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Associations of Organophosphate Ester Flame Retardant Exposures during Pregnancy with Gestational Duration and Fetal Growth: The Environmental influences on Child Health Outcomes (ECHO) Program

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Background: Widespread exposure to organophosphate ester (OPE) flame retardants with potential reproductive toxicity raises concern regarding the impacts of gestational exposure on birth outcomes. Previous studies of prenatal OPE exposure and birth outcomes had limited sample sizes, with inconclusive results.

Objectives: We conducted a collaborative analysis of associations between gestational OPE exposures and adverse birth outcomes and tested whether associations were modified by sex.

Methods: We included 6,646 pregnant participants from 16 cohorts in the Environmental influences on Child Health Outcomes (ECHO) Program. Nine OPE biomarkers were quantified in maternal urine samples collected primarily during the second and third trimester and modeled as $\log_2$-transformed continuous, categorized (high/low/nondetect), or dichotomous (detect/nondetect) variables depending on detection frequency. We used covariate-adjusted linear, logistic, and multinomial regression with generalized estimating equations, accounting for cohort-level clustering, to estimate associations of OPE biomarkers with gestational length and birth weight outcomes. Secondarily, we assessed effect modification by sex.

Results: Three OPE biomarkers [diphenyl phosphate (DPHP), a composite of dibutyl phosphate and di-isobutyl phosphate (DBUP/DIBP), and bis (1,3-dichloro-2-propyl) phosphate] were detected in >85% of participants. In adjusted models, DBUP/DIBP [odds ratio (OR) per doubling = 1.07; 95% confidence interval (CI): 1.02, 1.12] and bis(butoxyethyl) phosphate (OR for high vs. nondetect = 1.25; 95% CI: 1.06, 1.46), but not other OPE

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biomarkers, were associated with higher odds of preterm birth. We observed effect modification by sex for associations of DPHP and high bis(2-chloroethyl) phosphate with completed gestational weeks and odds of preterm birth, with adverse associations among females. In addition, newborns of mothers with detectable bis(1-chloro-2-propyl) phosphate, bis(2-methylphenyl) phosphate, and dipropyl phosphate had higher birth weight-for-gestational-age z-scores (β for detect vs. nondetect = 0.04–0.07); other chemicals showed null associations.

Discussion: In the largest study to date, we find gestational exposures to several OPEs are associated with earlier timing of birth, especially among female neonates, or with greater fetal growth. https://doi.org/10.1289/EHP13182

Introduction

Organophosphate esters (OPEs) have been increasingly used as flame retardants over the last decade as polybrominated diphenyl ether (PBDE) flame retardants were phased out in the mid-2000s over concerns regarding toxicity.[1] OPEs are widely applied as flame retardants and plasticizers in polyurethane foams used in furniture, baby products, electronics, textiles, and building materials.[2–4] Because they are not chemically bound to the polymers, they slowly volatilize into indoor air and then partition into dust.[2,5–7] Individuals are exposed to OPEs through ingestion of indoor dust, inhalation, dermal exposure, and dietary intake.[3,4] OPE metabolites have been frequently detected in urine samples from the US general population.[5,8] OPEs and their metabolites are expected to be less persistent in the human body, compared with PBDEs,[1] with half-lives being on the order of hours to days as estimated from animal[9–11] and human models.[12,13] The detection of OPEs and their metabolites in pregnant people,[14–16] as well as the cord blood,[17] placenta,[18] decidua and chorionic villi,[19] and amniotic fluid,[20] indicates maternal–fetal transfer of OPEs during pregnancy.

A growing body of literature indicates that gestational exposure to environmental chemicals contributes to adverse birth outcomes.[21–24] Laboratory studies suggest that OPEs have developmental and reproductive toxicity in animals.[25–33] For example, parental exposure of zebrafish to environmentally relevant concentrations of tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and tris(2-butoxyethyl) phosphate (TBOEP) adversely affected growth and survival of the offspring,[27–29] and prenatal exposure of rats to TDCPP increased the number of noticeably smaller pups and lowered body weight in the offspring.[30] In human studies, OPE levels measured prior to or during pregnancy have been associated with adverse reproductive outcomes, such as decreased fertilization, implantation, and live birth,[34,35] along with pregnancy loss[36] and spontaneous abortion.[37] Certain OPEs were also shown to interfere with thyroid function in toxicological models[38–41] and epidemiological studies.[42–46] They have also been linked to changes in peroxisome proliferator-activated receptor (PPAR) activity in *in vitro* models[47–49] and oxidative stress in animal[50,51] and human studies.[52,53] These biologic targets serve critical roles in multiple pathways involved in fetal growth,[54–57] metabolism,[58,59] and adipose tissue development.[60]

Adverse birth outcomes, including preterm birth and low birth weight (LBW), are risk factors for neonatal mortality and chronic morbidity, increasing risks of neurodevelopmental disabilities and respiratory and gastrointestinal complications.[57,61–63] There is growing recognition of the potential adverse health outcomes with early-term birth, and those born early term experience an increased risk for infant morbidity and mortality,[64] as well as for adverse cognitive and educational outcomes.[65,66] Despite the potential developmental toxicity of OPEs, epidemiological evidence examining associations between maternal prenatal urinary OPE metabolites and birth outcomes, such as gestational age or birth size, is inconclusive.[67–74] For example, previous studies reported adverse associations of bis(1,3-dichloro-2-propyl) phosphate (BDCPP), a composite of dibutyl phosphate and di-isobutyl phosphate (DBUP/DIBP), and isopropyl-phenyl phenyl phosphate (ip-PPP) with shorter gestational duration among females[67,74] and of BDCPP with shorter gestational age among males.[74] Other studies reported associations of diphenyl phosphate (DPHP) with greater risk of LBW[69] and of BDCPP and bis(butoxyethyl) phosphate (BBOEP) with lower birth weight and length.[70]

On the other side of the spectrum, high birth weight is associated with childhood obesity.[75–77] OPEs have been characterized as metabolism-disrupting compounds[78] and, thus, play a role in the development of obesity.[79] Childhood obesity is associated with a number of adverse health impacts, including diabetes and cardiovascular disease,[80] and is a growing concern worldwide.[81] One study observed a greater ponderal index, a measure of birth weight relative to birth length, associated with prenatal measurements of BDCPP.[68] In contrast, another study found a reduced risk of large-for-gestational-age (LGA) infants in relation to DPHP.[71] Finally, two studies found no strong associations with either gestational age or birth weight.[72,73] The inconsistent results, as well as the small to moderate sample sizes of previous studies, motivated further investigation of these associations in a larger population.

The Environmental influences on Child Health Outcomes (ECHO) Program, funded by the National Institutes of Health (NIH), combines 69 cohorts across the US to understand the impact of environmental exposures on children's health.[82,83] The present analysis leverages a large, diverse sample from 16 ECHO cohorts to quantify nine OPE biomarkers in urine samples of pregnant participants. We examined associations of urinary OPE biomarker concentrations with birth outcomes related to gestational age at birth (completed gestational weeks; preterm, early-term, late/postterm birth) and birth weight [birth weight-for-gestational-age (BW-GA) z-score, term LBW, small-for-gestational-age (SGA), and LGA]. As a secondary aim, we explored whether associations were modified by child's sex.

