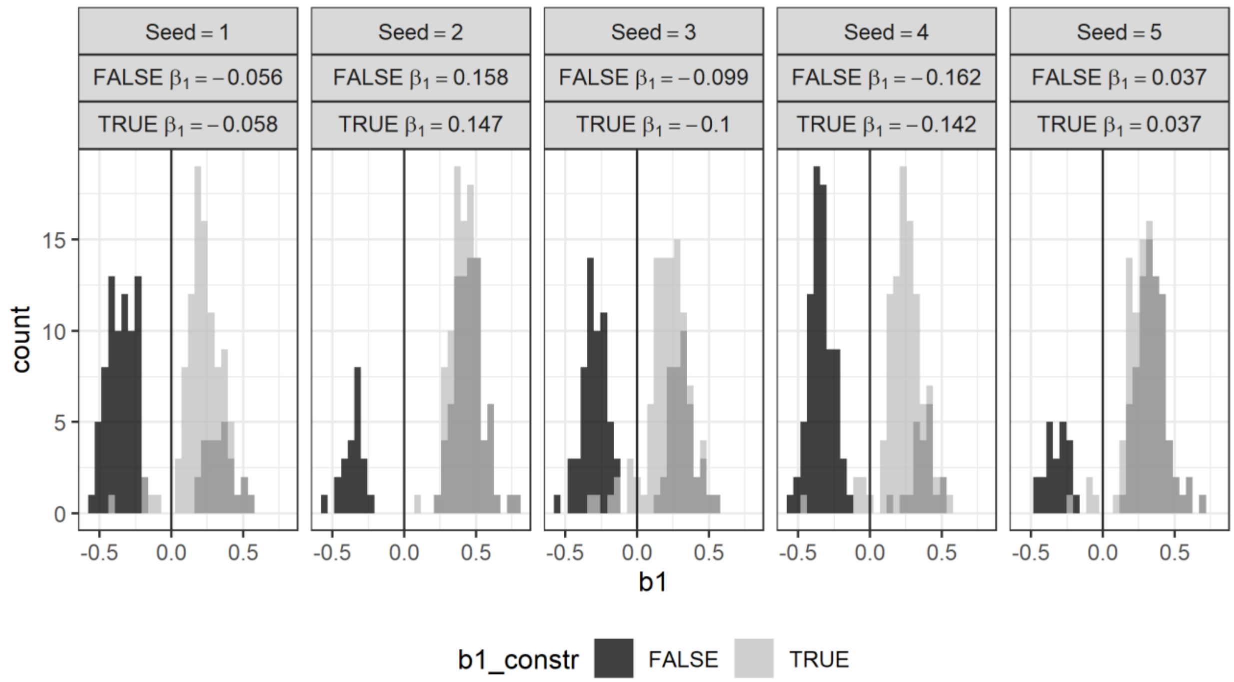
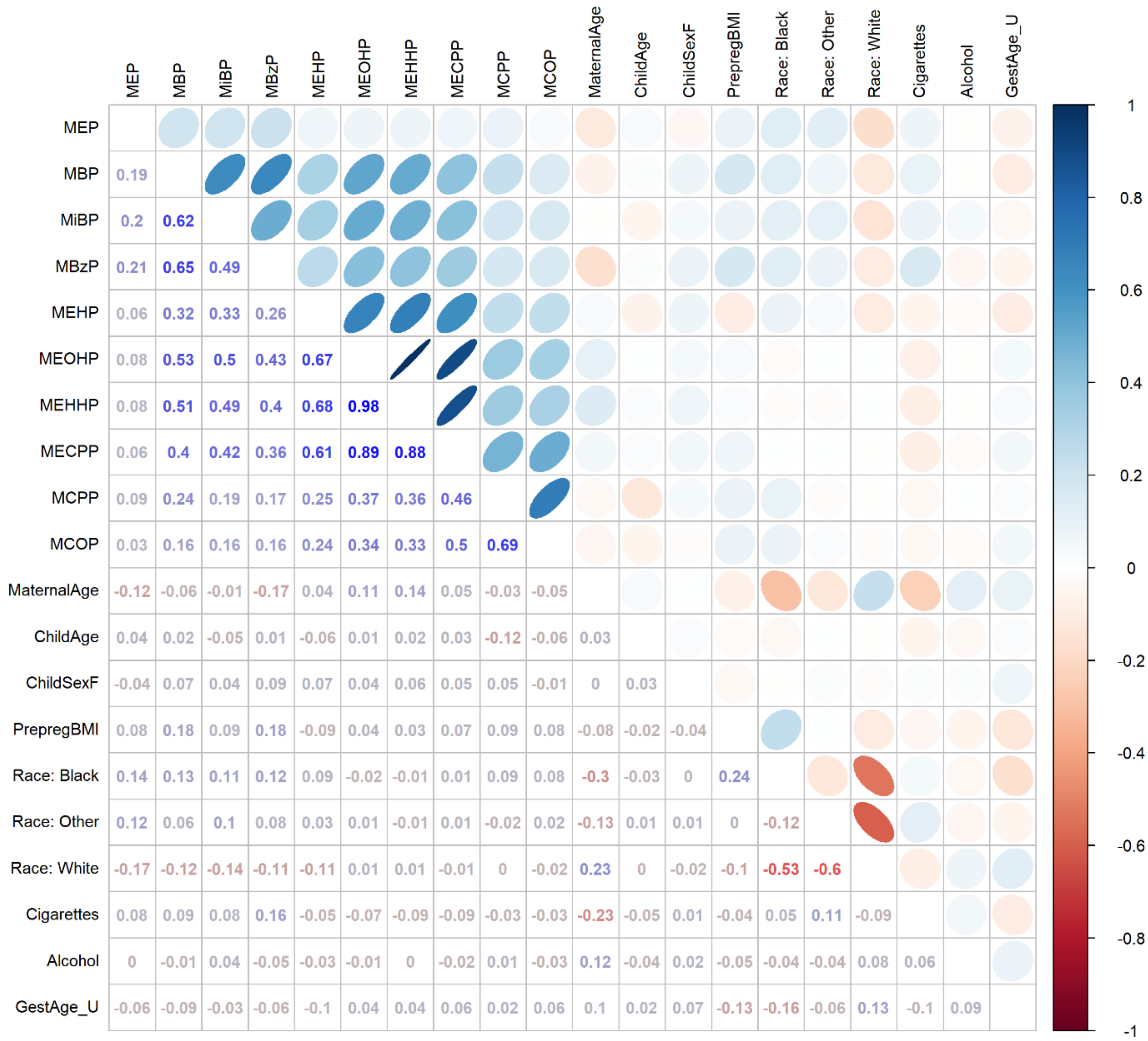
