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Sex-Specific Effects of Prenatal Organophosphate Ester (OPE) Metabolite Mixtures and Adverse Infant Birth Outcomes in the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) Pregnancy Cohort

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Abstract

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Background: Organophosphate esters (OPEs) are used as flame retardants and plasticizers in various consumer products. Limited prior research suggests sex-specific effects of prenatal OPE exposures on fetal development. We evaluated overall and sex-specific associations between prenatal OPE exposures and gestational age (GA) at birth and birthweight for gestational age (BW for GA) z-scores among the predominately low-income, Hispanic MADRES cohort.

Methods: Nine OPE metabolite concentrations were measured in 421 maternal urine samples collected during a third trimester visit (GA=31.5±2.0 weeks). We examined associations between single urinary OPE metabolites and GA at birth and BW for GA z-scores using linear regression models and Generalized Additive Models (GAMs) and effects from OPE mixtures using Bayesian Kernel Machine Regression (BKMR). We also assessed sex-specific differences in single metabolite analyses by evaluating statistical interactions and stratifying by sex.

Results: We did not find significant associations between individual OPE metabolites and birth outcomes in the full infant sample; however, we found that higher bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) was associated with earlier GA at birth among male infants (p=0.04), and a nonlinear, inverted U-shape association between the sum of dibutyl phosphate and di-isobutyl phosphate (DNBP+DIBP) and GA at birth among female infants (p=0.03). In mixtures analysis, higher OPE metabolite mixture exposures was associated with lower GA at birth, which was primarily driven by female infants. No associations were observed between OPE mixtures and BW for GA z-scores.

Conclusion: Higher BDCIPP and DNBP+DIBP concentrations were associated with earlier GA at birth among male and female infants, respectively. Higher exposure to OPE mixtures was associated with earlier GA at birth, particularly among female infants. However, we saw no associations between prenatal OPEs and BW for GA. Our results suggest sex-specific impacts of prenatal OPE exposures on GA at birth.

1. Introduction

Infant birth outcomes, such as gestational age (GA) at birth and birthweight, are important indicators of infant health and strong predictors of child neurodevelopment, obesity, and other cardiometabolic conditions.[1–5] Adverse birth outcomes, including preterm birth and low birthweight, disproportionately impact communities of color who are also more likely to experience a higher burden of environmental chemical exposures.[6–8] Accumulating epidemiological evidence stresses the potential for *in utero* environmental endocrine disrupting chemicals to adversely impact infant birth outcomes.[9–11] Emerging literature suggests that organophosphate esters (OPEs) are a class of endocrine disrupting chemicals.[12–14]

OPEs have increased in use as alternative flame-retardants to replace polybrominated diphenyl ethers (PBDEs) which were phased out due to bioaccumulation and neurotoxicity concerns.[15] However, OPEs are also commonly used as plasticizers and lubricants, contributing to their environmental ubiquity.[16,17] OPEs are found in a variety of consumer,

industrial, and electronic products, including clothing, polyurethane foams, textiles, and building materials.[15,18,19] Since OPEs are physically bound with a product matrix rather than chemically bound, they easily volatize and leach into surrounding environments during product use, settling into numerous environmental matrices (i.e., soil, surface water, sediment, and agricultural products) and dust particles in indoor environments, and enter the body through inhalation, dermal contact, and ingestion via dietary intake of OPE-contaminated food and drinking water.[20–26] Emerging literature indicates widespread exposure to OPEs among the general population, with high detection (>95%) of metabolites such as diphenyl phosphate (DPHP; parent compound= triphenyl phosphate (TPHP)) and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP; parent compound= tris(1,3-dichloropropyl) (TDCIPP)) in urine.[18,27] Widespread OPE metabolite concentrations have also recently been observed among vulnerable populations, including pregnant women.[27–32] Since OPEs have been found in the chorionic villi and uterine decidua of the placenta and amniotic fluid, suggesting in utero transfer of OPEs to the fetus,[33–36] there is a growing concern regarding exposures to these substances during critical periods of development.

Animal and in-vitro toxicological studies have reported adverse reproductive outcomes and early growth and development effects, including decreased birthweight, from OPE exposures.[37–42] However, no toxicological research has been conducted on the effects of OPEs on gestational duration and preterm birth. Hypothesized biological mechanisms include endocrine disruption, oxidative stress, and placental alterations.[34,38,39,43–51]

Limited epidemiological studies have explored the potential impacts of prenatal exposures to OPEs on infant birth outcomes, but the small number of studies that have been conducted have reported sex-specific effects on pre-term birth and low birthweight.[52,53] Additionally, most of the epidemiological literature on OPEs and infant birth outcomes has evaluated the effects of two OPE metabolites, DPHP and BDCIPP, in single chemical analyses, resulting in a limited understanding of the impacts of other OPEs on birth outcomes and their joint health effects. Furthermore, impacts of OPEs among structurally marginalized populations, such as Hispanic pregnant women, have been understudied.[18] This is of concern given the increasing use of OPEs and the ubiquity of exposures.[27]

In this study, we evaluated the prenatal impacts of nine OPE metabolites individually and in mixtures on infant GA at birth and BW for GA among 421 mother-infant dyads participating in the <u>M</u>aternal <u>A</u>nd <u>D</u>evelopmental <u>R</u>isks from <u>E</u>nvironmental and <u>S</u>ocial Stressors (MADRES) cohort study. Given prior toxicological and epidemiological evidence suggesting adverse OPE impacts on birth outcomes, with more pronounced impacts among female infants,[38,52,53] we hypothesized that higher exposure to both single OPE metabolites and mixtures would result in earlier GA at birth and lower BW for GA, particularly among female infants.

2.   Materials and Methods

2.1.   Study Sample

The MADRES study is an ongoing prospective pregnancy cohort of predominately low-income Hispanic/Latina women living in urban Los Angeles. A detailed description of

the MADRES study population and protocol has been previously described.[54] In brief, participants were recruited into the study at three partner community health clinics, one private obstetrics and gynecology practice in Los Angeles, and through limited self-referrals from community meetings and local advertisements. Eligible participants at the time of recruitment were: (1) less than 30 weeks' gestation, (2) over 18 years of age or older, and (3) fluent speaker of English or Spanish. Exclusion criteria included: (1) multiple gestation, (2) having a physical, mental, or cognitive disability that prevented participation or ability to provide consent, (3) current incarceration, and (4) HIV positive status. Written informed consent was obtained at study entry for each participant and the study was approved by the University of Southern California's Institutional Review Board.

Participants included in this analysis were recruited from November 2015 to October 2019. OPE metabolite concentrations were measured in all available MADRES participants' spot urine specimens collected during the third trimester study visit (N=426, mean ± SD gestational age at collection: 31.5 weeks±2.0 weeks). Five mother-infant dyads with missing information on key covariates or birth outcomes were excluded from the final analysis. A total of 421 mother-infant dyads with OPE metabolite concentrations, birth outcomes data, and information on key covariates were analyzed in this study. This subset of 421 participants from the MADRES cohort was similar to the full cohort on key demographic characteristics.

2.2. OPE Metabolite Analysis

Maternal single spot urine samples were collected in 90 mL sterile specimen containers. Urine specimens were aliquoted into 1.5 mL aliquot cryovials and stored at −80 °C prior to shipment. Specific gravity was measured in urine samples prior to flash freezing using a digital handheld refractometer (ATAGO PAL-10s pocket refractometer). Frozen samples were sent to the Wadsworth Center Human Health Exposure Analysis Resource (HHEAR) for the analysis of the following nine OPE metabolites: diphenyl phosphate (DPHP), sum of dibutyl phosphate and di-isobutyl phosphate (DNBP + DIBP), bis(1,3,-dichloro-2-propyl) phosphate (BDCIPP), bis(2-chloroethyl) phosphate (BCEP), bis(butoxethyl) phosphate (BBOEP), bis(1-chloro-2-propyl) phosphate (BCIPP), bis(2-ethylhexyl) phosphate (BEHP), bis(2-methylphenyl) phosphate (BMPP), and dipropyl phosphate (DPRP). Additional information on the analyzed metabolites, their corresponding parent compounds, and common applications are described in Table S1.

The nine OPE metabolites were analyzed following methods similar to those described elsewhere with some modifications.[26] Briefly, urine samples (0.5 mL) were aliquoted into pre-baked glass tubes and spiked with 1 ng of deuterated internal standard (IS) mixtures of OPEs and 1 mL of 10 mM ammonium acetate buffer (pH 5). The samples were passed through solid phase extraction (SPE) cartridges (STRATA-X-AW: 60 mg, 3cc, Phenomenex, Torrance, CA, USA) which were conditioned by successive passage with 2 mL of 5% (v/v) ammonia/methanol, 2 mL of methanol, and 2 mL of water. The samples were loaded with the valves partially opened. The SPE cartridges were then dried under vacuum for 3 min after washing with 1.0 mL of water. Analytes were eluted with 2 times 0.5 mL of 5% (v/v)

ammonia/methanol, concentrated under a gentle stream of nitrogen at 37 °C to near dryness, and reconstituted with 0.1 mL of acetonitrile.

High-performance liquid chromatography (HPLC, ExionLC™ system; SCIEX, Redwood City, CA, USA), coupled with an AB SCIEX QTRAP 5500+ triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA, USA), was used in the identification and quantification of target compounds. Nine OPE diester metabolites and corresponding 9 internal standards were separated by a Kinetex HILIC column (100 mm × 2.1 mm, 2.6 µm particle size; Phenomenex) serially connected to a Betasil C18 guard column (20 mm × 2.1 mm, 5 µm particle size; Thermo Scientific). The analytes were quantified by isotopic dilution method and an 11-point calibration curve (at concentrations ranging from 0.02 to 50 ng/mL) with the regression coefficient   0.998. Matrix spikes (synthetic and urine pool spiked with 1 ng of native standards and 1 ng of internal standards) were analyzed with real samples as quality control (QC) samples. For each batch of samples, replicates of reagent blanks, matrix blanks, and matrix spiked samples were processed. Replicates of HHEAR Urine Quality Control (QC) Pools Standard Reference Materials (SRM3672 and SRM3673, NIST, Gaithersburg, MD, USA) were analyzed with every batch of samples. Trace levels of all OPE diester metabolites were found in procedural blanks. OPE diester metabolite concentrations in samples were subtracted from their respective blank values. Matrix spiked samples had average recoveries of 70.4–133% (CV: ±9–19%). Repeated analysis of HHEAR Urine QC Pools A and B among batches showed coefficients of variation of ±12–31% and ±12–30% respectively. SRM3672 and SRM3673 had coefficients of variation of ±12–40% and ±12–27% respectively. The limit of detection (LOD) of target analytes ranged from 0.012 to 0.0441 ng/mL. Of note, due to the poor chromatographic separation and co-elution of peaks accompanying a similar mass transition for DNBP and DIBP in our mass spectrometer, a sum concentration for the metabolites of dibutyl phosphate and di-isobutyl phosphate (DNBP + DIBP) was analyzed in this study.