Methods

Study Population

In 2016, the NIH established the ECHO Program, an innovative and collaborative research initiative. The overarching scientific goal of ECHO is to advance understanding of the effects of a broad array of early environmental exposures on children's development and health outcomes with high public health impact. To achieve this goal, the ECHO Program brought together new and existing cohorts, leveraging previously collected biologic samples and other information on various environmental exposures (e.g., physical, chemical, social, behavioral). From 2017 to 2019, cohorts enrolled participants into the ECHO Program, but continued to collect data and samples under their own protocols. In late 2019, the ECHO Program initiated a common protocol that cohorts followed.

We invited all ECHO cohorts that had collected biologic samples prior to the initiation of the common protocol to participate in the present study. Sixteen ECHO cohorts that had prenatal maternal urine samples available for OPE quantification and participant-level data decided to participate in the present study. Each of these cohorts then selected participants according to their own criteria (Table S1). Data collected and submitted to ECHO prior to March 2022 were used for data analysis. Information about the participating cohorts, including their geographic locations, is provided in Table S1 and Figure S1, respectively. To maximize the sample size within budget constraints, we used a

single spot or first morning urine sample per participant, primarily collected during the second and third trimesters of pregnancy. In total, urinary OPE and dilution data (described below) were available for 7,048 of 12,873 total pregnant participants enrolled in ECHO from these cohorts. We excluded pregnancies with no available child information ($n = 82$), multiple births ($n = 10$), or missing birth outcome data (gestational age, birth weight, or biological sex at birth; $n = 309$). We excluded one child with a gestational age of >42 completed weeks because the Aris et al. method for calculating birth weight z-scores cannot be used for gestations of >42 completed weeks.[84] Therefore, our final analytic sample size was 6,646 mother–child dyads. A flowchart depicting inclusion/exclusion criteria is shown in Figure S2.

Institutional review boards (i.e., the ECHO single IRB or the ECHO cohorts' local IRBs) reviewed informed consent/assent forms, Health Insurance Portability and Accountability Act (HIPAA) authorization forms, recruitment materials, and other relevant information. Each ECHO cohort obtained written informed consent or the permission of the parent/guardian. The work of the ECHO Data Analysis Center (DAC) was approved through the Johns Hopkins Bloomberg School of Public Health IRB.

OPE Biomarker Analysis

Urine samples collected from each cohort were shipped on dry ice to the Human Health Exposure Analysis Resource (HHEAR) laboratory at the New York University Grossman School of Medicine. The laboratory methods were described in a previously published study that used data from one of the included cohorts[74] and are briefly summarized here. After solid-phase extraction, the identification and quantification of target compounds in urine samples were performed using high-performance liquid chromatography (HPLC; ExionLC system; SCIEX), coupled with an AB SCIEX QTRAP 5500+triple quadrupole mass spectrometer (Applied Biosystems). A Kinetex hydrophilic interaction liquid chromatography (HILIC) column (100 mm × 2.1 mm, 2.6 µm particle size; Phenomenex) coupled with a Betasil C18 guard column (20 mm × 2.1 mm, 5 µm particle size; Thermo Scientific) was used for the separation of nine OPE biomarkers and nine internal standards (ISs).

Quality control (QC) samples included synthetic and urine pool samples spiked with 1 ng of native standard (NS) and 1 ng of IS, which were analyzed with study samples. HHEAR Urine QC Pools A & B, as well as Standard Reference Materials (SRM3672 and SRM3673; National Institute of Standards and Technology), were analyzed with every sample batch. Reagent blanks demonstrated trace levels of all OPE biomarkers, thus OPE biomarker concentrations in the study samples were subtracted from the corresponding reagent blank values. Matrix-spiked samples showed average recoveries of 70.4%–133%, with coefficients of variation (CVs) of ±9%–19%. CVs for HHEAR Urine QC Pools A & B were ±12%–31% and ±12%–30%, respectively. For SRM3672 and SRM3673, CVs were ±12%–40% and ±12%–27%, respectively. Masked duplicate samples were also analyzed with the study samples. Among 191 masked duplicates provided by seven cohorts, those in which both were quantified at or above the limit of detection (≥LOD) were used to calculate relative percentage differences.[85]

The nine OPE biomarkers analyzed include *a*) BBOEP, a metabolite of TBOEP; *b*) bis(2-chloroethyl) phosphate (BCETP), a metabolite of tris(2-chloroethyl) phosphate (TCETP); *c*) bis(1-chloro-2-propyl) phosphate (BCPP), a metabolite of tris(1-chloro-2-propyl) phosphate (TCPP); *d*) BDCPP, a metabolite of TDCPP; *e*) bis(2-ethylhexyl) phosphate (BEHP), a metabolite of tris(2-ethylhexyl) phosphate (TEHP); *f*) bis(2-methylphenyl) phosphate (BMPP), a metabolite of tris(2-methylphenyl) phosphate (TMPP); *g*) DBUP/DIBP, metabolites of tributyl phosphate (TBUP) and its isomer tri-isobutyl phosphate (TIBP); *h*) DPHP, a major metabolite of triphenyl phosphate (TPHP); and *i*) dipropyl phosphate (DPRP), a metabolite of tripropyl phosphate (TPRP) (Table S2). DBUP/DIBP are reported as a composite because they coeluted and could not be quantified individually; therefore, they were quantified as a composite sum of both analytes. The LOD of target analytes ranged from 0.01 to 0.04 ng/mL.

Birth Outcomes

ECHO cohorts ascertained birth outcomes for those children born prior to 2019 via their own protocol, with most cohorts relying on maternal or child medical record abstraction (e.g., ultrasound or last menstrual period to estimate the due date), and others using parent report or cohort-obtained data, such as staff-reported information collected at a hospital birth visit. For children born in or after 2019, the ECHO protocol specified the data source, obtained through medical record abstraction. The primary method for obtaining birth outcomes for each cohort is listed in Table S1. We assessed gestational age at birth as a continuous outcome (completed gestational weeks) and categorized as preterm (<37 wk), early term (37–38 wk), full term (39–40 wk), and late/post-term (41–42 wk). We calculated sex-specific BW-GA z-scores based on the equations of Aris et al. and examined the continuous z-scores.[84] We also categorized birth weight for gestational age as binary variables corresponding to SGA and LGA (<10th percentile and >90th percentile, respectively)[84] and assessed term LBW (birth weight <2,500 g among births at ≥37 wk gestation).