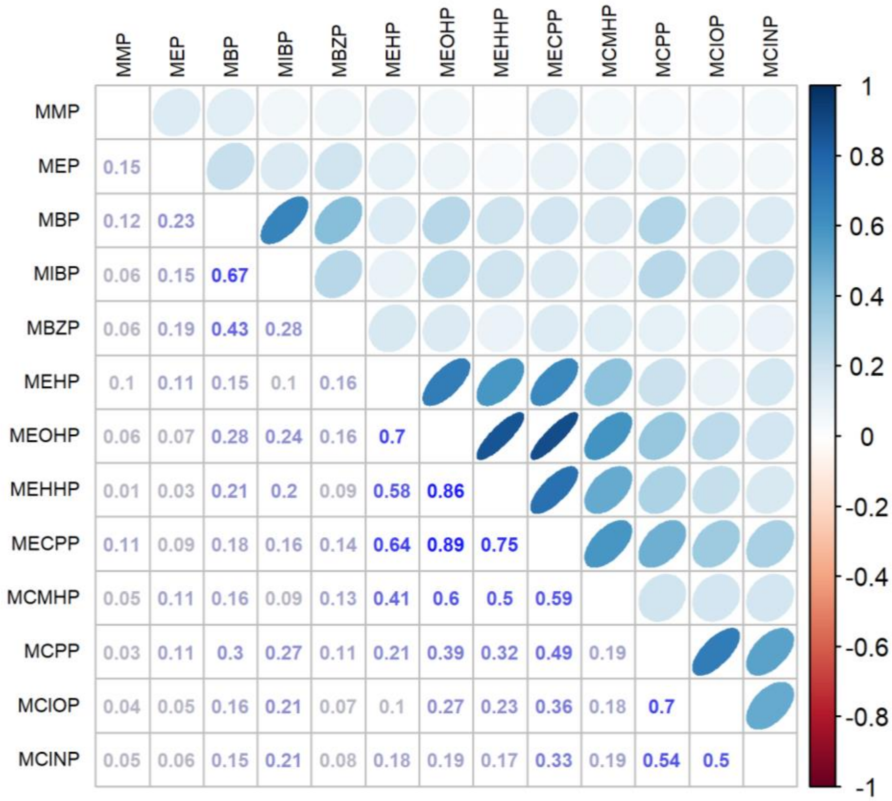