OPE metabolites with levels below the LOD were imputed using the LOD/ $\sqrt{2}$.[55] Metabolites were then specific gravity (SG) adjusted using the following standardization formula similarly used in prior OPE literature among other pregnancy cohorts: $Pc=P[(SGm-1)/(SG-1)]$, where Pc is the specific gravity corrected toxicant concentration (ng/mL), P is the observed toxicant concentration (ng/mL), SGm is the median SG value among the subset of participants analyzed in this study (median=1.016), and SG=the SG value of the sample.[56]

2.3. Birth Outcomes

Infant GA at birth was calculated using an accepted hierarchy of the following methods based on available data, in order of preference: (1) first trimester (<14 weeks gestation) ultrasound measurement of crown-rump-length (n=251, 59.6%), (2) second trimester (<28 weeks gestation) ultrasound measurement of fetal biparietal diameter (n=118, 28.0%), (3) physician's best clinical estimate from electronic medical records (n=51, 12.1%), and (4) estimated from last menstrual period (n=1, 0.2%).[57] Many participants had multiple estimates of GA available (79%), with estimates generally highly correlated with one another across methods (Spearman ρ=0.52–0.91), but higher order preference was placed on methods suggested to provide more accurate estimates of GA at birth.[57–59] Infant

birthweight for all participants was directly abstracted from electronic medical records. Sex-specific BW for GA z-scores were calculated for each participant using a nationally representative U.S. sample.[60] Infant sex was primarily abstracted from electronic medical records (n=410, 97.4%), followed by maternal-reported infant sex (n=11, 2.6%) for cases in which abstracted sex could not be obtained.

2.4. Covariates

Potential study covariates for GA at birth and birthweight models were identified *a priori* based on previous literature[28,32,52,53] and visualized using Directed Acyclic Graphs (DAGs) on DAGitty (see Supplemental Figure 1a and 1b).[61] All models were adjusted for all study design and sample collection variables and variables selected in the DAG minimal sufficient adjustment sets, barring some of the exceptions discussed below.

Maternal demographic and pregnancy-related covariates identified in prior literature and considered in DAGs included maternal age at study enrollment (years), income (<$30,000, $30,000, don't know), education (12th Grade, some college or technical school or completed 4 years of college, some graduate training after college), race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, Multiracial non-Hispanic, Other non-Hispanic), pre-pregnancy BMI (kg/m^2), parity (first born,   second born, missing), maternal hypertensive disorders of pregnancy (hypertensive [defined as having one or more of the following: preeclampsia-eclampsia, chronic hypertension, chronic hypertension with pre-eclampsia superimposed, gestational hypertension] or non-hypertensive), and infant sex (female, male). Minimal sufficient adjustment sets identified in DAGs for both GA at birth and birthweight included maternal age, pre-pregnancy BMI, parity, race/ethnicity, smoking during pregnancy, maternal hypertensive disorders of pregnancy, and socioeconomic status (i.e., income, education). Infant sex was additionally adjusted for in all full GA at birth models since it is an important predictor of GA at birth; however, since BW for GA z-scores were sex-specific, BW for GA z-score models did not include infant sex as a covariate. Pre-pregnancy BMI was calculated using participant reported pre-pregnancy weight and standing height measured by study staff in the first study visit using a commercial stadiometer (Perspectives Enterprises model P-AIM-101). Maternal age, income, education, race/ethnicity, and parity were collected via interviewer administered questionnaires in the participant's preferred language (English and/or Spanish). Maternal hypertensive disorders of pregnancy were abstracted from maternal prenatal records from health care providers. Sample collection variables, including season at sample collection (winter [December-February], spring [March-May], summer [June-August], autumn [September-November]) and gestational age at sample collection (in weeks), were collected at the time of urine sample collection. Maternal smoking during pregnancy was also considered as a potential covariate; however, given the low frequency of smoking reported among participants (~1.9%), prenatal smoking was not adjusted for in models. However, sensitivity analyses were performed excluding maternal participants who smoked during pregnancy. Although not identified as a potential covariate *a priori* based on previous literature, other sensitivity analyses included additionally adjusting for gestational diabetes and delivery method to assess the robustness of our results. Gestational diabetes diagnoses and delivery method were abstracted from maternal prenatal records from health care providers.

2.5. Statistical Analysis

Descriptive characteristics were calculated using means and frequencies. OPE metabolite distributions were explored using boxplots, geometric means, medians, percentile distributions, and metabolite detect frequencies. Since OPE metabolite distributions were right skewed, Kruskal Wallis tests were conducted to evaluate univariate associations between categorical covariates (i.e., education, income, race/ethnicity, parity, maternal hypertensive disorders during pregnancy, infant sex, season of sample collection) and OPE concentrations. Spearman correlations were performed to evaluate associations between continuous covariates (maternal age, pre-pregnancy BMI, and gestational age at sample collection) and OPEs as well as correlations between OPE metabolites.

Given that OPE concentrations were right skewed,[18] continuous OPE metabolites were natural log transformed prior to modeling. Unadjusted and adjusted linear regressions were performed to assess the relationship between individual prenatal OPEs and infant gestational age at birth and BW for GA z-scores. OPE metabolites with detect frequencies >60% were analyzed continuously (DPHP, DNBP+DIBP, BDCIPP, BCEP, BBOEP) and those with a detect frequency <60% were analyzed dichotomously as detect versus non-detect (BCIPP, BEHP, BMPP, DPRP), consistent with prior literature.[62–64] Model parameter estimates were back transformed and scaled to a doubling in OPE metabolite exposure. Modeling assumptions for all linear regressions, including linearity, homoscedasticity, and normality, were examined (and met) using scatterplots and histograms of model residuals, and all models assessed for influential outliers. A statistical interaction between each OPE metabolite and infant sex was also tested within independent models, with a p-value<0.05 defined as a statistically significant interaction. Regardless of whether statistical interaction terms were significant, all models were stratified by infant sex, given prior evidence of sex-specific effects of OPE metabolites on birth outcomes. Generalized Additive Models (GAMs) with a smoothing term for exposure variables were also performed to evaluate possible non-linear associations between continuously analyzed OPE metabolites and birth outcomes using the R package "mgcv." All GAM models were also stratified by infant sex.

Bayesian Kernel Machine Regression (BKMR) using the Gaussian predictive process (GPP) set at 100 knots was performed to evaluate the associations between the OPE mixture and infant birth outcomes. Only metabolites with a detect frequency >60% were included in BKMR models (n=5 metabolites; DPHP, DNBP+DIBP, BDCIPP, BCEP, BBOEP). BKMR is an advanced semi-parametric method that utilizes Gaussian kernel machine regression to estimate the effects of a high-dimensional matrix of predictors (e.g., interrelated environmental exposures) on a health outcome of interest.[65] Advantages of BKMR include the ability to estimate flexible exposure-response functions which may include non-linear effects and correlated exposures, thus accounting for potential confounding from co-exposures. Additionally, BKMR can evaluate all possible synergistic and antagonistic relationships between mixtures components without prior specification. In brief, the BKMR model for the current study is represented by the following equation:

$$Y_i = h(DPHP_i, DNBP + DIBP_i, BDCIPP_i, BCEP_i, BBOEP_i) + X_i\beta + \varepsilon_i$$

where Y_i represents our health outcome of interest (i.e., infant birth outcome) for participant i, $h(.)$ denotes the exposure-response function; β represents the vector of coefficients for model covariates (X_i), which are modeled parametrically; and ε represents residuals assumed to be independent, normally distributed, with a common variance. BKMR models for each outcome were stratified by sex to assess possible sex differences in the association between OPE mixtures and infant birth outcomes. Additionally, all OPE metabolites and infant GA at birth were natural log transformed, mean-centered, and standard deviation scaled prior to BKMR modelling. All continuous covariates were mean centered and scaled to one standard deviation.

Individual mixture component associations for GA at birth and BW for GA z-scores were ranked using posterior inclusion probabilities (PIPs) to assess the importance of each mixture component exposure in defining the exposure-outcome association. Exposure-response functions for each OPE holding all other exposures constant at their 50th percentiles were evaluated to assess the associations of individual OPEs, accounting for the rest of the mixture, with infant birth outcomes. The overall effect of simultaneously increasing all exposures in the mixtures was additionally evaluated to assess the relationship between the overall OPE mixture and infant GA at birth and BW for GA z-scores. Since BKMR is a Bayesian approach, common frequentist approaches, such as evaluation of statistical significance and the use of 95% Confidence Intervals, are not applicable. We used 95% credible intervals to determine the uncertainty in each exposure–outcome association; if the 95% credible interval did not span 0, we considered the metabolite or mixture to be associated with the outcome. Possible pairwise interactions between OPE metabolites were also investigated visually for each birth outcome by assessing the association between each OPE metabolite and birth outcome when varying a second OPE metabolite to its 25th, 50th, and 75th percentile (holding all other OPE metabolites at their 50th percentile) with non-parallel lines indicating possible pairwise interactions.