Covariates

We used Dagitty[86] to construct a directed acyclic graph (DAG) identifying confounders, mediators, and precision variables (Figure S3). Covariate information was collected by each ECHO cohort and harmonized by the ECHO DAC. We included as potential covariates maternal race/ethnicity (as a proxy for structural inequality and racism; non-Hispanic white, non-Hispanic black, Hispanic, others), maternal age at delivery (in years), maternal education (less than high school, high school degree/general educational development, some college/associated degree/trade school, bachelor's degree, masters/professional/doctorate degree), maternal marital status (married/living with a partner, widowed/separated/divorced, single/never married/partnered/not living together), maternal prepregnancy body mass index (BMI; in kilograms per meter squared), maternal smoking during pregnancy (yes, no), parity (0, 1, ≥2), and child's sex assigned at birth (male, female). We also included information related to timing of urine specimen collection including time of day, trimester, season, and year.

Statistical Analysis

We presented descriptive statistics of covariates and birth outcomes among participants included in our study sample and among participants from the 16 participating ECHO cohorts who were not included in our sample. Urinary dilution was measured as either specific gravity or creatinine in each cohort; therefore, we applied the approach described by Kuiper et al. to account for the influence of urinary dilution on biomarker concentrations.[87,88] Briefly, we multiplied OPE concentrations by the ratio of the cohort-specific median dilution value to the participant's dilution value[87,88] for specific gravity, the values were first subtracted from one.[89] We calculated Spearman correlation coefficients among dilution-standardized OPE biomarker concentrations and examined descriptive statistics to determine percentiles and the proportion of participants with concentrations ≥LOD.

For regression analyses, we modeled OPE biomarkers detected in >80% of participants (DBUP/DIBP, DPHP, BDCPP) as dilution-standardized continuous $\log_2$-transformed variables based on model fit statistics (compared with untransformed concentrations) and exposure distributions.[90] For OPE biomarker concentrations <LOD, we used machine-read values provided by the laboratory and replaced negative or zero values with 0.001 to facilitate $\log_2$ transformation. Instrument-derived values were negative for some biomarkers, as the background signal for those chemicals was subtracted from those of procedural blanks. We modeled OPE biomarkers detected in 50%–80% of participants (BCPP, BCETP, BBOEP) as three-level categorical variables, with the nondetect category defined as participants with values <LOD and the remaining two categories created by dichotomizing participants at the median of dilution-adjusted values ≥LOD (high- and low-exposure categories). Finally, we modeled OPE biomarkers detected in <50% of participants (BMPP, BEHP, DPRP) as binary variables dichotomized as nondetect (<LOD) or detect (≥LOD).

We estimated associations of each OPE biomarkers with birth outcomes in linear (continuous outcomes), logistic (binary outcomes), and multinomial logistic regression models [four-level categorized gestational age treating full term (39–40 wk) as the reference group][91] using generalized estimating equations, accounting for clustering at the cohort level. Given our large sample size, we adjusted for all measured variables on our DAG that served as confounders and risk factors of birth outcomes while excluding potential causal intermediates. We included maternal race/ethnicity, maternal age at delivery, maternal education, maternal marital status, maternal prepregnancy BMI, maternal smoking during pregnancy, parity, child's sex, and sample collection season and year. To assess potential nonlinear associations between continuous covariates (i.e., maternal age, prepregnancy BMI, and year of specimen collection) and OPE biomarker concentrations, we fit models using restricted cubic splines to examine the shape of covariate–outcome associations. Based on visual inspection of the shape of these associations and model fit statistics, we used continuous linear terms for sample collection year and maternal prepregnancy BMI. For maternal age at delivery, we used a restricted cubic spline with 3 knots, at the 25th, 50th, and 75th percentiles, to allow for nonlinear relationships with birth outcomes. To account for covariate data with <20% missingness, we used multiple imputation by chained equations, using all covariates, as well as the study cohort, as predictors. Because prior studies have reported sex-specific associations of some OPEs with birth outcomes,[67,69,70] we explored differences in associations by child's sex using stratified models. In addition, we tested for effect measure modification using the Wald p-value for the interaction term between child's sex and OPE biomarkers. If an interaction term was significant, we interpreted the sex-stratified estimates by comparing their magnitude and direction.

In a sensitivity analysis, we used a leave-one-cohort-out approach to evaluate the influence of each cohort on our results. For this analysis, we estimated associations of OPEs with birth outcomes as above, but we excluded one cohort at a time. For example, we ran 16 unique linear regression models of associations between DPHP and gestational age, with each model excluding participants from a different cohort. As a secondary analysis, we adjusted for potential copollutant confounding by jointly modeling all OPE biomarkers in the same regression model to examine independent effects of each compound.

We considered associations to be statistically significant if the p-value was <0.05 for main effects and <0.1 for interaction terms in the effect measure modification analysis. We did not make adjustment for multiple comparisons because this would lead to fewer errors of interpretation in our observational setting, as recommended by Rothman.[92] We conducted all analyses using SAS (version 9.4; SAS Institute, Inc.).

Results

Demographic and sample-related characteristics of 6,646 mother–child dyads from 16 cohorts are summarized in Table 1. Cohort participants were racially/ethnically diverse, with 52.5% non-Hispanic white, 19.5% non-Hispanic black, 18.9% Hispanic, and 9.0% others. The majority of the pregnant participants were married or living with a partner (76.2%); had no gestational diabetes, hypertension, or preeclampsia (84.0%); and did not smoke during pregnancy (92.8%). Prenatal maternal urine samples were collected during 2007–2020, and almost all were collected during the second or third trimester (99.6%). Approximately 6.8% of newborns were born preterm, 21.6% early term, 59.4% full term, and 12.2% late/postterm, and the median gestational age was 39 wk (25th, 75th percentile = 38, 40 wk; Table 2). The median birth weight was 3,360 g (25th, 75th percentiles = 3,040 and 3,685 g), and 6.3% of newborns were SGA and 16.0% were LGA. Among 6,197 newborns born at ≥37 wk gestation, 2.4% were term LBW. There were 5,825 participants from the 16 participating ECHO cohorts who did not meet our criteria for inclusion; their demographic characteristics are presented in Table S3.

Detection frequencies and distributions of dilution-standardized urinary OPE biomarker concentrations in all participants and by cohort are presented in Tables 3 and S4 and Figure S4, respectively. DPHP, DBUP/DIBP, and BDCPP were detected in 99.5%, 95%, and 87% of the study samples. The detection frequencies of BCETP, BBOEP, and BCPP were between 50% and 80%, and those of BMPP, BEHP, and DPRP were <36%. The highest median concentrations were observed for DPHP (0.92 ng/mL) and BDCPP (0.86 ng/mL), followed by BCETP (0.52 ng/mL), DBUP/DIBP (0.19 ng/mL), BCPP (0.12 ng/mL), and BBOEP (0.05 ng/mL). The nine OPE biomarkers were only weakly correlated with each other (Spearman's correlation coefficients = −0.05 to 0.26) (Table S5). Medians of relative percentage differences calculated from valid masked duplicate samples ranged from 6.2% to 16.9% for OPE biomarkers with detection frequencies of >85%, 13.3% to 26.6% for those with detection frequencies between 50% and 80%, and 17.8% to 53.6% for those with detection frequencies of <36% (Table S6).

