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Gestational exposure to organophosphate ester flame retardants and risk of childhood obesity in the environmental influences on child health outcomes consortium

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109071.

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Abstract

Introduction: Organophosphate esters (OPEs) are increasing in use as flame retardants and plasticizers and concerns have been raised given their endocrine-disrupting activities and possible obesogenic consequences. However, longitudinal studies on gestational OPE exposure and childhood obesity are scarce. This study examined whether OPE levels in maternal urine during pregnancy were associated with the risk of childhood obesity.

Methods: OPEs were analyzed in pregnancy urine samples of 5,087 individuals from 14 studies contributing to the Environmental influences on Child Health Outcomes (ECHO) Cohort. BDCPP, DBUP/DIBP, and DPHP, detected in > 80 % of the samples, were modeled continuously and by tertiles; whereas BCPP, BBOEP, and BCETP, detected in 50–80 % of samples, were modeled

categorically (not-detected, low, and high). Childhood obesity was defined by BMI z-score ≥ 95th percentile according to WHO (<2 years) and the CDC (≥2 years) metrics. Adjusted modified Poisson regression models assessed childhood obesity risk and the mixture effect was assessed using Bayesian kernel machine regression (BKMR).

Results: BMI measurements were available for 3,827 children in infancy (0.5–1.9 years), 3,921 children in early childhood (2.0–4.9 years), and 2,541 children in mid-childhood (5.0–10.0 years). Obesity was present in 16–21 % of children across age groups. In mid-childhood DBUP/DIBP second and third versus first tertiles were associated with increased obesity risk (RR 1.14; 95 % CI: 1.02, 1.28; and RR 1.11; 95 % CI: 0.97, 1.27; respectively); whereas BDCPP second and third versus first tertiles reflected an inverse association with obesity risk (RR 0.85; 95 % CI: 0.80, 0.91 and RR 0.91; 95 % CI: 0.77, 1.07; respectively). No association with obesity risk was observed for DPHP, BCPP, BBOEP, and BCETP. Directions observed were consistent with those seen in BKMR models.

Conclusions: This study identified mixed associations between gestational OPE exposure and childhood obesity. Further investigation across a comprehensive range of OPE exposures is warranted.

Keywords

OPE; Childhood obesity; Pregnancy; Flame retardants

1. Introduction

Organophosphate esters (OPEs) are used commercially as flame retardants and plasticizers, and are found in various household and industrial products, including polyurethane foam, furniture, electronics, construction materials, infant products, textiles, and fabrics (Dou and Wang, 2023; Liu et al., 2021; Wei et al., 2015; Yang et al., 2022). OPEs volatilize from products, and have been found in indoor dust, water, soil, (Du et al., 2019; Stapleton et al., 2009) and even remote areas like the Arctic (Xie et al., 2022). The widespread use of OPEs has steadily risen in recent decades as they replaced polybrominated diphenyl ethers (PBDEs) as flame retardants in the mid-2000s (Yang et al., 2022). This shift occurred due to the known link between PBDEs and adverse developmental, reproductive, and neurological outcomes, (Dodson et al., 2012; Linares et al., Mar 2015) as well as the fact that OPEs have substantially shorter half-lives—ranging from hours to days—compared to the years-long half-life of PBDEs (Carignan et al., 2013; Ohoro et al., 2021; Wang and Song, 2024). Since those widespread replacements, OPE production has surged, reaching over 1 million tons in 2018, far beyond previous PBDE manufacturing levels (Fu et al., 2020). As a result, human exposure to OPEs is pervasive, (Boyle et al., 2019; Cequier et al., 2015) with detected OPE metabolite concentrations ubiquitous in pregnant populations (Castorina et al., 2017; Hoffman et al., 2017; Percy et al., 2020). Data from toxicological and epidemiological studies indicate that these metabolites have endocrine disrupting qualities (Dishaw et al., 2014; Gravel et al., 2020; Kojima et al., 2013; Li et al., 2023; Trowbridge et al., 2021; Yao et al., 2021). Endocrine-disrupting chemicals (EDCs) have been shown to influence obesity(Gupta et al., 2020) and glucose intolerance (Kahn et al., 2020) among other adverse

health outcomes (Gore et al., 2015) with prenatal exposure linked to fetal epigenetic programming and metabolic homeostasis (Rabotnick et al., 2023).