The "bkmr" package in R was used for the BKMR analysis.[66] The Markov Chain Monte Carlo (MCMC) sampler was used to obtain 100,000 posterior samples of model parameters, with the first half of iterations used as burn-in and chains thinned to every 10th iteration to reduce potential autocorrelation. Trace plots were visually inspected to assess model convergence, with all models indicating occurrence of convergence. BKMR models were assumed to have non-informative prior distributions in primary models, the default specified in the R package. However, since BKMR can be sensitive to the choice of model priors, sensitivity analyses were conducted to evaluate whether results from the primary model were robust to alternative prior assumptions. The parameter b, which controls the smoothness of the exposure-outcome relationship, was varied to a lower degree of smoothness (b=50) and to a higher degree of smoothness (b=1000).

Data were managed and linear regression models were analyzed using SAS v9.4 (SAS Institute, Inc., Cary, NC, USA). GAMs and BKMR models were performed using R (v 4.1.0). The significance level for single chemical metabolite models was set at an alpha of 0.05.

3. Results

3.1. Participant Characteristics

Maternal and infant characteristics of the study population are shown in Table 1. Maternal participants were on average 28.9±6.1 years old at study recruitment, had a pre-pregnancy BMI of 28.6±6.7 kg/m^2, and were predominantly Hispanic (77.9%). More than half of participants had at most a high school education (57.0%) and 47.5% of participants had an annual household income of <$30,000. Very few (1.9%) maternal participants smoked during pregnancy; however, 21.1% had one or more hypertensive disorders of pregnancy. Infants were primarily second born or more (62.0%), with 9.3% born preterm (<37 weeks) and 3.8% born with a low birth weight (2,500 grams). Infants were born at an average gestational age of 39.1±1.5 weeks. This subset of the MADRES cohort was similar to the full cohort on key demographic characteristics including income, ethnicity, maternal age, education, infant sex, and recruitment site.

Distributions for all measured OPE metabolites in urine are shown in Table 2. Five metabolites had detection frequencies 60% (DPHP, DNBP+DIBP, BDCIPP, BCEP, BBOEP) and four metabolites had detection frequencies between 23.8% and 53.9% (BCIPP, BEHP, BMPP, DPRP). OPE concentrations ranged from 0.004 ng/mL to 168.00 ng/mL. BDCIPP had the highest median metabolite concentration (1.29 ng/mL) across all OPE metabolites measured in this sample. Figure 1 illustrates Spearman correlations between all measured OPE metabolites in the full sample and stratified by sex. In general, most OPE metabolites were significantly correlated with one another, although correlations were generally weak, with the highest correlations observed between BDCIPP and DPHP in both the full sample (ρ= 0.31, p<0.01) and sex-stratified Spearman correlations (female ρ= 0.35, p<0.01; male ρ= 0.26, p<0.01). Compared to a representative US sample of National Health and Nutrition Examination Survey (NHANES) participants (Table S2), MADRES participants' median BDCIPP concentrations (1.29 ng/mL) and BCEP concentrations (0.53 ng/mL) were higher than NHANES participants' median BDCIPP (0.87 ng/mL) and BCEP concentrations (0.39 ng/mL). However, MADRES participants' median DPHP metabolite concentrations (0.77 ng/mL) and BCIPP concentrations (0.18 ng/mL) were similar to NHANES participants' median DPHP concentrations (0.79 ng/mL) and BCIPP concentrations (0.19 ng/mL).

Univariate associations between OPE metabolite concentrations and covariates are shown in Supplemental Tables 3a, 3b, and 3c. Participants whose 3rd trimester urinary specimens were collected during the summer had higher median concentrations of DPHP (0.88 ng/mL) and BDCIPP (1.99 ng/mL) when compared to samples collected from participants in the winter (median DPHP= 0.63 ng/mL; median BDCIPP=0.99 ng/mL), spring (median DPHP=0.73 ng/mL; median BDCIPP= 0.92 ng/mL), and autumn (median DPHP=0.86 ng/mL; median BDCIPP=1.36 ng/mL) seasons. Additionally, specimens collected during the summer and autumn had higher median concentrations of BCEP (summer=0.62 ng/mL; autumn=0.62 ng/mL) when compared to those collected in the winter (median BCEP=0.36 ng/mL) and spring (median BCEP=0.49 ng/mL) seasons. Participants who were underweight prior to the pregnancy had higher median concentrations of BCEP (0.79 ng/mL) when compared to

normal weight (0.42 ng/mL), overweight (0.70 ng/mL), and obese (0.40 ng/mL) participants. Participants who reported not knowing their annual household income had lower median DPHP levels (0.67 ng/mL) compared to those reporting an annual household income of <\$30,000 (0.85 ng/mL) and \$30,000 (0.85 ng/mL). Maternal participants with any hypertensive disorder of pregnancy had significantly higher median BDCIPP metabolite concentrations (1.49 ng/mL) than those with no hypertensive disorders of pregnancy (1.18 ng/mL). Significant differences were observed between income levels and the detection of BEHP, with higher detect frequencies of BEHP among participants with an annual household income <\$30,000 (31.50%) when compared to those with an income of \$30,000 (22.00%) and those who reported not knowing their income (18.18%). Higher detect frequencies of BMPP were observed in mothers who had male infants (44.66%) compared to female infants (33.02%).

3.2. Individual Metabolite Associations with Birthweight and Gestational Age at Birth

As shown in Tables 3 and 4, no significant associations were observed between maternal OPE metabolites and infant birth outcomes in either unadjusted or covariate-adjusted linear regression models for the full sample. Similarly, there were no significant associations between OPEs and infant birth outcomes when using GAMs, but there was some evidence of non-linear patterns (Figure 2 and Figure 3). In particular, the pattern between DNBP+DIBP and GA at birth and BBOEP and GA at birth and BW for GA had an inverted U-shape.

When we examined sex-specific associations using linear regression models, we found a significant interaction between prenatal BDCIPP concentrations and infant sex on GA at birth (p=0.04). In stratified models, a significant inverse association between BDCIPP and GA at birth was observed among males (β=−0.12; 95% CI: −0.24, −0.01) but not among females (β = −0.00001; 95% CI: −0.09, 0.09). Although the interaction between DNBP+DIBP and sex was not statistically significant (p=0.10), there was a marginally significant inverse association observed between DNBP+DIBP and GA at birth among female infants (β=−0.20; 95% CI: −0.40, 0.00). The associations observed in linear regression models between BDCIPP and GA at birth were consistent to those observed in sex-stratified GAMs (Figure 2), with a significant and linear inverse association between higher BDCIPP concentrations and earlier GA at birth among males (p=0.04). However, there was evidence of a non-linear and inverted U-shape association between DNBP+DIBP and GA at birth among female infants (p= 0.01), with a significantly earlier GA at birth at higher concentrations of DNBP+DIBP (p=0.03). There was also some evidence of non-linear patterns between BBOEP and GA at birth among males (p= 0.03) and DNBP+DIBP and BW for GA z-scores among females (p=0.03) and males (p=0.03), although the associations between each metabolite and infant birth outcome in both models were not statistically significant.

In sensitivity analyses excluding participants who smoked during pregnancy (n=8) and models additionally adjusting for gestational diabetes (n= 37; 8.8%), exposure effect estimates in linear regression models (Table S4–S7) and associations observed using GAMs (Figure S2–S5) were not meaningfully changed for either outcome (GA at birth and BW for GA z-scores). Similarly, models additionally adjusting for delivery method yielded similar

effect estimates to the primary results in both linear regression models (Table S8–S9) and associations when using GAMs (Figure S6–S7).

3.3.   Associations of OPE mixtures with BW for GA z-scores and Gestational Age at Birth

Table 5 shows PIP ranks for both the full sample and sex-stratified mixtures models to quantify the importance of each OPE metabolite in the joint mixture effects on each birth outcome. In the overall sample, DNBP+DIBP had the highest PIP for GA at birth while BBOEP had the highest PIP for BW for GA z-scores. In models stratified by infant sex, among female infants, DNBP+DIBP had the highest PIP for the GA at birth and BW for GA z-score models. Among male infants, BDCIPP had the highest PIP for the GA at birth model and DNBP+DIBP had the highest PIP for the BW for GA z-score model.

Relationships between each metabolite and GA at birth, fixing other metabolites at their median values and adjusting for key covariates, are shown in Figure 4A. We found an inverse linear association between BDCIPP and GA at birth and an inverse, somewhat linear association between DPHP and BBOEP and GA at birth, with a slight increase in GA at birth at moderate concentrations of this metabolite. For DNBP+DIBP and GA at birth, there was an inverted U-shaped association, consistent with the non-linear pattern observed between DNBP+DIBP and GA at birth when using GAMs. However, effect estimates evaluating the difference in GA at birth for a change in the specified metabolite from the 25th to the 75th percentile, holding all other metabolites in the mixture at their median and adjusting for key covariates, had 95% Credible Intervals that spanned 0 (Table S10). The cumulative association between the overall metabolite mixture and GA at birth had a non-monotonic inverted U-shaped association, with lower GA at birth at higher metabolite levels when compared to their median values, and 95% Credible Intervals which did not cross 0 from the 80th to the 95th percentile (Figure 4B).

The relationship between the OPE mixture and GA at birth varied by infant sex (Figure 5 and 6). In models for female infants, the exposure-response function for DPHP appeared to be inverse and linear whereas the exposure-response function for BDCIPP appeared to be positive and linear (Figure 5A). The association between DNBP+DIBP and GA at birth followed an inverted U-shape, with higher GA at birth values observed for moderate DNBP+DIBP concentrations. However, all effect estimates evaluating the difference in GA at birth for a change in the specified metabolite from the 25th to the 75th percentile, holding all other metabolites in the mixture at their median and adjusting for key covariates, had 95% Credible Intervals that spanned 0 (Table S10). At high concentrations, the overall metabolite mixture was associated with a lower GA at birth, with 95% Credible Intervals not crossing 0 when metabolites were set to their 90th and 95th percentile when compared to their median values (Figure 5B).