We did not observe associations between prenatal maternal urinary concentrations of DPHP or BDCPP and gestational duration in the overall study population (Table 4). However, associations of DPHP with continuous gestational age and with preterm and early-term birth differed by sex (p for interaction term between OPE and sex; p_{int} <0.02) (Figure 1 and Table S7). Among females, higher DPHP concentration was associated with shorter gestational age [regression coefficients (β) = −0.03 wk; 95% confidence interval (CI): −0.06, −0.01] and higher odds of preterm vs. full-term birth [odds ratio (OR) per doubling in concentration = 1.12; 95% CI: 1.05, 1.19], whereas among males higher DPHP concentrations were associated with greater gestational age (β = 0.02 wk; 95% CI: 0.00, 0.04). DBUP/DIBP was associated with higher odds of preterm birth (OR = 1.07; 95% CI: 1.02, 1.12) in all newborns. When stratified by child's sex, DBUP/DIBP was associated with shorter gestational age (β = −0.03 wk; 95% CI: −0.06, −0.001) and higher odds of preterm birth (OR = 1.09; 95% CI: 1.03, 1.16) among female newborns only, although the tests for interaction were not statistically significant (p_{int} > 0.33).

The low-exposure category of BCETP, compared with the nondetect category, was associated with lower odds of late/postterm vs. full-term birth among all births (OR = 0.83; 95% CI:

Table 1. Demographic and sample-related characteristics among 6,646 ECHO mother–child dyads.

Characteristics	*n* (%)[a]
Maternal race/ethnicity	
Non-Hispanic white	3,470 (52.5)
Non-Hispanic black	1,288 (19.5)
Hispanic	1,251 (18.9)
Other races/ethnicities[b]	597 (9.0)
Missing	40
Maternal education	
Less than high school	535 (8.6)
High school degree/GED or equivalent	1,337 (21.4)
Some college, no/associate degree, trade school	1,115 (17.9)
Bachelor's degree	1,727 (27.7)
Masters, professional, or doctorate degree	1,522 (24.4)
Missing	410
Maternal marital status	
Married or living with a partner	4,768 (76.2)
Widowed, separated, divorced	280 (4.5)
Single, never married, partnered, not living together	1,213 (19.4)
Missing	385
Maternal age at delivery (y)	
<20	209 (3.1)
20–24	975 (14.7)
25–29	1,653 (24.9)
30–34	2,218 (33.4)
35–39	1,290 (19.4)
≥40	301 (4.5)
Parity	
0	2,566 (42.8)
1	1,994 (33.3)
≥2	1,436 (23.9)
Missing	650
Prepregnancy BMI (kg/m^2)	
Underweight (<18.5)	177 (2.8)
Normal weight (18.5–24.9)	2,866 (46)
Overweight (25–29.9)	1,607 (25.8)
Obese (>30)	1,586 (25.4)
Missing	410
Tobacco use during pregnancy	
No	5,123 (92.8)
Yes	396 (7.2)
Missing	1,127
Child's sex	
Female	3,250 (48.9)
Male	3,396 (51.1)
Trimester at sample collection	
1 (0–13 wk)	29 (0.4)
2 (14–26 wk)	2,928 (44.1)
3 (27 wk to the end of pregnancy)	3,689 (55.5)
Sample collection season	
Winter (December–February)	1,481 (22.3)
Spring (March–May)	1,881 (28.3)
Summer (June–August)	1,736 (26.1)
Autumn (September–November)	1,548 (23.3)
Sample collection year	
2007	189 (2.8)
2008	330 (5.0)
2009	456 (6.9)
2010	554 (8.3)
2011	798 (12.0)
2012	824 (12.4)
2013	516 (7.8)
2014	593 (8.9)
2015	400 (6.0)
2016	508 (7.6)
2017	488 (7.3)
2018	720 (10.8)
2019	263 (4.0)
2020	7 (0.1)

Note: BMI, body mass index; ECHO, Environmental influences on Child Health Outcomes; GED, general educational development.
[a]Percentage was calculated without missing observations.
[b]Other races/ethnicities include Asian, native Hawaiian or other Pacific Islanders, American Indian or Alaska native, and multiple race.

Table 2. Gestational length and birth weight outcomes among 6,646 ECHO mother–child dyads.

	n (%)[a]		
Birth outcomes	All (*n* = 6,646)	Females (*n* = 3,250)	Males (*n* = 3,396)
Gestational age at birth (completed weeks)			
Preterm (20–36)	449 (6.8)	221 (6.8)	228 (6.7)
Early term (37–38)	1,436 (21.6)	659 (20.3)	777 (22.9)
Full term (39–40)	3,947 (59.4)	1,964 (60.4)	1,983 (58.4)
Late/postterm (40–42)	814 (12.2)	406 (12.5)	408 (12.0)
Birth weight (g)			
200–2,499	365 (5.5)	204 (6.3)	161 (4.8)
2,500–3,999	5,644 (84.9)	2,824 (86.9)	2,820 (83.0)
≥4,000	637 (9.6)	222 (6.8)	415 (12.2)
Term LBW[a]			
No	6,047 (97.6)	2,939 (97.0)	3,108 (98.1)
Yes	150 (2.4)	90 (3.0)	60 (1.9)
SGA (<10th percentile BW-GA *z*-score)			
No	6,227 (93.7)	3,032 (93.3)	3,195 (94.1)
Yes	419 (6.3)	218 (6.7)	201 (5.9)
LGA (>90th percentile BW-GA *z*-score)			
No	5,580 (84.0)	2,752 (84.7)	2,828 (83.3)
Yes	1,066 (16.0)	498 (15.3)	568 (16.7)

Note: BW-GA, birth weight for gestational age; ECHO, Environmental influences on Child Health Outcomes; LBW, low birth weight; LGA, large for gestational age; SGA, small for gestational age.
[a]Among 6,197 term births.

0.73, 0.95). The associations of the high category of BCETP with preterm birth and gestational age differed by sex ($p_{int} < 0.01$), indicating higher odds of preterm birth and shorter gestational age among females [OR = 1.27 (95% CI: 1.03, 1.58) for preterm birth; β = −0.13 wk (95% CI: −0.24, −0.03) for gestational age] and lower odds of preterm birth and longer gestational age among males [OR = 0.77 (95% CI: 0.55, 1.06) for preterm birth; β = 0.06 wk (95% CI: −0.06, 0.18) for gestational age]. The high-exposure category of BBOEP was associated with shorter gestational age (β = −0.07 wk; 95% CI: −0.14, −0.01) and higher odds of preterm vs. full-term birth (OR = 1.25; 95% CI: 1.06, 1.46) in all newborns. The association between the high category of BBOEP and early-term birth differed by sex ($p_{int} = 0.03$), with lower odds among females (OR = 0.75; 95% CI: 0.60, 0.94) and higher odds among males (OR = 1.10; 95% CI: 0.89, 1.35). The high category of BCPP was associated with higher odds of early-term birth compared with full-term birth (OR = 1.18; 95% CI: 1.05, 1.32). Three binary OPE biomarkers were not associated with gestational duration, except for an association of detectable BEHP with lower odds of late/postterm vs. full-term birth (OR = 0.84; 95% CI: 0.72, 0.97).