Figure S2. Pearson Correlation Coefficients between 10 Specific Gravity-Adjusted, log10-Transformed Maternal Urinary Phthalate Metabolites and 10 Covariates in the TIDES Study



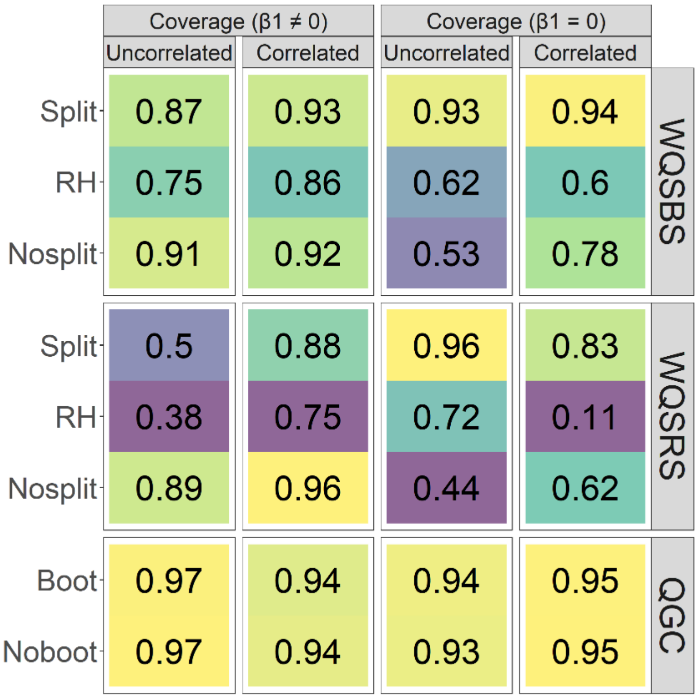
MEP: monoethyl phthalate, MBP: monobutyl phthalate, MiBP: monoisobutyl phthalate, MBzP: monobenzyl phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MCPP: mono(3-carboxypropyl) phthalate, MCOP: monocarboxyoctyl phthalate, GestAge_U: gestational age at urine collection. See Section S2.1 for more details.

Figure S3. Pearson Correlation Coefficients between log_{10}-transformed Maternal Third Trimester Urinary Phthalate Metabolites in the CANDLE Study



Additional information on the CANDLE variables and methods can be found in the published manuscript of this analysis.[7] MMP: monomethyl phthalate, MEP: monoethyl phthalate, MBP: monobutyl phthalate, MIBP: monoisobutyl phthalate, MBZP: monobenzyl phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MCMHP: mono(2-carboxymethylhexyl) phthalate, MCPP: mono(3-carboxypropyl) phthalate, MCIOP: monocarboxyisooctyl phthalate, MCINP: monocarboxyisononyl phthalate.