Similar to results for female infants, the univariate exposure-response association between BCEP and GA at birth was null for male infants (Figure 6A). However, in contrast to findings for female infants, a marginal inverse association was identified between BDCIPP and GA at birth for males, with a change in log BDCIPP from the 25th to the 75th percentile when all other metabolites were set at the median associated with a decrease in GA at birth of −0.11 (−0.26, 0.03) standard deviations (Table S10). A positive association was identified

between DNBP+DIBP and GA at birth at low to moderate concentrations and DPHP and BBOEP had an inverse, non-linear association with GA at birth. However, similar to the full sample and female stratified analysis, all metabolite single effect estimates had 95% Credible Intervals that crossed 0 (Table S10). Compared to the overall model, the male stratified cumulative association between the overall metabolite mixture and GA at birth had a similar non-monotonic inverted U-shape, but all 95% Credible Intervals spanned 0 (Figure 6B).

For both the full and sex-stratified BW for GA z-score models (Figure 4C, 5C, 6C), the univariate exposure-response association between BCEP and BW for GA at birth was null. In models for female infants, DPHP and BW for GA z-scores had a slight non-linear, inverse association which was similar to the linear inverse association observed among all infants but varied from the inverted U-shape association observed for males. In models for all infants, associations between DNBP+DIBP and BW for GA z-scores and BBOEP and BW for GA z-scores had an inverted U-shape, with a more pronounced shape among females but a U-shape association between DNBP+DIBP and BW for GA z-scores among males and a J shaped association between BBOEP and BW for GA z-scores. Among male models, an inverse, non-linear association was identified between BDCIPP and BW for GA z-scores; however, an inverted U-shape association was observed among females. All individual metabolite associations (holding the rest of the metabolites constant at their median values) had single effect estimates with 95% Credible Intervals that spanned the null when the specified metabolite was changed from the 25th to the 75th percentile (Table S11). Similarly, there was no evidence for a cumulative association between the full and sex-stratified metabolite mixtures and BW for GA z-scores (Figure 4D, 5D, 6D).

Pairwise interactions between OPE metabolites and birth outcomes were visually explored and several potential interactions were identified (Figure S8). In the full sample, for the GA at birth model, possible interactions were visually identified between BDCIPP and DNBP+DIBP, such that the inverse association between BDCIPP and GA at birth appeared to be stronger at higher levels of DNBP+DIBP (Figure S8A). Additional possible interactions visually identified between metabolites and GA at birth models included BBOEP and DNBP+DIBP, and DPHP and DNBP+DIBP. No pairwise interactions were visually identified for GA at birth in models for female infants (Figure S8C). In models for male infants, a potential pairwise interaction between BDCIPP and DPHP was visually observed, with the inverse association between BDCIPP and GA at birth being stronger at higher levels of DPHP (Figure S8E). The positive association between DNBP+DIBP and GA at birth also appeared to vary by levels of DPHP, such that the association was slightly attenuated at higher levels of DPHP. In the full sample, the inverse association between BDCIPP and BW for GA z-scores was stronger at lower quantiles of BCEP (Figure S8B). The inverse association between BDCIPP and BW for GA z-scores was stronger at higher quantiles of DNBP+DIBP. In models for female infants, the association between BDCIPP and BW for GA z-score varied by levels of DNBP+DIBP (Figure S8D). In models for male infants, the positive association between BBOEP and BW for GA z-score was stronger at higher levels of DPHP and a stronger inverse association between BCEP and BW for GA z-score was observed higher levels of DPHP (Figure S8F). Additionally, the association

between BBOEP and BW for GA z-scores among males was stronger at higher quantiles of DNBP+DIBP and DPHP but attenuated at higher quantiles of BDCIPP.

Results from sensitivity analyses excluding mothers who reported smoking during pregnancy (N=8), were consistent with the primary analysis, with a slight attenuation in associations (Figure S9–S10). Alternative prior assumptions were also explored at lower (b=50) and higher (b=1000) degrees of smoothness. Results from models assuming a lower degree of smoothness were very similar to primary results and results were inversely linear for models assuming a higher degree of smoothness (Figure S11–S16). These results were consistent with the expected results when relaxing and constricting degrees of smoothness, suggesting our results were robust. Sensitivity analyses additionally adjusting for gestational diabetes (Figure S17–S18) and delivery method (Figure S19–S20) were similarly consistent with the primary analysis, with some stronger associations observed between higher OPE mixtures and earlier GA at birth in males when adjusting for delivery method.

4. Discussion

We found evidence that prenatal OPE exposures adversely impact infant GA at birth in sex specific ways when using both traditional single exposure models and a flexible environmental mixture modeling approach, among a sample of predominately low-income, Hispanic participants. Specifically, we found that higher prenatal BDCIPP concentrations were associated with an earlier GA at birth among males in single exposure models. This metabolite also ranked as the highest predictor for GA at birth among males when using a mixture modeling approach. Among female infants, higher exposures to prenatal DNBP+DIBP concentrations were associated with earlier GA at birth when using flexible single exposure models, and DNBP+DIBP similarly ranked as the most important predictor for GA at birth in mixture models, with a possible non-linear association identified. Additionally, higher cumulative OPE metabolite concentrations were associated with an earlier GA at birth, both in the full sample and among females only. There was no evidence of an association between OPEs and BW for GA. Overall, our results stress the importance of considering sex specific impacts of prenatal OPE exposures on children's health and additionally underline the importance of evaluating the impacts of OPE exposures as a mixture on birth outcomes.

The few epidemiological studies that have evaluated sex specific effects on associations between prenatal OPE exposures and infant birth outcomes have shown conflicting results. A case-control study published by Luo et al. in 2020 among women in Wuhan, China found that third trimester DPHP levels were associated with significantly increased risk of low birthweight which, after stratification by sex, only remained significant among females.[53] However, median DPHP concentrations among the Wuhan Maternal and Child Healthcare Hospital prospective birth cohort (Table S2) were substantially lower across both cases (0.06 ng/mL) and controls (0.05 ng/mL) when compared to DPHP concentrations in the MADRES sample (0.77 ng/mL), suggesting possible differences in exposure distributions which may result from a variety of factors, including varying sources of exposure, potentially contributing to the discrepancies in results. A similar study by Hoffman et al. published in 2018 conducted in the Pregnancy Infection and Nutrition Study (PIN), a pregnancy cohort

of predominately white (79.7%) and college educated (69.6%) women in North Carolina, found that higher prenatal exposure to BDCIPP was associated with increased odds of preterm delivery among female infants.[52] Another study by Crawford et al. published in 2020 on 56 primarily college educated (45.0%) and non-Hispanic white (64.0%) women found that BDCIPP was associated with increased infant length at birth and birthweight in males but DPHP was negatively associated with abdominal circumference at birth in infants overall and female weight.[67] Median BDCIPP concentrations among participants in the Women and Infants Hospital of Rhode Island cohort (1.18 ng/mL) were slightly lower than concentrations in the MADRES cohort (1.29 ng/mL), but were fairly comparable overall; however, these slight differences, along with other demographic and exposure collection differences, may have contributed to the discrepancies in results. A small study published by Kuiper et al. in 2020 among predominately white (53%) and college educated women (60%) enrolled in the Origins of Child Health and Resilience in Development (ORCHARD) pregnancy cohort (n=76) found no significant associations between OPE metabolites collected throughout pregnancy and infant BW for GA z-scores or GA at delivery, although inverse patterns observed between BDCIPP and DPHP and BW for GA z-scores and GA at delivery were similar to our results.[31] Median BDCIPP concentrations among the MADRES study were two-fold higher than concentrations among ORCHARD participants (0.51 ng/mL) but DPHP concentrations were lower among MADRES participants compared to concentrations among ORCHARD participants (1.12 ng/mL). Another study on 340 mother-infant dyads participating in the Health Outcomes and Measures of the Environment (HOME) cohort located in Cincinnati, Ohio found positive associations between 16-week BCEP and 26-week DPHP with gestational age, but inverse associations between BCEP at 16 weeks and birthweight among female newborns and 26 week DNBP and ponderal index at birth among male newborns.[68] Geometric mean concentrations of DPHP (1.82 ng/mL) and BCEP (0.60 ng/mL) among HOME participants were generally higher than geometric mean concentrations observed among MADRES participants but BDCIPP concentrations (0.80 ng/mL) were relatively lower.

Our study found sex-specific adverse impacts of prenatal BDCIPP on male GA at birth and DNBP+DIBP on female GA at birth in individual metabolite models. OPE mixtures analyses similarly indicated the strongest influence of BDCIPP on male GA at birth and DNBP+DIBP on female GA at birth. Our mixtures analysis overall showed that higher exposure to the overall OPE mixture (i.e., higher percentiles of exposures) was associated with adverse impacts on infant GA at birth, with more pronounced associations on female infants. Discrepancies in findings across each of these studies may be driven by multiple factors, including the previously discussed differences in exposure distributions across studies, along with varying geographic characteristics, underpowered samples to detect associations, and varying exposure measurement methods (i.e., number of measurements, GA at collection, and varying years of collection) which may contribute to exposure misclassification. For instance, while OPEs were measured at a single timepoint in pregnancy in our study (~ 31.5 weeks), the PIN study (~27 weeks), and the Wuhan Maternal and Child Healthcare Hospital prospective birth cohort (third trimester), OPEs were measured multiple times throughout pregnancy in the Women and Infants Hospital of Rhode Island cohort (~12, 28, 35 weeks), the HOME study (~16 and 26 weeks), and the

ORCHARD study (~ 15.3, 22.3, 30.9 weeks), with more exposure misclassification likely in studies with a single timepoint. Additionally, variability in the geographical location and the years samples were collected may further contribute to differences in exposure distributions, given increasing OPE use in previous decades and state/country specific regulations which may impact OPE usage.[32]