Table 3. Distributions of dilution-standardized urinary OPE biomarker concentrations among 6,646 ECHO pregnant participants.

OPE biomarkers	LOD (ng/mL)	*n* (%) >LOD	Percentile				
			5th	25th	50th	75th	95th
DPHP	0.03	6,613 (99.5)	0.26	0.54	0.92	1.78	8.33
DBUP/DIBP	0.04	6,343 (95)	0.06	0.12	0.19	0.30	0.88
BDCPP	0.02	5,784 (87)	<LOD	0.31	0.86	1.70	5.02
BCETP	0.02	4,589 (69)	<LOD	<LOD	0.52	1.58	8.22
BBOEP	0.02	4,398 (66)	<LOD	<LOD	0.05	0.09	0.25
BCPP	0.02	3,494 (53)	<LOD	<LOD	0.12	0.75	3.45
BMPP	0.01	2,383 (36)	<LOD	<LOD	<LOD	0.03	0.13
BEHP	0.02	1,963 (30)	<LOD	<LOD	<LOD	0.04	0.55
DPRP	0.03	1,690 (25)	<LOD	<LOD	<LOD	0.03	0.31

Note: BBOEP, bis(butoxyethyl) phosphate; BCETP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BEHP, bis(2-ethylhexyl) phosphate; BMPP, bis(2-methylphenyl) phosphate; DBUP/DIBP, composite of dibutyl phosphate and di-isobutyl phosphate; DPHP, diphenyl phosphate; DPRP, dipropyl phosphate; ECHO, Environmental influences on Child Health Outcomes; LOD, limit of detection; OPE, organophosphate ester.

Table 4. Associations between prenatal maternal urinary OPE biomarkers and gestational duration in the ECHO cohorts.

	Gestational age (wk) ($n = 6,646$)		Preterm ($n = 449$) [vs. full term ($n = 3,947$)]		Early term ($n = 1,436$) [vs. full term ($n = 3,947$)]		Late/postterm ($n = 814$) [vs. full term ($n = 3,947$)]	
OPE biomarkers	β (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Continuous (log_2-transformed, dilution-standardized)								
DPHP	−0.01 (−0.02, 0.01)	0.51	1.02 (0.96, 1.09)	0.51	0.98 (0.95, 1.01)	0.21	1.00 (0.95, 1.04)	0.83
DBUP/DIBP	−0.02 (−0.06, 0.02)	0.31	1.07 (1.02, 1.12)	0.01	1.00 (0.94, 1.06)	0.95	0.99 (0.96, 1.03)	0.66
BDCPP	−0.01 (−0.02, 0.01)	0.43	1.00 (0.96, 1.04)	0.92	1.01 (0.99, 1.02)	0.36	0.99 (0.97, 1.00)	0.09
High/low (compared with nondetect)								
BCETP—low	−0.01 (−0.10, 0.09)	0.88	0.96 (0.77, 1.20)	0.71	0.96 (0.82, 1.12)	0.57	0.83 (0.73, 0.95)	0.01
BCETP—high	−0.03 (−0.12, 0.06)	0.55	0.97 (0.79, 1.20)	0.81	0.96 (0.85, 1.09)	0.53	0.94 (0.81, 1.08)	0.35
BBOEP—low	0.01 (−0.07, 0.08)	0.84	1.06 (0.87, 1.29)	0.55	0.91 (0.76, 1.10)	0.34	1.03 (0.87, 1.21)	0.74
BBOEP—high	−0.07 (−0.14, −0.01)	0.03	1.25 (1.06, 1.46)	0.01	0.92 (0.79, 1.07)	0.26	1.02 (0.80, 1.31)	0.85
BCPP—low	0.08 (−0.01, 0.18)	0.08	0.83 (0.66, 1.03)	0.09	1.04 (0.91, 1.20)	0.53	1.14 (0.97, 1.36)	0.12
BCPP—high	−0.01 (−0.09, 0.07)	0.79	0.97 (0.77, 1.22)	0.78	1.18 (1.05, 1.32)	0.01	1.07 (0.92, 1.23)	0.39
Detect (compared with nondetect)								
BMPP	−0.01 (−0.09, 0.06)	0.72	1.00 (0.86, 1.16)	1.00	1.04 (0.91, 1.19)	0.53	1.02 (0.86, 1.21)	0.82
BEHP	−0.08 (−0.19, 0.03)	0.18	1.01 (0.83, 1.22)	0.94	1.03 (0.89, 1.18)	0.73	0.84 (0.72, 0.97)	0.02
DPRP	0.09 (−0.02, 0.19)	0.10	0.90 (0.69, 1.18)	0.45	1.02 (0.93, 1.13)	0.63	1.18 (0.98, 1.43)	0.08

Note: Linear or multinomial regression models, fitted using generalized estimating equations with a random effect for cohort, were used to estimate βs or ORs, respectively, and their corresponding 95% CIs and *p*-values. Regression models were adjusted for maternal race/ethnicity, maternal age at delivery, maternal education, maternal marital status, maternal prepregnancy BMI, maternal smoking during pregnancy, parity, child's sex, and sample collection season and year. BBOEP, bis(butoxyethyl) phosphate; BCETP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BEHP, bis(2-ethylhexyl) phosphate; BMPP, bis(2-methylphenyl) phosphate; CI, confidence interval; DBUP/DIBP, composite of dibutyl phosphate and di-isobutyl phosphate; DPHP, diphenyl phosphate; DPRP, dipropyl phosphate; ECHO, Environmental influences on Child Health Outcomes; OPE, organophosphate ester; OR, odds ratio.

We did not observe evidence of associations of DPHP, DBUP/DIBP, BDCPP, BBOEP, and BEHP with fetal growth (Table 5). The low and high categories of BCPP and detectable BMPP and DPRP (compared with nondetectable) were associated with greater BW-GA *z*-score (βs = 0.07 for low and high BCPP categories and BMPP, 0.04 for DPRP) in the overall population. Similarly, the high category of BCPP (OR = 0.52; 95% CI: 0.31, 0.89) and detectable DPRP (OR = 0.72; 95% CI: 0.55, 0.94) were associated with lower odds of term LBW. There were no statistically significant associations for SGA or LGA among all births, except for an association between the high category of BCETP and lower odds of SGA (OR = 0.83; 95% CI: 0.71, 0.96). When stratified by child's sex, lower odds of SGA were observed among male newborns only in association with BDCPP, BCETP, BCPP, and BMPP, although most of the tests for interaction were not statistically significant (Table S8).