Childhood obesity is an escalating global public health concern, with prevalence and severity increasing among children at younger ages (Afshin et al., 2017; Apperley et al., 2022; Skinner et al., 2018). Obesity is implicated in several clinical outcomes including elevated risk of diabetes, hypertension, non-alcoholic fatty liver disease, cancer, and other health issues (Smith et al., 2020; Weihrauch-Blüher et al., 2019; Weihrauch-Blüher and Wiegand, 2018). Furthermore, childhood obesity often persists into adulthood, leading to greater morbidity and earlier mortality (Llewellyn et al., 2016). Environmental pollutants, including EDCs, have been proposed as contributors to this rising obesity trend due to their influences on hormonal processes related to adipose tissue development, appetite, satiety, weight regulation, and energy balance (Gupta et al., 2020). Toxicologic evidence has shown that OPE exposure may increase the risk of obesity as these chemicals may disrupt energy homeostasis through estrogen receptor alpha (ERα)-mediated pathways resulting in altered feeding efficiency, insulin tolerance, fat mass, and ghrelin levels (Vail et al., 2020; Vail et al., 2022). In mice, gestational exposure to OPEs led to disruption of endocrine metabolism and consequent impacts on offspring's energy and glucose regulation, suggesting a possible obesogenic effect in the offspring, with sex-specific effects (Walley et al., 2021). In humans, OPE metabolites have been detected in the placenta, suggesting maternal-fetal transfer (Ding et al., 2016; Wang et al., 2021; Zhao et al., 2017). However, the extent to which gestational OPE exposures may lead to an elevated risk of obesity in children, as well as the potential existence of sex-specific effects, remains understudied (Chen et al., 2023).

To address this knowledge gap, we assessed whether OPE levels measured in maternal urine during pregnancy were associated with the risk of childhood obesity in the offspring. We also assessed possible sex-specific associations. We hypothesized that gestational exposure to higher levels of OPEs was associated with increased risk of childhood obesity. This study highlights an important public health issue and could inform potential regulations on the manufacture and use of OPEs. The current study was conducted among a geographically and racially and ethnically diverse U.S. population of individuals who participated in the Environmental influences on Child Health Outcomes (ECHO) research consortium, a program funded by the National Institutes of Health.

2. Methods

2.1. Study population

We analyzed data from 14 longitudinal studies within the ECHO program. The ECHO program investigates how environmental exposures during pregnancy and early childhood, including physical, chemical, social, behavioral, biological, and environmental factors, impact child health and development (Blaisdell et al., 2022). All pregnancies within this study occurred between 2006 and 2020. The study underwent review and obtained approval from Institutional Review Boards (IRBs), including the ECHO Cohort single IRB and the local IRBs of individual ECHO study sites. Additionally, Health Insurance Portability and Accountability Act (HIPAA) authorization was obtained for access to medical records. Written informed consent was also obtained from pregnant participants in each ECHO study

site at the time of study enrollment as well as child assent for enrolled children starting at age eight.

2.2. OPE analysis

Single spot or first morning urine samples were collected from participants during the 2nd or 3rd trimester of pregnancy (mean ± standard deviation = 27 ± 5 weeks gestation). Samples were frozen for storage prior to being shipped on dry ice to the Wadsworth Center Human Health Exposure Analysis Resource (WC-HHEAR) laboratory for OPE measurement. OPE metabolites were measured using high-performance liquid chromatography-tandem mass spectrometry methods (HPLC, ExionLC™ system; MS/MS from SCIEX, Redwood City, CA, USA) with some modifications (Wang et al., 2019). Details of laboratory methods are reported in the supplemental materials.

The measured OPE metabolites included bis(butoxyethyl) phosphate (BBOEP), bis(2-chloroethyl) phosphate (BCETP), bis(1-chloro-2-propyl) phosphate (BCPP), bis (1,3-dichloro-2-propyl) phosphate (BDCPP), bis (2-ethylhexyl) phosphate (BEHP), bis(2-methylphenyl) phosphate (BMPP), bis-(2-propylheptyl)-phthalate (DPHP), dipropyl phosphate (DPRP) and the composite of dibutyl phosphate and di-isobutyl phosphate (DBUP/DIBP). The two metabolites DBUP and DIBP were reported as a composite (DBUP/DIBP) because they coeluted during analysis and could not be quantified separately. Further, we only included OPEs with at least 50 % of samples above the limit of detection (LOD). In our study, the LOD for these analytes ranged from 0.0115 to 0.0441 μg/L.