Although the biological mechanisms that contribute to OPE impacts on birth outcomes are largely unknown, several hypothesized sex-specific mechanisms have been proposed.[18,69] One of the primary underlying mechanisms suggested by growing literature is the sex-specific impacts of OPE disruptions on the endocrine system, particularly thyroid hormones, which play a critical role in fetal development.[14,70,71] Previous epidemiological literature has found positive associations between prenatal DBUP and thyroid stimulating hormone (TSH) in newborns, specifically female infants, with results suggesting partial mediation by oxidative stress on DNA damage and lipid peroxidation.[14] Associations between BDCIPP and lower levels of newborn triiodothyronine and thyroxine have also been observed, with marginal associations between DPHP and DNBP and lower triiodothyronine and thyroxine levels, but no observed sex-specific interactions.[72] However, animal studies in male zebrafish have observed non-monotonic associations between TDCIPP and testosterone, hypothesized to occur via impacts on estrogenic and antiandrogenic activity on zebrafish.[73,74] Observational studies have also observed associations between concentrations of TDCIPP in dust and BDCIPP in urine with altered hormone levels in adult men.[75,76] Additionally, OPE metabolites may also disrupt the hypothalamic pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and hypothalamic pituitary-gonadal (HPG) axes along with nuclear receptors of the endocrine system, including estrogen receptors, androgen receptors, and glucocorticoid receptors, which are involved in important regulatory mechanisms for fetal development and metabolism.[12,77–79] There are biological indications that these effects may be sex specific given the sex differences in infants' estrogen receptor expression and the estrogen-like effects of OPEs acting on various hormone related pathways.[80,81]

The adverse effects of OPEs on placental development is another hypothesized underlying mechanism for the observed sex-specific association between OPEs and birth outcomes.[33] Prior epidemiological studies have found associations between higher OPEs and increased oxidative stress and reduced immunoreactivity of integrin alpha-1 (ITGA1) and vascular endothelial-cadherin (CDH5) in uterine-invading cytotrophoblast (CTB) cells which may result in placental disruptions and pregnancy complications.[33] Although there is limited literature on the sex-specific effects of OPEs on placentation, some studies suggest sex-specific fetal placentation, with varying responses to environmental insults by fetal sex.[82] For example, a study evaluating brominated flame retardants found that placenta samples of male infants had higher concentrations of PBDEs and thyroid levels despite similar maternal serum concentrations across sex.[83] These sex-specific findings were hypothesized to have resulted from sex differences in the chemical uptake of thyroid hormone transporting membrane proteins in placental tissue, impacting maternal supply of thyroid hormones to support fetal growth.[83] Since placental disruptions and pregnancy complications have been associated with adverse birth outcomes, the possible sex-specific impacts of OPEs on placental functioning may contribute to the sex-specific differences in birth outcomes.[82,84]

Given the observed non-monotonic shape between the OPE mixture and infant GA at birth and sex differences in our results, further research evaluating endocrine disruption as a possible underlying mechanism is warranted.

Different OPEs are applied to a variety of consumer products as flame retardants and plasticizers, resulting in concurrent exposures to multiple OPEs.[19] Mixtures modeling approaches, such as BKMR, provide us with the opportunity to evaluate the co-occurring impacts of multiple OPEs on infant birth outcomes. For instance, we observed various possible pairwise interactions, suggesting possible synergistic associations between different OPE metabolites and infant birth outcomes which merit further research. Although we observed similar associations between sex-specific single exposure models and mixtures models, there were some minor differences in our results in models evaluating all infants. For example, even though we saw possible inverse patterns, we did not observe significant associations between the individual effects of OPE metabolites on GA at birth among all infants in single metabolite models while we observed lower GA at birth among all infants with a higher cumulative OPE metabolite exposure in mixtures models. This slight difference between the individual chemical and the mixture approach highlights the value of using mixtures methods to get a comprehensive understanding of the impacts of OPEs on infant health, as most individuals are exposed simultaneously to multiple OPE metabolites which may be correlated and may interact with one another.[27]

The present study has many important strengths. For one, this study was based on a prospective pregnancy cohort with urine specimens collected before the outcomes of interest. Secondly, measures of urinary OPE metabolites were used to assess exposures and are generally considered reliable indicators of OPE exposures.[19] Additionally, the population evaluated in this study is comprised largely of women originating from Latin America, who are historically underrepresented in U.S. biomedical and population health research, therefore advancing opportunities to address environmental health disparities and inform solutions for environmental justice. We also evaluated various OPE metabolites which are understudied, such as DNBP+DIBP, BCEP, and BBOEP, which advances opportunities for risk assessment and subsequent regulations and interventions. An additional strength was the use of a flexible environmental mixture modeling approach to assess the association between mixtures of OPE metabolites and birth outcomes.

This study also has some limitations. For one, only single spot urine samples collected during the third trimester were measured to assess OPE exposures throughout pregnancy which might have led to some exposure misclassification given the relatively short half-life of OPEs.[85–88] However, previous studies indicate moderate to good reproducibility for DPHP and BDCIPP levels throughout pregnancy, although literature on the reproducibility of the remaining metabolites is limited.[28,56] Additionally, despite adjusting for many key covariates identified in the literature, residual confounding could still be present, especially for covariates such as secondhand smoke. We were further underpowered to evaluate clinically relevant cut-offs of our birth outcomes dichotomously, such as preterm birth (37 weeks) and low birthweight (2500 grams) as the number of babies born with these conditions was relatively small. Although a big strength of our cohort's demographic characteristics is the ability to elucidate possible disparities in the impacts of OPEs on

early health outcomes, this may limit the generalizability of our results. The timing of OPE collection (mean GA at collection: 31.5 weeks) was an additional limitation of this study given that it may have resulted in survival bias through the exclusion of some extremely preterm (<28 weeks) and very preterm (28–32 weeks) births, since they would not have reached this sample collection timepoint prior to delivery. However, it is important to note that extremely preterm births and very preterm births are particularly rare among the full MADRES cohort (extremely preterm=0.3%; very preterm= 0.9%), minimizing some of our concerns regarding the potential impacts of survival bias on our results. Additionally, if higher exposures to OPEs truly result in adverse impacts on GA at birth, the timing of OPE collection would have likely biased results towards the null since infants most impacted would have been excluded from the analysis.

5. Conclusions

Our results suggest sex-specific adverse effects of exposure to OPEs on infant GA at birth. Since infant GA at birth is an important predictor of lifelong health, this study highlights the potential for longlasting health implications of toxic environmental exposures during pregnancy and the importance of chemical reduction strategies to support healthy fetal development. Future research aimed at investigating the underlying mechanisms between OPE exposures and GA at birth is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request and after approval by the USC Institutional Review Board.

Abbreviations:

BBOEP	bis(butoxethyl) phosphate
BCEP	bis(2- chloroethyl) phosphate
BCIPP	bis(1-chloro-2-propyl) phosphate
BDCIPP	bis(1,3-dichloro-2-propyl) phosphate
BEHP	bis(2-ethylhexyl) phosphate
BKMR	Bayesian Kernel Machine Regression
BMPP	bis(2-methylphenyl) phosphate
BW	birthweight
CrI	Credible Interval
DPHP	diphenyl phosphate
DPRP	dipropyl phosphate
DNBP+DIBP	sum of dibutyl phosphate and di-isobutyl phosphate
GA	gestational age
HHEAR	Human Health Exposure Analysis Resource
LOD	limit of detection
MADRES	Maternal And Developmental Risks from Environmental and Social Stressors
ND	not detected
OPEs	organophosphate esters
PIPs	posterior inclusion probability
SG	specific gravity

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Highlights

- Early GA at birth was associated with organophosphate esters in sex-specific ways.

- Higher BDCIPP was associated with earlier GA at birth among male infants.

- Higher DNBP+DIBP was associated with earlier GA at birth among female infants.

- Higher organophosphate ester mixtures were associated with earlier GA at birth.

- Individual OPE metabolites and mixtures were not associated with BW-for-GA.
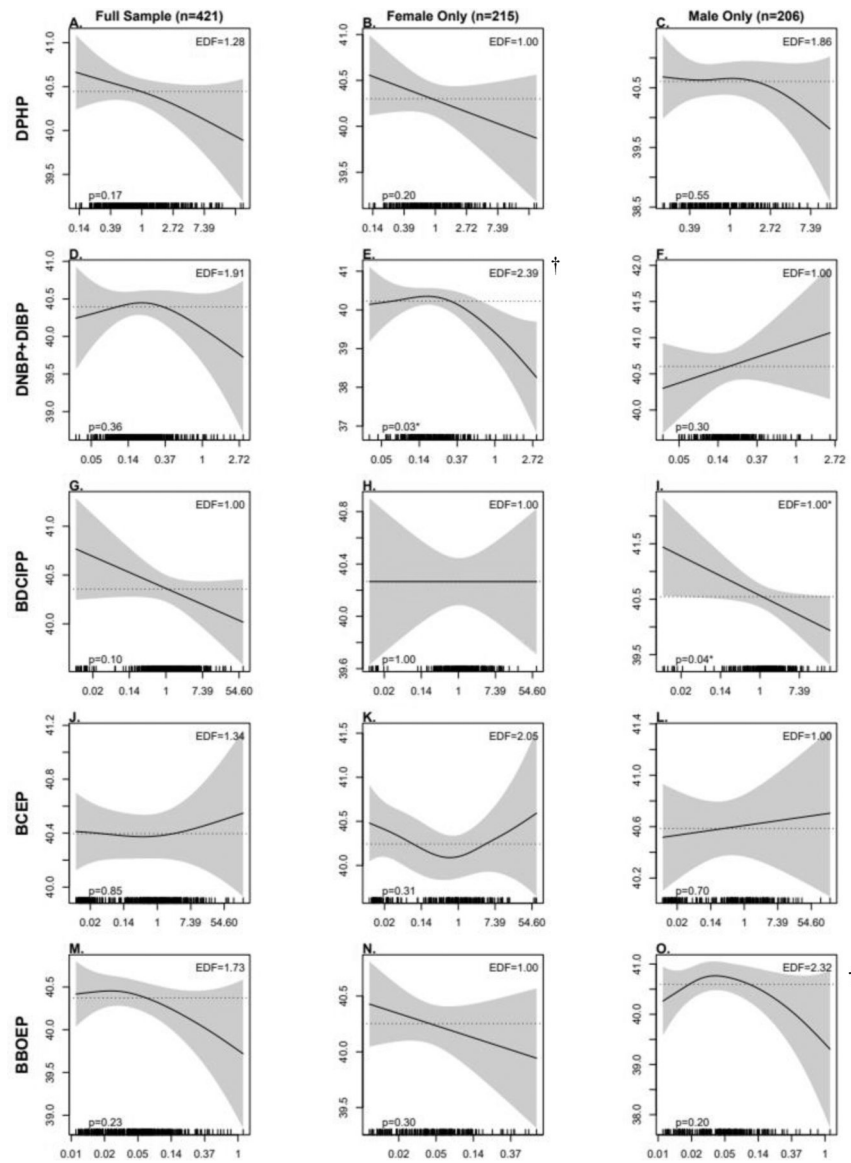
A. **Full Sample (N=421)**