Leave-one-out analyses confirmed the robustness of the results to the exclusion of each cohort (Figures S5–S7 and Excel Tables S1–S3). Excluding the two largest cohorts, Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE; $n = 1,453$) or New Hampshire Birth Cohort Study (NHBCS; $n = 1,317$), the two largest cohorts, slightly attenuated or strengthened some associations, but the directions of the estimates were not changed. When jointly modeling all OPE biomarkers in the same regression model to adjust for potential copollutant confounding, the results were similar to the primary results (Tables S9 and S10).

Discussion

In this large, geographically and sociodemographically diverse ECHO sample that included over 6,600 participants from across the US, several OPE biomarkers were frequently detected in prenatal maternal urine samples. We observed that DBUP/DIBP and the high-exposure category of BBOEP were associated with decreased gestational duration, specifically, greater odds of preterm birth. Child's sex appeared to modify associations of higher DPHP and the high category of BCETP both with continuous gestational age at birth and with preterm birth, with adverse findings among female newborns. On the other hand, we observed modest associations of detectable BCPP, BMPP, and DPRP with increased fetal growth, specifically greater BW-GA *z*-score and lower odds of term LBW, although we did not observe a corresponding increased risk of LGA birth or sex-dimorphic association.

Most prior studies of urinary OPE metabolite concentrations in pregnant people have primarily quantified DPHP and BDCPP, with few studies exploring di-*n*-butyl phosphate (DNBP), BCPP, BCETP, and BBOEP (Table S11).[14,16,67,68,70,71,93,94] Higher median concentrations of DPHP were observed in pregnancy cohorts in North Carolina (1.31 ng/mL; 2001–2006),[67] Ohio (1.36–2.16 ng/mL in different trimesters; 2003–2006),[16] and Puerto Rico (1.55 ng/mL; 2011–2015)[93] compared with those in our ECHO participants (0.91 ng/mL; 2007–2020). Other US studies conducted in California,[14] Massachusetts,[71] Rhode Island,[94] and Maryland[68] showed comparable or slightly lower median concentrations of DPHP. For BDCPP, pregnancy cohorts in North Carolina (1.85 ng/mL),[67] Puerto Rico (1.41 ng/mL),[93] and Rhode Island (0.94–1.55 ng/mL; 2014)[94] had higher median concentrations than the present study (0.88 ng/mL), whereas other US cohorts had comparable or lower median levels. Median concentrations of BCETP were higher in the North Carolina cohort (0.63–0.83 ng/mL)[67] but lower in the Rhode Island cohort (0.25–0.38 ng/mL)[94] when compared with the present study (0.52 ng/mL). Only the Ohio cohort quantified DNBP (0.24 ng/mL),[16] comparable with our DBUP/DIBP concentrations (0.19 ng/mL). A Chinese birth cohort based in Wuhan (2014–2016) showed considerably lower median concentrations of DPHP (0.23 ng/mL) and BDCPP (0.10 ng/mL) than the US studies but found higher median concentrations of BBOEP (0.15 ng/mL) compared with the present study (0.05 ng/mL).[70] There are a multitude of possible reasons for these differences, including differences in OPE sources by geographic region, sampling year and season, and sociodemographic characteristics. Further studies on possible sources and exposure pathways could help clarify the observed differences and help determine methods for reducing exposures.

At least eight prior epidemiological studies have examined birth outcomes in association with prenatal exposure to OPEs, with most of them reporting sex-specific associations.[67–73] Two studies based on the Wuhan birth cohort reported findings that were generally consistent with our study.[69,70] For example, among 339 participants, prenatal urinary concentrations of DPHP and sum of OPE metabolites were associated with higher risk of