Concentrations of OPEs in urine were dilution corrected using specific gravity or creatinine, depending on availability in the ECHO study site. Prior to dilution correction, we imputed any value below the LOD with the machine-read values provided by the laboratory. To standardize the correction method for urinary dilution across samples, we adopted the approach outlined by Kuiper et al (Kuiper et al., 2021; Kuiper et al., 2022; Oh et al., Jan 2024). For samples corrected using creatinine, OPE concentrations were adjusted by multiplying by the ratio of the ECHO site-specific median dilution value to the participant's dilution value (Kuiper et al., 2021; Kuiper et al., 2022). For those using specific gravity, the values were first subtracted from one (Boeniger et al., Oct 1993).

2.3. Childhood obesity assessment

To define obesity, we used weight and height measurements collected within 30 days of each other during three different age groups: infancy (0.5–1.9 years), early childhood (2.0–4.9 years), and middle childhood (5.0–10.0 years). These age groups were used to be consistent with previous ECHO wide analyses (Aris et al., 2022). We used the height and weight measurements obtained from child medical records or during study-related clinic visits. BMI was calculated using weight (kg)/height (m^2), where height is either standing height (≥ 24 months) or recumbent length (< 24 months). Age-and-sex-specific BMI z-scores were then calculated based on the growth curves provided by the World Health Organization (WHO) (measurements < 2 years of age) and the Centers for Disease Control and Prevention (CDC) (measurements ≥ 2 years of age) metrics, as recommended by the CDC (Kuczmarski et al., 2000; Grummer-Strawn et al., 2010). Extreme z-scores deemed biologically implausible

were removed (CDC, 2023; CDC, 2019). For children under 2 years of age, extreme values were defined as WHO BMI z-scores < −5 or > 5. For children aged 2 years and older, extreme values were defined as CDC Modified BMI z-scores < −4 or > 8 (CDC, 2023; CDC, 2019). If there was more than one BMI measurement within the age group for each child, the highest after data cleaning was used in the analysis. We defined childhood obesity as a BMI z-score at or above the 95th percentile (Ogden and Flegal, 2010).

2.4. Covariates

We selected covariates based on a literature review which were then visualized using a directed acyclic graph (DAG) with the DAGitty program (Supplemental Figure S1) (Textor et al., 2011). Covariates included in the main analysis were maternal age (years), highest level of maternal education (up to high school degree/GED, some college but no degree, Bachelor's degree, and Master's degree or above), pre-pregnancy BMI (kg/m^2), parity (multiparous vs. nulliparous), any maternal smoking during pregnancy (yes vs. no), and child year of birth. Covariates also included race and ethnicity, as a proxy for structural inequities and for disparities in both detected OPE levels (Wang et al., 2019; Ma et al., 2019; Bobb et al., 2018) and disease burden of childhood obesity (Skinner et al., 2018). Race and ethnicity were modeled as Hispanic (all), non-Hispanic White, non-Hispanic Asian, non-Hispanic Black, multiple races, and other races/ethnicities which included: Native Hawaiian or other Pacific Islander, American Indian or Alaskan Native, or missing/unknown (missing <0.5 %). The source of covariate data varied by ECHO sites and included study visits, medical records, and questionnaires. Data were then harmonized by the ECHO Data Analysis Center (DAC). Further details on this process can be found in the supplemental materials. Child sex and age were not separately adjusted for, as they were factored into the outcome. Our DAG identified the minimal sufficient adjustment set for estimating the total effect of gestational OPE exposure on childhood obesity to be child birth year, ECHO site, maternal age at delivery, maternal education, maternal race/ethnicity, maternal smoking in pregnancy, parity, and pre-pregnancy BMI.

2.5. Statistical analysis

Distributions of gestational OPE metabolites were summarized for the full unique sample, for participants involved in each age group analysis, and by individual ECHO study site. Spearman's correlations assessed relationships of the metabolites (continuously) within the full unique sample and by participants involved in each age group analysis.

We assessed associations between individual OPE metabolites and childhood obesity at each age group by using adjusted modified Poisson regression models with robust standard errors where children with BMI below the 95th percentile served as the reference group. We employed modified Poisson models to estimate relative risk (RR) for all OPE metabolites due to the high prevalence of childhood obesity within each age group (>16 %) (Zou, 2004). For metabolites that were detected in at least 80% of samples, we imputed the value of the remaining samples below the LOD with the machine-read values provided by the laboratory which were then log2 transformed. Any machine read values that were negative or zero were replaced with 0.001 prior to transformation. For the metabolites that were detected in 50%-80% of samples, we modeled the metabolites categorically: non-detected (<LOD), low

exposure (detected but less than the sample median of dilution adjusted values), and high exposure (≥ sample median of dilution adjusted values). For metabolites that were detected in at least 80% of samples, we carefully considered the shape of associations present in the analysis, initially examining associations in tertiles to accommodate potential non-linearity. If non-linearity was suggested, continuous linear associations were considered secondary analyses.