B. **Females Only (N=215)**
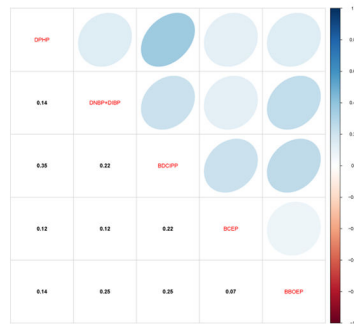
C. Males Only (N=206)

Figure 1:
Spearman Correlations of Organophosphate Ester Metabolites (ng/mL) in Third Trimester
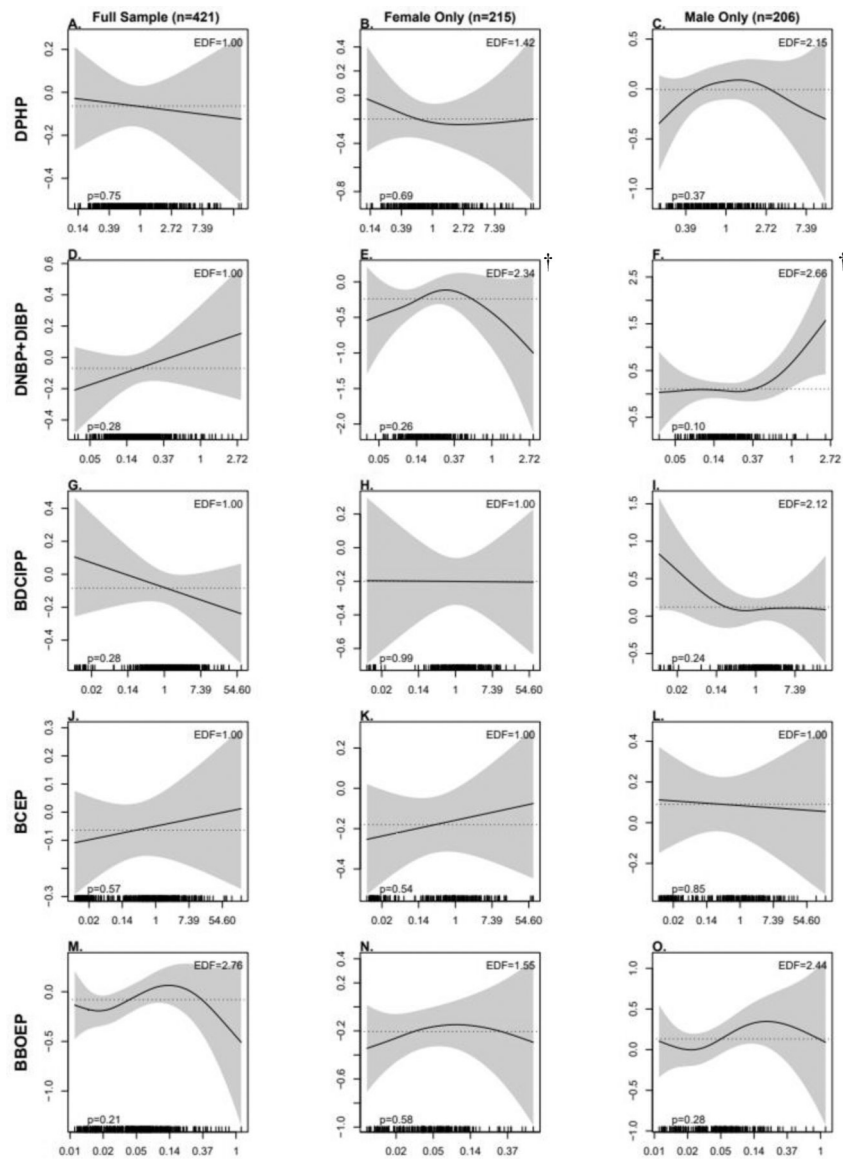Maternal Urine

Figure 2:

Associations Between Prenatal OPE Urinary Metabolite Concentrations (ng/mL) and Gestational Age at Birth, Using Generalized Additive Models (GAMs)

Models adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, infant sex, and maternal hypertensive disorders of pregnancy. Note: OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate. *Significant association between metabolite and GA at birth; † Significant non-linearity.

Figure 3:
Associations Between Prenatal OPE Metabolite Concentrations (ng/mL) and Birthweight for Gestational Age (BW for GA) Z-scores, Using Generalized Additive Models (GAMs)
Models adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, and maternal hypertensive disorders of pregnancy. Note: OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate.
*Significant association between metabolite and GA at birth; †Significant non-linearity.

GA at Birth
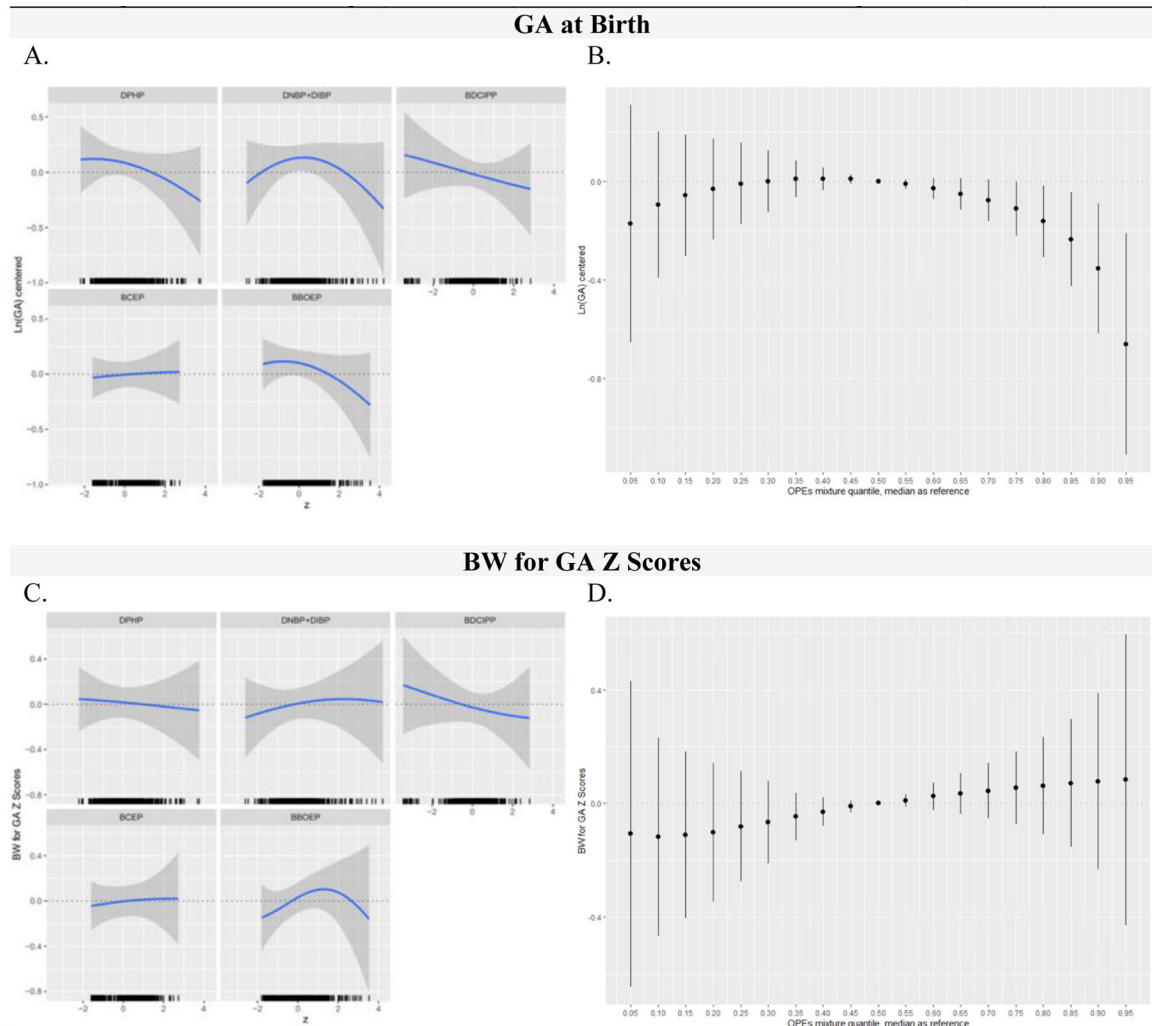
BW for GA Z Scores

Figure 4:
OPE Metabolite Mixtures (ng/mL) and Infant Gestational Age at Birth (weeks) and Birthweight for Gestational Age (BW for GA) Z Scores in Full Models, Using BKMR (N=421)

Figure 4 includes the univariate relationship between each metabolite and birth outcome, while other metabolites are fixed at their medians, and a rug plot showing the distribution of the specified metabolite along the x-axis of each panel (column 1) and the cumulative metabolite mixture results showing the estimated difference in the birth outcome when setting all metabolites to the percentile specified on the x-axis compared with setting all metabolites to their median values (column 2). All GA at birth outcome models were adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, infant sex, and maternal hypertensive disorders of pregnancy. All BW for GA z score outcome models were adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, and maternal hypertensive disorders of pregnancy. OPE metabolites and GA at birth were natural log-transformed, mean centered, and standard

deviation scaled. Continuous covariates were mean-centered and standard deviation scaled.

Note: BKMR, Bayesian Kernel Machine Regression; OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate.

GA at Birth

A.

B.

BW for GA Z Scores

C.

D.