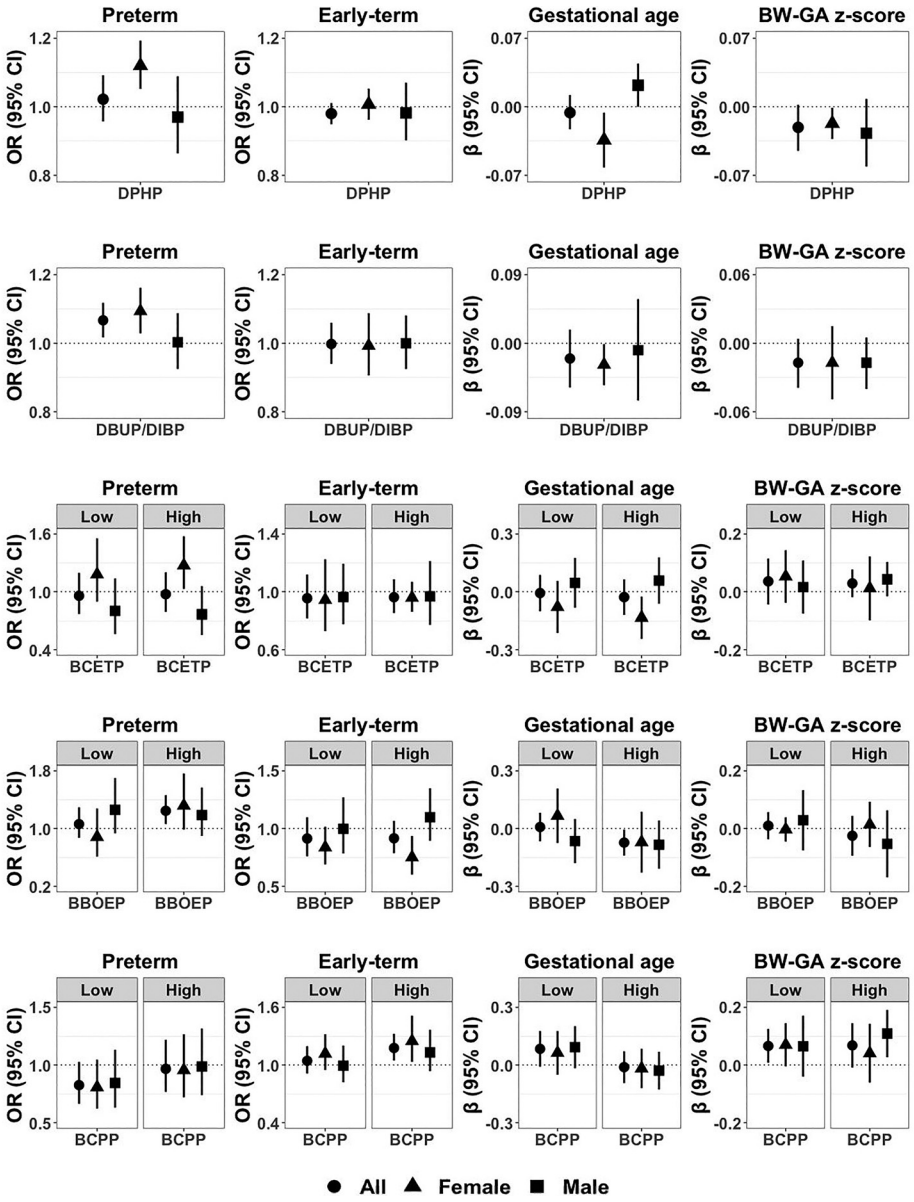

Figure 1. Associations of DPHP, DBUP/DIBP, BCETP, BBOEP, and BCPP with preterm ($n = 449$) and early-term ($n = 1,436$), compared with full-term birth ($n = 3,947$), gestational age (in weeks) ($n = 6,646$), and BW-GA z-score ($n = 6,646$) among all newborns in the ECHO cohorts, and stratified by child's sex (females: $n = 3,250$, males: $n = 3,396$). Point estimates indicate regression coefficients or odds ratios (ORs), and error bars indicate 95% confidence intervals (CIs). Regression models were adjusted for maternal race/ethnicity, maternal age at delivery, maternal education, maternal marital status, maternal prepregnancy BMI, maternal smoking during pregnancy, parity, child's sex, and sample collection season and year. Sample size of each birth outcome by child's sex is presented in Table 2, and numeric data regarding regression coefficients, ORs, 95% CIs, and p-values for main effects and interaction terms between child's sex and OPE biomarkers are presented in Tables 4, 5, S7, and S8. Note: BBOEP, bis(butoxyethyl) phosphate; BCETP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; BMI, body mass index; BW-GA, birth weight for gestational age; DBUP/DIBP, composite of dibutyl phosphate and di-isobutyl phosphate; DPHP, diphenyl phosphate; ECHO, Environmental influences on Child Health Outcomes.

LBW, especially among female newborns.[69] Their later study investigating trimester-specific associations among 213 pregnant people from the same population observed that BDCPP and BBOEP in the third trimester were inversely associated with birth weight and length unadjusted for gestational age, and associations were stronger among males than females.[70] They also found that DPHP in the first trimester was associated with lower birth weight, especially among females. In line with our findings, a Boston-area cohort including 90 pregnant people reported that DPHP and a mixture of DPHP and BDCPP were associated with lower odds of LGA.[71] Similar to our sex-stratified results, the North Carolina cohort of 349 pregnant people observed that prenatal urinary concentrations of BDCPP and ip-PPP were associated with shorter gestational age and higher odds of preterm birth among female newborns, whereas DPHP was associated with longer gestational age and lower odds of preterm birth among males.[67] On the other hand, a Baltimore-area cohort of 90 pregnant people reported that BDCPP was associated with greater ponderal index, a measure of weight-for-length similar to BMI,[68] and two other studies did not observe strong associations with any of the birth outcomes studied.[72,73]

Some inconsistent results may be attributable to differences in population characteristics and urinary OPE metabolite levels, as well as smaller sample sizes, of prior studies. In particular, our study indicates that DBUP/DIBP is highly detected (>95%) in our large sample of US pregnant people and that it may be

Table 5. Associations between prenatal maternal urinary OPE biomarkers and fetal growth in the ECHO cohorts.

	BW-GA *z*-score ($n = 6,646$)		Term LBW ($n = 150$) [vs. term non-LBW ($n = 6,047$)][a]		SGA ($n = 419$) [vs. non-SGA ($n = 6,227$)]		LGA ($n = 1,066$) [vs. non-LGA ($n = 5,580$)]	
OPE biomarkers	β (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Continuous (log_2-transformed, dilution-standardized)								
DPHP	−0.02 (−0.05, 0.00)	0.01	1.05 (0.96, 1.15)	0.28	1.05 (0.99, 1.11)	0.11	0.97 (0.92, 1.02)	0.17
DBUP/DIBP	−0.02 (−0.04, 0.00)	0.11	0.91 (0.78, 1.06)	0.22	1.02 (0.96, 1.08)	0.58	0.97 (0.94, 1.01)	0.11
BDCPP	0.00 (−0.01, 0.00)	0.33	0.98 (0.95, 1.01)	0.14	0.99 (0.97, 1.01)	0.18	0.98 (0.97, 1.00)	0.05
High/low (compared with nondetect)								
BCETP—low	0.04 (−0.04, 0.12)	0.38	0.98 (0.60, 1.61)	0.94	0.91 (0.69, 1.19)	0.49	1.13 (0.95, 1.34)	0.18
BCETP—high	0.03 (−0.02, 0.08)	0.24	0.90 (0.59, 1.39)	0.64	0.83 (0.71, 0.96)	0.01	1.04 (0.92, 1.18)	0.56
BBOEP—low	0.01 (−0.04, 0.06)	0.68	0.91 (0.65, 1.26)	0.56	0.87 (0.74, 1.04)	0.12	0.99 (0.90, 1.10)	0.90
BBOEP—high	−0.03 (−0.09, 0.04)	0.48	1.04 (0.74, 1.45)	0.84	1.04 (0.92, 1.19)	0.52	0.97 (0.84, 1.13)	0.70
BCPP—low	0.07 (0.01, 0.13)	0.03	0.76 (0.58, 1.00)	0.05	0.80 (0.61, 1.04)	0.10	1.06 (0.90, 1.25)	0.46
BCPP—high	0.07 (−0.01, 0.15)	0.09	0.52 (0.31, 0.89)	0.02	0.84 (0.62, 1.12)	0.23	1.04 (0.86, 1.25)	0.68
Detect (compared with nondetect)								
BMPP	0.07 (0.02, 0.11)	0.004	0.97 (0.64, 1.46)	0.88	0.85 (0.72, 1.00)	0.06	1.10 (0.95, 1.28)	0.20
BEHP	−0.03 (−0.08, 0.02)	0.19	1.29 (0.99, 1.67)	0.06	1.11 (0.93, 1.32)	0.24	0.95 (0.81, 1.11)	0.50
DPRP	0.04 (0.00, 0.07)	0.03	0.72 (0.55, 0.94)	0.02	0.88 (0.74, 1.06)	0.18	1.08 (0.93, 1.26)	0.31

Note: Linear or multinomial regression models, fitted using generalized estimating equations with a random effect for cohort, were used to estimate βs or ORs, respectively, and their corresponding 95% CIs and *p*-values. Regression models were adjusted for maternal race/ethnicity, maternal age at delivery, maternal education, maternal marital status, maternal pre-pregnancy BMI, maternal smoking during pregnancy, parity, child's sex, and sample collection season and year. BBOEP, bis(butoxyethyl) phosphate; BCETP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BEHP, bis(2-ethylhexyl) phosphate; BMI, body mass index; BMPP, bis(2-methylphenyl) phosphate; BW-GA, birth weight for gestational age; CI, confidence interval; DBUP/DIBP, composite of dibutyl phosphate and di-isobutyl phosphate; DPHP, diphenyl phosphate; DPRP, dipropyl phosphate; ECHO, Environmental influences on Child Health Outcomes; LBW, low birth weight; LGA, large for gestational age; OPE, organophosphate ester; OR, odds ratio; SGA, small for gestational age.
[a]LBW vs. non-LBW among 6,197 non-preterm births (≥37 wk gestation).

associated with increased risk of preterm birth. However, DBUP and DIBP have not been frequently quantified in previous US studies and were detected with low frequency in the Chinese studies (Table S11), which were rarely examined in association with adverse birth outcomes. One of the included cohorts, Maternal And Developmental Risks from Environmental and Social stressors (MADRES), conducted site-specific analyses using 421 Southern Californian pregnant people, who were also included in the present study, and reported that DBUP/DIBP was associated with shorter gestational duration,[74] underscoring the necessity for further explorations into the potential role of this compound as a contributing factor to shortened gestational durations.