All models were adjusted for the covariates listed above. All covariates had little missing data (<7%). For all missing values for covariates, with the exception of race/ethnicity, we imputed values using multiple imputation by chained equations (MICE) (Azur et al., 2011). We generated 50 imputed datasets with 100 burn-in iterations. Predictive mean matching was used for continuous pre-pregnancy BMI, and the discriminant function method was applied to categorical variables such as maternal education, smoking during pregnancy, and parity. The SAS MI procedure was used for imputation, followed by MIANALYZE to combine results from the modified Poisson regression, forming single statistical inferences based on Rubin's (1987) combining rule. Race/ethnicity data (<0.5 % missing) were grouped into "other" because the assumptions for imputation—that the missing data either followed random patterns or mirrored the available data—were not met (Azur et al., 2011). Research suggests that individuals who choose not to provide race and ethnicity data often belong to underrepresented demographic groups (Moscou et al., 2003). Furthermore, all models accounted for ECHO study sites by a cluster on site to consider correlation and the variability in recruitment eligibility and possible geographic differences.

Bayesian kernel machine regression (BKMR) was used to model OPEs as a mixture (Bobb et al., Jul 2015). BKMR is highly flexible, accommodating non-linear associations and complex interactions (Bobb et al., Jul 2015). Metabolites detected in more than 60% of samples(Howe et al., 2020; Hernandez-Castro et al., 2023) were included in BKMR models. BKMR models were completed using a complete-case analysis due to the inability to use MICE for the mixture analysis. Each BKMR model was fit using probit regression for binary outcomes with 10,000 Markov Chain Monte Carlo iterations (Bobb et al., 2018). Convergence was assessed using trace plots and the Rhat statistic (Bobb et al., 2018; Gelman and Rubin, 1992). Results of the BKMR mixture analysis were summarized with the posterior inclusion probabilities (PIPs) and plots of the exposure response function. Cross-section response plots summarized the univariate association between each OPE and the outcome, holding the other OPEs constant at their medians. Bivariate response plots summarized the associations between two OPEs and the outcome, showing the response function for one OPE while fixing the second OPE at quantiles of 0.1, 0.25, 0.5, 0.75, and 0.9, and holding the other OPEs constant at their medians.

To determine if associations were modified by child sex, statistical interactions were added to models individually for highly detected OPEs (>80% of samples > LOD). We also stratified these models by child sex to assess potential effect modification. Multiple sensitivity analyses were conducted. Models were restricted to participants with obesity outcome data collected at all three assessment points in infancy, early childhood, and middle childhood to account for variations in participants across age groups in the main analysis. We also conducted a leave-one-ECHO site-out approach to evaluate the influence of each

site on our results. Finally, we compared results by referencing obesity to normal weight, by excluding children with overweight (≥85th percentile and < 95th percentile), and then by referencing overweight (≥85th percentile) to normal weight, excluding those classified with obesity. This comparison allowed us to thoroughly investigate how associations were influenced by using more refined criteria rather than comparing obesity to all other categories in main models.

2.6. Analytic sample

Initially, there were 7,038 individuals with OPE data measured in pregnancy, of which 6,893 were singleton pregnancies. Among these, 5,335 had at least one measurement of child height and weight collected within 30 days of each other between ages six months and 10 years, which allowed for the calculation of BMI. We excluded 23 children with biologically implausible extreme z-score BMI data (CDC, 2023; CDC, 2019). Of the remaining 5,312 ECHO children, we removed 105 mother–child pairs for child weight and/or height being self-reported, parent-reported, or from unknown sources, leaving 5,207 pairs. To maintain sample independence, if multiple children of the same mother participated in ECHO, we retained only the eldest child resulting in the removal of 75 younger siblings and a sample size of 5,132 children. Lastly, we excluded any ECHO study site contributing fewer than 30 participants at any single age group, resulting in a final sample size of 5,087 unique mother–child pairs. Among these, 3,827 children had a BMI measure during infancy, 3,921 during early childhood, and 2,541 during middle childhood; 1,772 children had BMI measures in all three age groups (see flowchart in Supplemental Figure S2). The included ECHO study sites, number of participating mother–child pairs, years of study recruitment, and their geographic enrollment locations are listed in Supplemental Table S1. Source of child growth (EHR vs. study measured) by individual ECHO sites is shown in Supplemental Table S2.