Figure 5:

OPE Metabolite Mixtures (ng/mL) and Infant Gestational Age at Birth (weeks) and Birthweight for Gestational Age (BW for GA) Z Scores in Female Stratified Models, Using BKMR (N=215)

Figure 5 includes the univariate relationship between each metabolite and birth outcome, while other metabolites are fixed at their medians, and a rug plot showing the distribution of the specified metabolite along the x-axis of each panel (column 1) and the cumulative metabolite mixture results showing the estimated difference in the birth outcome when setting all metabolites to the percentile specified on the x-axis compared with setting all metabolites to their median values (column 2). All GA at birth outcome models were adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, infant sex, and maternal hypertensive disorders of pregnancy. All BW for GA z score outcome models were adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, and maternal hypertensive disorders of pregnancy. OPE

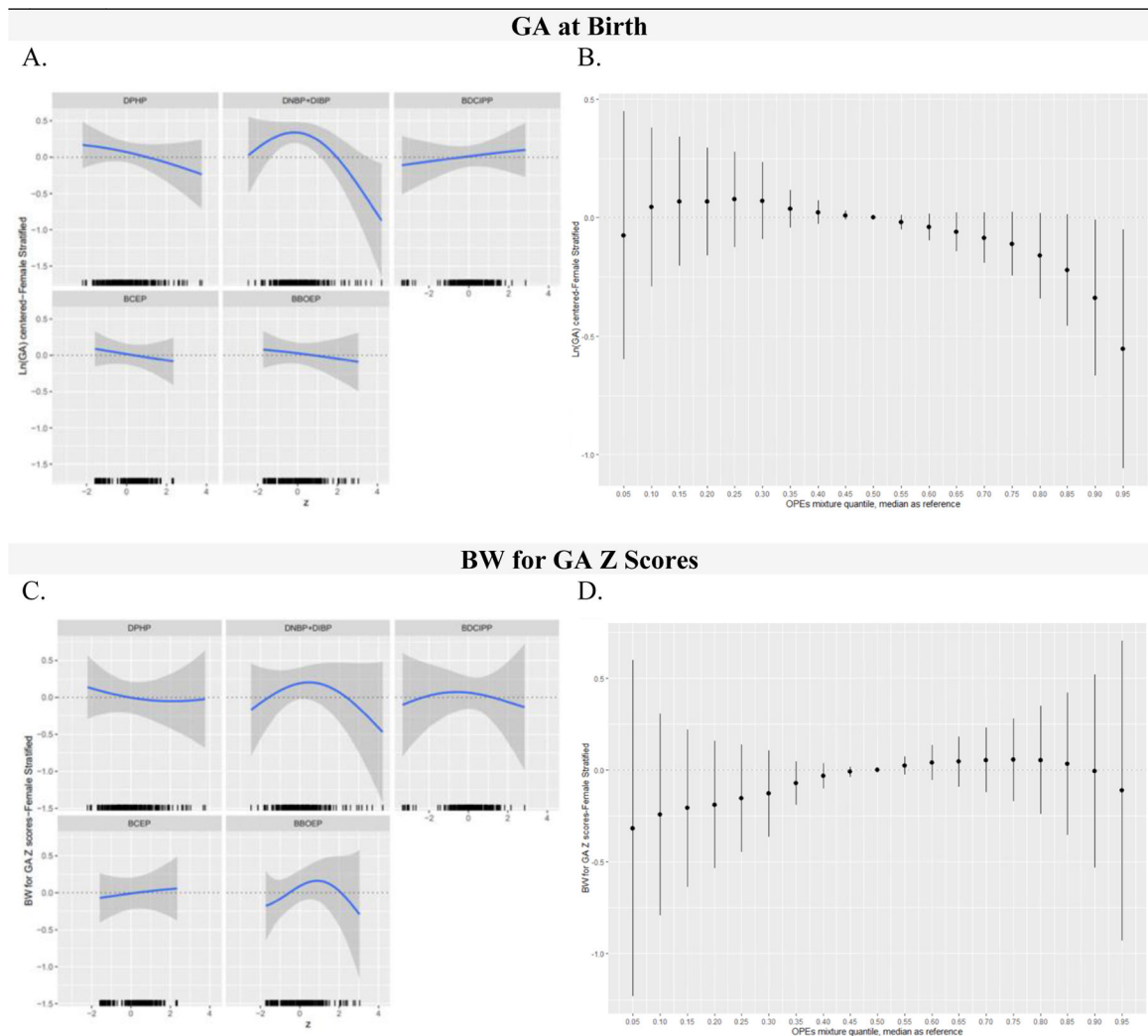metabolites and GA at birth were natural log-transformed, mean centered, and standard deviation scaled. Continuous covariates were mean-centered and standard deviation scaled. Note: BKMR, Bayesian Kernel Machine Regression; OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate.

Figure 6:

OPE Metabolite Mixtures (ng/mL) and Infant Gestational Age at Birth (weeks) and Birthweight for Gestational Age (BW for GA) Z Scores in Male Stratified Models, Using BKMR (N=206)

Figure 6 includes the univariate relationship between each metabolite and birth outcome, while other metabolites are fixed at the median, and a rug plot showing the distribution of the specified metabolite along the x-axis of each panel (column 1) and the cumulative metabolite mixture results showing the estimated difference in the birth outcome when setting all metabolites to the percentile specified on the x-axis compared with setting all metabolites to their median values (column 2). All GA at birth outcome models were adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, infant sex, and maternal hypertensive disorders of pregnancy. All BW for GA z score outcome models were adjusted for recruitment site, maternal age, season of sample collection, gestational age at sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, and maternal hypertensive disorders of pregnancy. OPE metabolites were natural log-transformed, mean centered, and standard deviation scaled. Continuous covariates were mean centered and standard deviation scaled. Note:

BKMR, Bayesian Kernel Machine Regression; OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate.
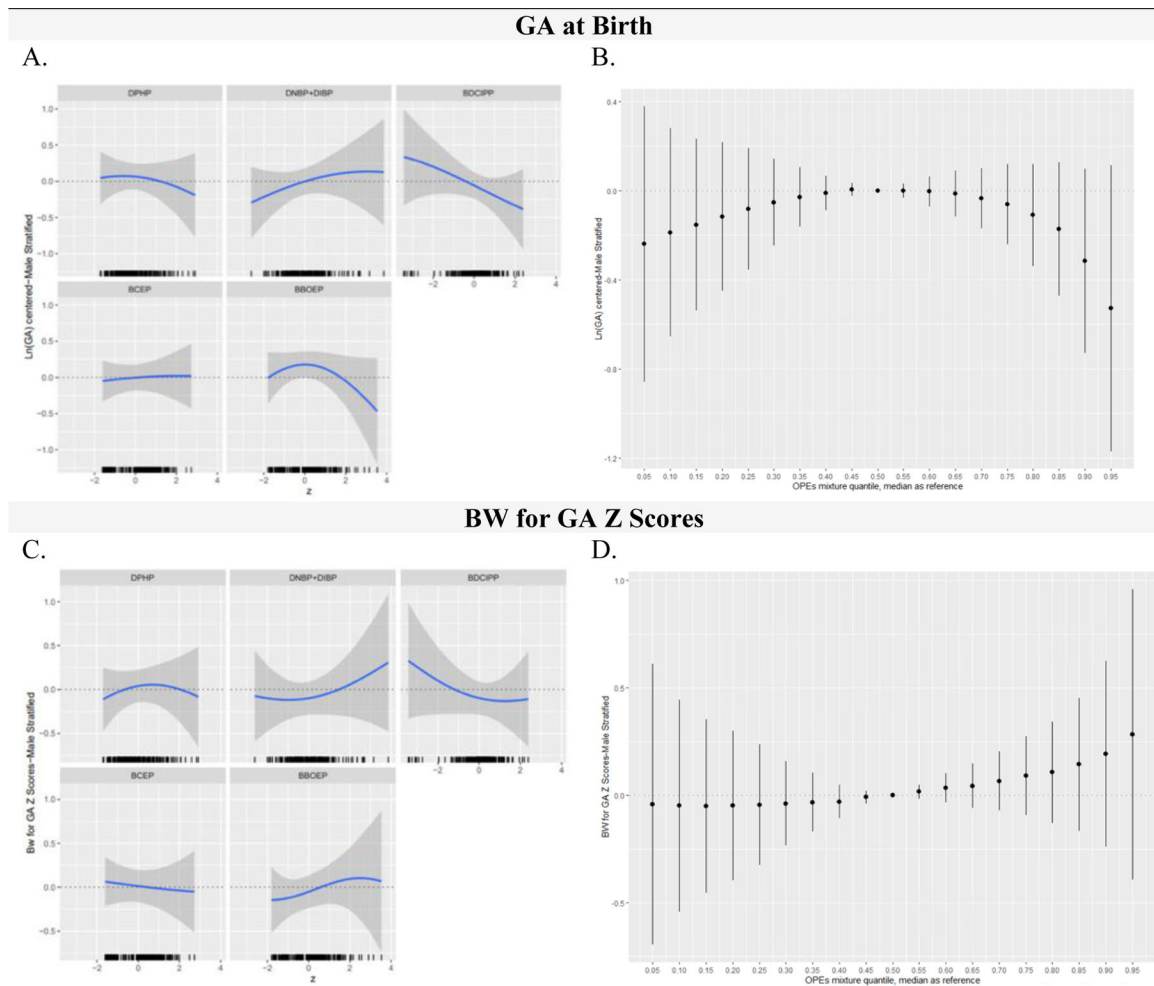
Table 1:

Participant Characteristics (N=421)