There are several potential mechanisms by which prenatal OPE exposure could disrupt the timing of birth and explain observed sex-specific differences. One of the underlying mechanisms that may link OPE exposure with altered birth outcomes is thyroid hormone disruption, which plays an essential role in fetal development.[95,96] Several epidemiological studies suggest that prenatal OPE exposure may disrupt neonatal thyroid hormone levels in sexually dimorphic ways.[43,44,46] Prenatal maternal urinary concentrations of DPHP and DBUP were associated with higher levels of thyroid stimulating hormone (TSH) in newborns, especially among females. These associations were partially mediated by the oxidative stress of DNA damage.[43] Higher BBOEP in the third trimester was associated with higher neonatal TSH, especially among males, whereas higher DPHP in the third trimester was associated with lower neonatal TSH among females.[44] DNBP, DPHP, and BDCPP were associated with lower levels of neonatal triiodothyronine and thyroxine.[46] Prenatal OPE metabolites, such as DPHP and BDCPP, were also associated with altered thyroid hormone levels in pregnant people.[43,45,46] Maternal thyroid disruption during pregnancy was further associated with higher risks of preterm birth and LBW.[97,98] Oxidative stress and inflammation induced by OPEs could also provide a mechanistic link between exposures and preterm birth.[43,53,55,56] Finally, similar to other endocrine disrupting chemicals, OPEs could also contribute to abnormal placental development and functions in sex-dependent manners.[99,100]

Disruption of maternal metabolic functions and other endocrine systems by OPEs could also alter fetal growth.[57] OPEs can activate PPARs that play critical roles in energy homeostasis and lipid metabolism.[47–49] PPAR activation has previously been proposed as a mechanism linking other environmental chemical exposures, such as phthalates[101] and per- and polyfluoroalkyl substances,[102] to weight gain. PPAR activation could therefore potentially explain the associations with higher BW-GA *z*-scores that we observed for three of the compounds.[79] The parent compound of DPHP and 2-ethylhexyl diphenyl phosphate (EHDPP) exhibited PPAR-γ activation in human placental choriocarcinoma cells.[59] Mice perinatally exposed to a mixture of parent compounds of DPHP, BDCPP, and dicresyl phosphate showed higher neonatal body weight and PPAR-γ activation in the hypothalamus and liver, especially in female pups.[103]

The present study has several strengths. This is by far the largest study quantifying OPE biomarkers in the urine of pregnant people and examining their associations with birth outcomes. We used a geographically and sociodemographically diverse study population, combining 16 pregnancy/birth cohorts across the US. The quantification of urinary OPE biomarkers was performed by a single laboratory, minimizing measurement error. Furthermore, leave-one-out analyses suggested robustness of our results across the cohorts. In addition, this research considered a range of birth outcomes, enabling us to make inferences about the effect of the OPE exposures on duration of gestation and fetal growth,[104] considering the full range of early and late gestational age outcomes and size-for-gestation outcomes. We used generalized estimating equations to address cohort variability in birth outcome ascertainment methods (e.g., medical record abstraction, maternal self-report), but there is a slight concern regarding the potential for decreased accuracy when using self-report methods. It should be also noted that our study population had a slightly lower prevalence of preterm birth (6.8%) and LBW (5.5%) compared with the US national statistics for singleton births (8.8% and 6.9%, respectively).[105] This is attributed not only to the inclusion criteria for this analysis (i.e., the availability of a prenatal urine sample for measurement of urinary OPE biomarkers) but also to the fact that the majority of cohorts sought to recruit pregnant people without

severe pregnancy conditions. There were two high-risk autism spectrum disorder cohorts [Early Autism Risk Longitudinal Investigation (EARLI) and Markers of Autism Risk in Babies-Learning Early Signs (MARBLES)] and one cohort that enrolled pregnant people who were cigarette smokers [Vitamin C to Decrease Effects of Smoking in Pregnancy on Infant Lung Function (VCSIP)], but these three cohorts accounted for only 7% of the study population. In addition, the number of pregnancies contributed by the 16 cohorts varied from 20 to 1,453, and each cohort provided different proportions of their full study sample to this analysis (Table S1). Therefore, our study findings may not be generalizable to all the participating cohorts or to the US birthing population, which includes individuals with numerous other risk factors for birth outcomes.

Another limitation is the measurement of concentrations of OPE biomarkers in a single spot or first morning urine sample collected primarily during mid- to late-pregnancy, which reflects only recent exposure because of their short half-lives.[106] Previous studies have reported intraclass correlation coefficients of urinary DPHP, DNBP, BDCPP, and BCETP ranging from 0.2 to 0.7, indicating low to moderate reproducibility over a 4–6 month period in mid- to late-pregnancy.[16,68,94,107] Although OPE exposure likely stems from the home environment, which is fairly constant over time, transplacental transfer, as well as seasonal factors, such as greater air partitioning in warmer months and variations in indoor time and ventilation frequency, can influence OPE exposure levels in pregnant people across the pregnancy.[15] Therefore, further epidemiological studies using repeated measurements of urinary OPE biomarkers are warranted to reduce exposure misclassification and to investigate potential periods of heightened susceptibility. It should be also noted that DPHP is a nonspecific metabolite of several OPEs, including TPHP, resorcinol bis(diphenylphosphate), and EHDPP.[108,109] This implies that DPHP does not differentiate between prenatal exposure to OPEs with varying levels of toxicity. Last, we conducted neither a mixtures analysis to examine overall or joint effects of OPE mixtures nor investigations into nonlinear associations between the three continuous OPE biomarkers and birth outcomes. Future studies could address whether specific combinations of OPEs have additive or synergistic effects and explore potential nonlinear relationships to provide a more comprehensive understanding of the impact of prenatal OPE exposures on birth outcomes.

Conclusion

Our study, based on a large, diverse sample of the US population, found that greater prenatal exposure to several OPEs related to elevated risks of preterm birth and shorter gestational age, especially among female newborns. Some OPEs were modestly associated with higher BW-GA *z*-scores, a risk factor for childhood obesity. Although the magnitudes of the associations are modest, the number of births that may be impacted by these compounds is large given the widespread exposures to emerging OPE flame retardants among US pregnant people.

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