3. Results

The characteristics of all study participants and by age group are provided in Table 1. Mothers on average were 30.2 ± 5.7 years of age at time of delivery and had an average pre-pregnancy BMI of 26.9 ± 6.7 kg/m^2 with 25% of the sample having obesity before pregnancy. Nearly half of mothers had attained at least a college education and 51% were non-Hispanic White, 20% non-Hispanic Black, 19% Hispanic, and a smaller subset of 5% being non-Hispanic Asian. Across age groups, there were 16–21% of children with obesity (Table 1). Characteristics were similar to those with OPE concentrations available in ECHO but who were excluded from the analysis based on inclusion criteria (N = 1,937, Supplemental Table S3).

Three metabolites were detected in at least 80 % of samples: BDCPP (87%), DBUP/DIBP (96%), and DPHP (99%). An additional three metabolites were detected in 50–80% of samples: BBOEP (66%), BCETP (69%), and BCPP (52%). Three metabolites were detected in less than 50 % of the samples and were not included in the analysis: BMPP (36%), BEHP (30%), and DPRP (26%). The highest median concentration was observed for DPHP (0.92 μg/L), followed by BDCPP (0.89 μg/L). Full distributions of the OPEs are shown in Table 2 and by each ECHO study site in Supplemental Figure S2. The percent of children

with obesity within each tertile of BDCPP, DBUP/DIBP and DPHP as well as category of BBOEP, BCETP, and BCPP are shown in Supplemental Tables 4 and 5, respectively. OPE distributions by age groups were similar to those observed in the full unique sample (Supplemental Table S6). Metabolites were weakly correlated with each other (Spearman R = −0.07 to 0.26, Supplemental Figure S3). OPE distributions were similar to those with OPE concentrations available in ECHO but who were excluded from the analysis based on inclusion criteria (N = 1,937, Supplemental Table S7).

3.1. Associations of gestational DBUP/DIBP, BDCPP, and DPHP exposure with childhood obesity

Results for obesity risk at each age group across tertiles of DBUP/DIBP, BDCPP, and DPHP exposure are shown in Fig. 1; whereas Supplemental Figure S4 reports the association between continues levels of DBUP/DIBP, BDCPP, and DPHP and childhood obesity. The cut points for tertiles are shown in Supplemental Table S8.

Gestational exposure to DBUP/DIBP, when analyzed in tertiles, showed no associations with obesity in infancy. In early childhood when compared with the first tertile (T1), the second tertile (T2) was inversely associated with the risk of obesity (T2 vs. T1: RR 0.88; 95 % CI 0.78, 1.00). However, this association was attenuated for the third tertile (T3 vs T1: 0.98; 95 % CI: 0.82, 1.16). In contrast, in middle childhood the second tertile was associated with an increased risk of obesity (T2 vs T1: 1.14; 95 % CI: 1.02, 1.28), whereas this positive association was attenuated for the third tertile (T3 vs T1:1.11; 95 % CI: 0.97, 1.27). Gestational exposure to DBUP/DIBP, when modeled continuously, exhibited no association with the risk of obesity in any age group (Infancy: 1.02 per doubling of exposure; 95 % CI: 0.96, 1.09; Early Childhood: 0.99 per doubling of exposure; 0.93, 1.06; Middle Childhood: 1.02 per doubling of exposure; 95 % CI: 0.96, 1.09).

For BDCPP when modeled as tertiles, evidence of non-linear associations was observed, the second tertile was associated with a higher risk of obesity in infancy (T2 vs T1: 1.14; 95 % CI: 1.07, 1.21), which was attenuated for the third tertile (T3 vs T1: 1.02; 95 % CI: 0.90, 1.17). In early childhood, no association with obesity risk was observed in association with BDCPP (T2 vs. T1: 1.03; 95 % CI: 0.91, 1.17; T3 vs T1: 1.17; 95 % CI: 0.91, 1.51;). In middle childhood, the second tertile of BDCPP was inversely associated with childhood obesity risk (T2 vs. T1: 0.85; 95 % CI: 0.80, 0.91) whereas the inverse association was attenuated for the third tertile (T3 vs T1: 0.91; 95 % CI: 0.77, 1.07). Gestational exposure to BDCPP, when modeled continuously, showed no association with increased risk of obesity in infancy (1.01 per doubling of exposure; 95 % CI: 1.00, 1.02) or early childhood (1.01 per doubling of exposure; 95 % CI: 0.99, 1.04). However, consistent with the analysis by tertiles, an inverse association was observed for the risk of obesity in middle childhood (0.98 per doubling of exposure; 95 % CI: 0.96, 0.99).