Figure S4: Confidence Interval Coverage Rates for Mixture Coefficient Estimates in 500 Simulations for Nonzero or Zero Mixture Coefficients Between Correlation Conditions



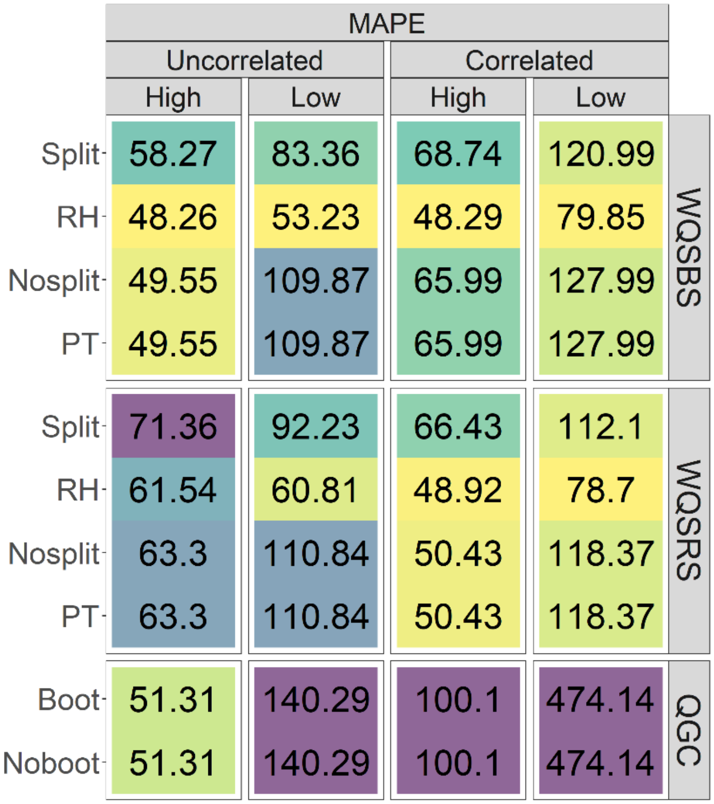
Within each performance measure and simulation exposure correlation condition (i.e., uncorrelated predictors or correlated predictors with a variance-covariate matrix derived from a real dataset), tiles filled in with a yellower color indicate better performance, while those filled in with a more purple color indicate worse performance. Coverage ($\beta_1 \neq 0$) = confidence interval coverage rate when β_1 is nonzero, Coverage ($\beta_1 = 0$) = confidence interval coverage rate when β_1 is zero.

Figure S5: Model Performance Measures for Mixture Coefficient Estimates in 500 Simulations for Nonzero or Zero Mixture Coefficients Between Correlation Conditions when the "b1_constr" Constraint was Set to be True

		Power		FPR		MAPE (β1 ≠ 0)		MAE (β1 = 0)		Coverage (β1 ≠ 0)		Coverage (β1 = 0)	
		Uncorr	Corr	Uncorr	Corr	Uncorr	Corr	Uncorr	Corr	Uncorr	Corr	Uncorr	Corr
WQSBS	Split	0.52	0.77	0.05	0.05	35.99	29.61	0.08	0.05	0.89	0.91	0.95	0.95
WQSBS	RH	0.79	0.97	0.08	0.07	32.7	22.79	0.06	0.04	0.73	0.85	0.92	0.93
WQSBS	Nosplit	1	0.99	0.49	0.23	26.41	22.28	0.14	0.06	0.91	0.92	0.51	0.77
WQSBS	PT	0.9	0.97	0.07	0.05	26.41	22.28	0.14	0.06				
WQSRS	Split	0.39	0.76	0.03	0.04	52.52	30.49	0.05	0.04	0.55	0.87	0.96	0.91
WQSRS	RH	0.6	0.98	0.02	0.04	50.65	25.04	0.03	0.01	0.39	0.75	0.9	0.24
WQSRS	Nosplit	1	0.99	0.56	0.24	21.25	18.02	0.11	0.06	0.91	0.95	0.43	0.64
WQSRS	PT	0.89	0.97	0.06	0.06	21.25	18.02	0.11	0.06				
QGC	Boot	0.85	0.92	0.06	0.06	26.28	23.59	0.08	0.05	0.97	0.94	0.94	0.94
QGC	Noboot	0.85	0.93	0.07	0.05	26.28	23.59	0.08	0.05	0.97	0.94	0.93	0.95