	Mean (SD)/Freq(%)
Maternal Characteristics	
Age (years)	28.9 (6.1)
Education	
High School	240 (57.0%)
Some College or College Graduate	152 (36.1%)
Graduate School	29 (6.9%)
Income	
Don't Know	121 (28.7%)
Less than $30,000	200 (47.5%)
$30,000 or more	100 (23.8%)
Race and Ethnicity	
White, non-Hispanic	29 (6.9%)
Black, non-Hispanic	49 (11.6%)
Hispanic	328 (77.9%)
Multiracial, non-Hispanic	5 (1.2%)
Other, non-Hispanic	10 (2.4%)
Personal Smoking During Pregnancy	
No	413 (98.1%)
Yes	8 (1.9%)
Hypertensive	
Non-Hypertensive	332 (78.9%)
Hypertensive	89 (21.1%)
Pre-eclampsia	39 (9.3%)
Chronic Hypertension	10 (2.4%)
Chronic Hypertension and Pre-eclampsia	12 (2.9%)
Gestational Hypertension	28 (6.7%)
Pre-Pregnancy BMI (kg/m^2)	28.6 (6.7)
Infant Characteristics	Mean (SD)/Freq(%)
Sex	
Female	215 (51.1%)
Male	206 (48.9%)
Birth Order	
First Born	146 (34.7%)
Second or more	261 (62.0%)
Missing	14 (3.3%)
Gestational Age at Birth (weeks)	39.1 (1.5)
Birthweight (grams)	3302.9 (475.4)
BW for GA z-score	−0.1 (1.0)
Preterm Birth (<37 weeks)	

	Mean (SD)/Freq(%)
Yes	39 (9.3%)
No	382 (90.7%)
Low Birthweight (<2500 grams)	
Yes	16 (3.8%)
No	405 (96.2%)

Table 2:

Distribution of Specific Gravity Adjusted OPE Concentrations (ng/mL) in Maternal Urine (N=421)[a]

	Percentiles				Distributions		
Metabolite	25th	50th	75th	Min-Max	Geometric Mean	Detect Frequency	LOD (ng/mL)
DPHP	0.47	0.77	1.46	0.12–25.59	0.88	99.76%	0.0281
DNBP+DIBP	0.12	0.17	0.26	ND-3.01	0.19	97.62%	0.0441
BDCIPP	0.61	1.29	2.29	ND-68.00	1.08	94.77%	0.0174
BCEP	0.03	0.53	1.62	ND-168.00	0.31	68.41%	0.0200
BBOEP	0.02	0.04	0.07	ND-1.17	0.04	64.85%	0.0199
BCIPP	ND	0.18	0.77	ND-40.56	0.13	53.92%	0.0204
BMPP	ND	0.01	0.04	ND-0.69	0.02	38.72%	0.0115
BEHP	ND	ND	0.04	ND-4.42	0.03	25.42%	0.0170
DPRP	ND	ND	0.05	ND-2.85	0.03	23.75%	0.0278

[a]Metabolite concentrations below the LOD have been imputed (LOD/ 2) and specific gravity adjusted.

Note: OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Diisobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate; BCIPP, Bis(1-chloro-2-propyl) phosphate; BMPP, Bis(2-methylphenyl) phosphate; BEHP, Bis(2-ethylhexyl) phosphate; DPRP, Dipropyl phosphate; LOD, Limit of Detection; ND, Not Detected.

Table 3:

Associations Between Individual OPE Urinary Metabolites (ng/mL) and Gestational Age at Birth (weeks)

	Full Unadjusted Models β (95% CI) (N=421)	Full Adjusted Models[a] β (95% CI) (N=421)	Metabolite and Infant Sex Interaction P-value (N=421)	Female Only Adjusted Models[b] β (95% CI) (N=215)	Male Only Adjusted Models[b] β (95% CI) (N=206)
DPHP[†]	−0.09 (−0.20, 0.02)	−0.09 (−0.20, 0.02)	0.97	−0.09 (−0.23, 0.05)	−0.07 (−0.26, 0.12)
DNBP+DIBP[†]	−0.04 (−0.19, 0.10)	−0.05 (−0.19, 0.10)	0.10	−0.20 (−0.40, 0.00)	0.12 (−0.11, 0.36)
BDCIPP[†]	−0.06 (−0.13, 0.01)	−0.06 (−0.13, 0.01)	0.04*	−0.00 (−0.09, 0.09)	−0.12 (−0.24, −0.01)*
BCEP[†]	−0.00 (−0.04, 0.04)	0.00 (−0.04, 0.04)	0.32	−0.02 (−0.08, 0.03)	0.01 (−0.05, 0.08)
BBOEP[†]	−0.07 (−0.18, 0.03)	−0.07 (−0.17, 0.03)	0.87	−0.08 (−0.22, 0.07)	−0.04 (−0.20, 0.12)
BCIPP			0.32		
Non-detect	REF	REF		REF	REF
Detect	0.18 (−0.11, 0.46)	0.14 (−0.14, 0.41)		−0.01 (−0.38, 0.36)	0.25 (−0.18, 0.68)
BMPP			0.85		
Non-detect	REF	REF		REF	REF
Detect	−0.17 (−0.46, 0.12)	−0.12 (−0.41, 0.16)		−0.11 (−0.50, 0.27)	−0.09 (−0.53, 0.35)
BEHP			0.78		
Non-detect	REF	REF		REF	REF
Detect	−0.04 (−0.36, 0.29)	0.04 (−0.28, 0.36)		0.06 (−0.38, 0.50)	0.02 (−0.47, 0.52)
DPRP			0.40		
Non-detect	REF	REF		REF	REF
Detect	−0.00 (−0.34, 0.33)	−0.00 (−0.33, 0.32)		−0.13 (−0.57, 0.31)	0.22 (−0.30, 0.73)

[a] Model adjusted for recruitment site, maternal age, season of sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, infant sex, maternal hypertensive disorders during pregnancy

[b] Model adjusted for recruitment site, maternal age, season of sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, maternal hypertensive disorders of pregnancy

[†] Beta estimate back transformed to a doubling in exposure.

Note: OPE, Organophosphate Ester; CI, Confidence Interval; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate; BCIPP, Bis(1-chloro-2-propyl) phosphate; BMPP, Bis(2-methylphenyl) phosphate; BEHP, Bis(2-ethylhexyl) phosphate; DPRP, Dipropyl phosphate.

Table 4:

Associations Between Individual OPE Urinary Metabolites (ng/mL) and Birthweight for Gestational Age (BW for GA) Z-scores

	Full Unadjusted Models β (95% CI) (N=421)	Full Adjusted Models[a] β (95% CI) (N=421)	Metabolite and Infant Sex Interaction P-value (N=421)	Female Only Adjusted Models[a] β (95% CI) (N=215)	Male Only Adjusted Models[a] β (95% CI) (N=206)
DPHP[†]	0.01 (−0.07, 0.08)	−0.01 (−0.09, 0.06)	0.40	−0.03 (−0.13, 0.08)	0.03 (−0.09, 0.15)
DNBP+DIBP[†]	0.04 (−0.06, 0.15)	0.06 (−0.05, 0.16)	0.62	0.01 (−0.15, 0.17)	0.10 (−0.04, 0.25)
BDCIPP[†]	−0.03 (−0.08, 0.02)	−0.03 (−0.07, 0.02)	0.48	−0.00 (−0.07, 0.07)	−0.05 (−0.12, 0.03)
BCEP[†]	0.00 (−0.03, 0.03)	0.01 (−0.02, 0.04)	0.79	0.01 (−0.03, 0.06)	−0.00 (−0.05, 0.04)
BBOEP[†]	0.06 (−0.02, 0.13)	0.04 (−0.03, 0.11)	0.69	0.03 (−0.08, 0.14)	0.07 (−0.03, 0.17)
BCIPP			0.28		
Non-detect	REF	REF		REF	REF
Detect	0.00 (−0.19, 0.20)	−0.02 (−0.22, 0.17)		0.11 (−0.17, 0.40)	−0.15 (−0.42, 0.12)
BMPP			0.19		
Non-detect	REF	REF		REF	REF
Detect	0.10 (−0.10, 0.30)	0.06 (−0.13, 0.26)		0.22 (−0.07, 0.52)	−0.05 (−0.33, 0.22)
BEHP			0.30		
Non-detect	REF	REF		REF	REF
Detect	−0.06 (−0.29, 0.16)	−0.09 (−0.32, 0.13)		−0.24 (−0.58, 0.10)	0.02 (−0.29, 0.33)
DPRP			0.65		
Non-detect	REF	REF		REF	REF
Detect	0.11 (−0.12, 0.34)	0.10 (−0.13, 0.32)		0.04 (−0.30, 0.38)	0.16 (−0.17, 0.48)

[a] Model adjusted for recruitment site, maternal age, season of sample collection, race/ethnicity, pre-pregnancy BMI, income, education, infant birth order, maternal hypertensive disorders of pregnancy.

[†] Beta estimate back transformed to a doubling in exposure

Note: OPE, Organophosphate Ester; DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2-chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate; BCIPP, Bis(1-chloro-2-propyl) phosphate; BMPP, Bis(2-methylphenyl) phosphate; BEHP, Bis(2-ethylhexyl) phosphate; DPRP, Dipropyl phosphate.

Table 5:

Posterior Inclusion Probabilities (PIPs) for OPE Urinary Metabolites and Gestational Age at Birth and Birthweight for Gestational Age (BW for GA) Z-scores Across Full and Sex-Stratified BKMR Mixture Models

	Full Model (N=421)		Sex-Stratified Models			
	GA at Birth	BW for GA Z Score	GA at Birth		BW for GA Z Score	
			Female (N=215)	Male (N=206)	Female (N=215)	Male (N=206)
DPHP	0.37	0.26	0.23	0.37	0.26	0.37
DNBP+DIBP	**0.41** [a]	0.32	**0.82** [a]	0.39	**0.33** [a]	**0.42** [a]
BDCIPP	0.33	0.34	0.14	**0.54** [a]	0.25	0.41
BCEP	0.16	0.28	0.20	0.26	0.26	0.25
BBOEP	0.38	**0.40** [a]	0.20	0.46	0.29	0.41

[a] Highest value.

Note: OPE, Organophosphate Ester; Bayesian Kernel Machine Regression (BKMR); DPHP, Diphenyl phosphate; DNBP+DIBP, Sum of Dibutyl phosphate and Di-isobutyl phosphate; BDCIPP, Bis(1,3-dichloro-2-propyl) phosphate; BCEP, Bis(2- chloroethyl) phosphate; BBOEP, Bis(butoxethyl) phosphate.