Gestational exposure to DPHP, when modeled by tertiles or continuously, showed no association with the risk of obesity in any age group (Fig. 1 and Supplemental Figure S4).

3.2. Associations of gestational BBOEP, BCETP, and BCPP, with childhood obesity

Gestational exposures to BBOEP, BCETP, and BCPP, modeled as non-detected (reference), low exposure (detected but lower than the median), and high exposure (median and above), were not associated with childhood obesity in infancy, early childhood, or middle childhood (Fig. 2).

3.3. BKMR OPE mixture results with childhood obesity

Five of the nine OPEs (BDCPP, DBUP/DIBP, DPHP, BCETP, and BBOEP), were detected in more than 60% of samples and were included in BKMR models (Infancy n = 3,166, Early Childhood n = 3,368, Middle Childhood n = 2,325). PIPs for individual OPEs across all age groups were generally similar (Supplemental Table S9). In middle childhood, BDCPP had the highest PIP suggesting a potentially greater contribution to the mixture than the other OPEs. Exposure-response function plots generated from BKMR analyses were similar to results of individual modeled OPEs. BKMR exposure–response function plots for middle childhood obesity depicted a curvilinear inverse association for BDCPP (Fig. 3), similar to the tertile analysis. Fig. 3 showed a relatively null association for DBUP/DIBP, BCETP and DPHP, and a suggestive positive association for BBOEP and obesity risk in middle childhood. For infancy, BDCPP, BBOEP, and BCETP exhibited suggestive positive associations with obesity risk, while DBUP/DIBP and DPHP suggested a null or flat association (Supplemental Figure S5). For early childhood obesity risk, DBUP/DIBP suggested an inverse association, whereas DPHP and BBOEP, indicated suggestive positive associations, and BDCPP and BCETP had flatter associations (Supplemental Figure S6). Bivariate exposure-outcome relations of one OPE exposure with childhood obesity showed mostly parallel lines and curves, showing little evidence of interaction between OPEs in the mixture in all age groups (Supplemental Figures S7–S9).

3.4. Associations of BDCPP, DBUP/DIBP, and DPHP with childhood obesity by child sex

When assessing whether child sex modified the association between gestational OPE exposure and childhood obesity across different age groups, potential differences by sex in some age groups were observed (Fig. 4). Among females, the second tertiles of both BDCPP and DPHP were associated with increased risk of obesity in infancy for (T2 vs. T1: 1.22; 95 % CI: 1.03, 1.44 and 1.23; 95 % CI: 1.06, 1.42, respectively). Among males these associations were decreased (BDCPP T2 vs. T1: 1.10; 95 % CI: 0.94, 1.28 and DPHP 0.98; 95 % CI: 0.82, 1.17). When modeling the metabolites continuously, a significant interaction by sex was detected in middle childhood for both BDCPP ($P_{interaction}$ = 0.02) and DPHP ($P_{interaction}$ = 0.01). Upon stratifying the models by child sex, BDCPP showed a slightly stronger inverse association with obesity risk in middle childhood (0.97 per doubling of exposure; 95 % CI: 0.95, 0.99) in boys than in girls (0.99 per doubling of exposure; 95 % CI: 0.98, 0.99). Similarly, for DPHP, sex-stratified models revealed a null association with risk of obesity in female children compared to lower risk in male children (females: 1.01 per doubling of exposure; 95 % CI: 0.97, 1.05; males: 0.96 per doubling of exposure; 95 % CI: 0.91, 1.01). No other significant interaction terms were observed with child sex at other age groups within continuous models (Supplemental Figure S10).

3.5. Sensitivity analysis for associations of OPEs and childhood obesity

In sensitivity analyses restricted to the 1,772 children who had BMI assessed in all three age groups considered in this study, results remained comparable to those obtained using all available data (Supplemental Figures S11–S13). When conducting leave-one-site-out sensitivity analyses to assess whether results were driven by individual ECHO study sites, the directions of associations remained consistent for metabolites at each age group (Supplemental Figure S14). Results also remained consistent across all models when the risk for obesity was assessed in comparison to normal weight (i.e., excluding children with overweight) and when the risk for overweight was assessed in comparison to normal weight (Supplemental Table S10).