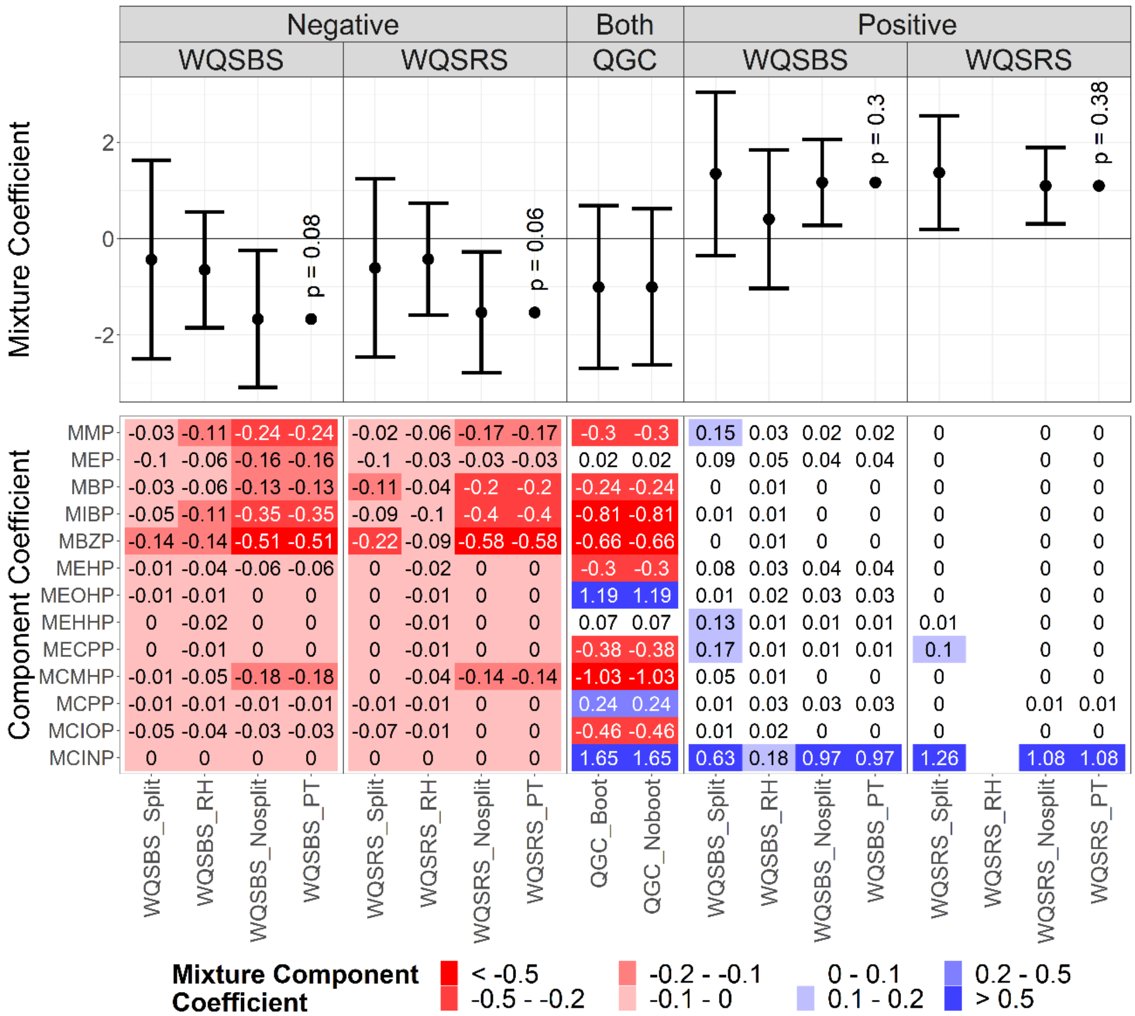
These were the simulation results when setting the "b1_constr" constraint to be true. Within each performance measure and simulation exposure correlation condition (i.e., uncorrelated predictors or correlated predictors with a variance-covariate matrix derived from a real dataset), tiles filled in with a yellower color indicate better performance, while those filled in with a more purple color indicate worse performance. Confidence interval coverage results are missing for PT WQSr models since the permutation test does not produce confidence intervals. FPR = false positive rate, MAPE = mean absolute percent error (when β_1 is nonzero), MAE = mean absolute error (when β_1 is zero), Coverage ($\beta_1 \neq 0$) = confidence interval coverage rate when β_1 is nonzero, Coverage ($\beta_1 = 0$) = confidence interval coverage rate when β_1 is zero, WQSBS = bootstrap weighted quantile sum regression, WQSRS = random subset weighted quantile sum regression, QGC = quantile g-computation, RH = repeated holdout, PT = permutation test.

Figure S6: MAPE for High and Low Mixture Weight Estimates Rescaled as Component-Specific Coefficients in 500 Simulations for Nonzero Mixture Coefficients Between Correlation Conditions when the “b1_constr” Constraint was Set to be True



These were the simulation results when setting the “b1_constr” constraint to be true. Within each simulation exposure correlation condition (i.e., uncorrelated predictors or correlated predictors with a variance-covariate matrix derived from a real dataset) and class of weights (i.e., high or low), tiles filled in with a yellower or greener color indicate better performance, while those filled in with a more blue and purple color indicate worse performance. MAPE = mean absolute percent error (when β_1 is nonzero), WQSBS = bootstrap weighted quantile sum regression, WQSRS = random subset weighted quantile sum regression, QGC = quantile g-computation, RH = repeated holdout, PT = permutation test.

Figure S7: Mixture Coefficient and Component Coefficient Results for All Models Evaluating Associations between Prenatal Maternal Phthalate Mixtures and Female Child FSIQ in the CANDLE Cohort when the "b1_constr" Constraint was Set to be True



These were the results when setting the "b1_constr" constraint to be true. The top forest plot shows means and 95% CIs for mixture coefficient estimates in the negative and positive directions for WQSr models or for both directions for the QGC models. The bottom heat map shows the corresponding mixture component-specific coefficients for each model, direction, and measured phthalate metabolite. These mixture component-specific coefficient values are color coded by value with darker red values being more negative and darker blue values being more positive. These colors highlight the coefficient values in the bottom heat map; they do not contain any information beyond the printed numeric values. Numeric values for the top forest plot are provided in Table S3. MMP: monomethyl phthalate, MEP: monoethyl phthalate, MBP: monobutyl phthalate, MIBP: monoisobutyl phthalate, MBZP: monobenzyl phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MCMHP: mono(2-carboxymethylhexyl) phthalate, MCPP: mono(3-carboxypropyl) phthalate, MCIOP: monocarboxyisooctyl phthalate, MCINP: monocarboxyisononyl phthalate.

References

1. Renzetti S, Gennings C, Curtin PC. gWQS: An R Package for Linear and Generalized Weighted Quantile Sum (WQS) Regression. *Journal of Statistical Software.* 2019.
2. Ye Y. *Interior algorithms for linear, quadratic, and linearly constrained non-linear programming*, Ph. D. thesis, Department of ESS, Stanford University; 1987.
3. Fletcher R. *Practical methods of optimization.* 2nd ed. Chichester ; New York: Wiley; 1987.
4. *gWQS: Generalized Weighted Quantile Sum Regression. R package version 3.0.4* [computer program]. 2021.
5. Anderson MJ, Legendre P. An empirical comparison of permutation methods for tests of partial regression coefficients in a linear model. *J Stat Comput Sim.* 1999;62(3):271-303.
6. Day DB, Collett BR, Barrett ES, Bush NR, Swan SH, Nguyen RHN, Szpiro AA, Sathyanarayana S. Phthalate mixtures in pregnancy, autistic traits, and adverse childhood behavioral outcomes. *Environ Int.* 2021;147:106330.
7. Loftus CT, Bush NR, Day DB, Ni Y, Tylavsky FA, Karr CJ, Kannan K, Barrett ES, Szpiro AA, Sathyanarayana S, LeWinn KZ. Exposure to prenatal phthalate mixtures and neurodevelopment in the Conditions Affecting Neurocognitive Development and Learning in Early childhood (CANDLE) study. *Environ Int.* 2021;150:106409.