4. Discussion

This study conducted an innovative investigation on in utero exposure to various OPEs measured in maternal urine during pregnancy and their associations with childhood obesity across different age groups, addressing an important but understudied public health issue. The study utilized data from the nationally representative and racially and ethnically diverse ECHO consortium in the US. Although gestational exposure to several OPE metabolites did not show strong evidence of association with childhood obesity, gestational exposure to DBUP/DIBP was associated with increased obesity risk whereas gestational exposure to the second tertile of BDCPP was associated with an inverse association with obesity risk in middle childhood. However, a non-monotonic dose–response relationships emerged for these metabolites. In addition, notably U-shaped and inverted U-shaped patterns with the child obesity risk were observed for DBUP/DIBP and BDCPP across the age groups. We also observed a small potential increase in risk of obesity in girls compared to boys for BDCPP and DPHP exposure. When assessing five OPEs concurrently through BKMR, no association with obesity at any age group was observed overall. However, the findings overall remained consistent with the directions observed in individual model assessments. Other studies looking at OPE exposures and childhood outcomes have detected non-linear inverted U-shaped relationships between gestational OPE exposure and neurobehavioral outcomes(Hernandez-Castro et al., 2023) and birth outcomes (Oh et al., Jan 2024). Further research is needed to elucidate the underlying mechanisms driving these non-linear associations and their implications for public health interventions targeting obesity and related metabolic disorders.

Prenatal exposure to OPEs may impact fetal programming, potentially contributing to health issues in childhood and adulthood, aligning with the Developmental Origins of Health and Disease (DOHaD) hypothesis (Haugen et al., 2015). While some early literature suggests prenatal OPE exposure may lead to lower infant birthweight, (Crawford et al., 2020; Luo et al., 2020; Luo et al., 2021) and gestational DBUP/DIBP exposure to higher odds of preterm birth and DPHP exposure with lower birthweight within the ECHO consortium (Oh et al., Jan 2024), little is known about their influence on long-term childhood weight and obesity. The only other longitudinal study known to date that assessed OPE exposure in pregnancy and childhood obesity was conducted by Chen et al. in a Shanghai, China population of 733 mother–child pairs, with obesity assessed at 0.5, 1.0, 4.0, and 6.0 years of age (Chen

et al., 2023). Of the eight OPE assessed during pregnancy, BBOEP and BDCPP, were also included in the current analysis. Median dilution-corrected values were higher in the ECHO pregnant population for BDCPP (0.11 μg/L) compared to the Shanghai population but slightly lower for BBOEP (0.06 μg/L). In the Chen et al. study, neither BDCPP nor BBOEP were significantly associated with the risk of obesity at any age but associations tended to be positive (Chen et al., 2023). However, Chen et al. found possible effect modification by breastfeeding duration for BDCPP, with those who were breastfed less than four months of age having an increased risk of obesity in early childhood compared to those who were breastfed longer (Chen et al., 2023). We were not able to assess possible effect modification by breastfeeding duration due to lack of data availability, however, this data is actively being collected as part of the ECHO-wide protocol and will allow assessment in the future. BKMR models for the full mixtures in Chen et al. supported the individual results and the overall OPE mixture tended to be associated with higher adiposity measures for BDCPP and BBOEP in the mixture.

A study using the National Health and Nutrition Examination Survey (NHANES: 2013–2014) assessed the cross-sectional relationships of five OPEs and childhood obesity among 784 children aged 6–19 years (Boyle et al., 2019). Overall, DPHP (median 1.43 μg/L), BCPP (median 0.20 μg/L), and BDCPP (median 1.56 μg/L) concentrations were higher in these children than in pregnant individuals in the present analysis, which spans a broader range of years (2006–2020). In NHANES, children's levels of BDCPP and DPHP had non-significant inverse associations with obesity. BCPP, which was only modeled as detected vs. non-detected, showed a non-significant positive association (Boyle et al., 2019). Given the cross-sectional design the authors speculated that OPEs potentially accumulating in adipose tissue (Sousa et al., 2023) could result in reduced urinary biomarker concentrations, potentially leading to the observed inverse association with childhood obesity (Boyle et al., 2019).

We are in the early stages of understanding the biological mechanisms linking OPE exposure to obesity. While laboratory investigations on OPEs and metabolic outcomes are scarce, existing evidence suggests potential links with adiposity. For instance, in vitro studies have indicated that OPEs like tributyl phosphate (TBUP) and tris(2-butoxyethyl) phosphate (TBOEP) exhibit high peroxisome proliferator-activated receptor gamma (PPARγ) ligand binding potential at high doses, indicating a possible role fetal programming and in promoting obesity development (Fang et al., 2015; Green et al., Mar 2017). Furthermore, animal studies have demonstrated that exposure to flame retardant mixtures containing OPEs during prenatal and early postnatal stages can lead to increased body weight in both male and female rats (Patisaul et al., 2013). Additionally, in vitro exposure to these mixtures has been shown to trigger adipocyte differentiation, suggesting a potential role of OPEs in adipogenesis (Pillai et al., 2014). The primary metabolite of Tris (1,3-dichloro-2-propyl) phosphate (TDCPP) is BDCPP, and TDCPP has shown sex-specific adiposity, fasting hyperglycemia, and insulin resistance in male mice (Tenlep et al., 2023). This study specifically found that TDCPP activated farnesoid X receptor (FXR) and pregnane X receptor (PXR), while it inhibited the androgen receptor (AR) (Tenlep et al., 2023). Cross-sectional epidemiologic studies in adults have found that higher levels of OPEs were associated with concurrent obesity, central obesity, hyperglycemia and metabolic

syndrome (Boyle et al., 2019; Hoffman et al., 2017; Li et al., 2024; Luo et al., 2020; Romano et al., 2017).

The present study has several strengths. It represents the largest investigation to date to assess the association between urinary OPE biomarkers measured during pregnancy and childhood obesity across multiple early life age groups, extending up to 10 years of age. Our study included a diverse sample, incorporating harmonized data from 14 pregnancy studies across the United States. This diversity not only captures geographic variation but also encompasses a wide range of sociodemographic backgrounds, including racial and ethnic identities and education levels. Furthermore, OPE biomarkers were measured by a single laboratory using standardized protocols, minimizing variability, and ensuring consistency in measurement across all study participants. This meticulous approach enhances the reliability and comparability of results, strengthening the validity of the study findings. We also had access to high-quality covariates of interest with relatively low missingness (<7%) that were harmonized across ECHO sites. We conducted Multiple Imputation by Chained Equations (MICE) for covariates to reduce the likelihood of introducing selection bias into our analysis, rather than running complete case models. Additionally, we utilized a clinically relevant endpoint of obesity to enhance the applicability of our findings in real-world settings. Our large sample size also allowed examination of associations by child sex, an important effect modifier. Finally, an innovative strength of the study was the evaluation of OPE mixtures using BKMR methods to account for OPEs concurrently, considering the simultaneous exposures encountered in real-life settings.

Our study also has certain limitations that may affect the interpretation of our findings. We recognize that OPEs are rapidly metabolized in the body, (Hou et al., 2020) and our study only included one measurement per participant across two trimesters in pregnancy. OPE exposures may fluctuate throughout pregnancy and thus a single measurement may not accurately capture an individual's typical exposure levels, we were also unable to determine the influence of OPE exposure in early pregnancy which may have a stronger influence on fetal programming (Haugen et al., 2015). However, reproducibility, as measured by interclass correlations, of certain OPEs across pregnancy have been moderate to high (Romano et al., 2017; Hoffman et al., 2014). Future studies should include numerous timepoints in pregnancy for urine collection and prioritize early pregnancy. Furthermore, although our study included a wide range of OPEs, examined in previous epidemiologic literature, some were not measured as there are 12 established and characterized OPEs and upwards of 83 emerging OPEs (Ye et al., 2023), which may have implications for the comprehensiveness of our analysis and the potential for associations with unmeasured OPEs that may influence childhood obesity risk. Despite our efforts to adjust for potential confounding variables, as in all observational studies, there remains the possibility of residual confounding from unmeasured or inadequately controlled factors that may influence the association between gestational OPE exposure and childhood obesity such as diet exposures or breastfeeding. However common covariates included in previous studies on OPE exposure in pregnancy and obesity were also included in this assessment. There may also be effect modification and mitigation of this association by healthy eating and physical activity during childhood, which should be explored in future studies given their role in obesity. The assessment of childhood obesity was conducted at various time points during

early life age groups, which allows for the examination of obesity trends over time but may not capture changes in obesity status beyond the assessed time points. Finally, our sample size varied across age groups, due to children not being old enough to be included in the sample or loss to follow-up within ECHO study sites. However, results were consistent when limiting analyses to children with measurements at all age groups.

5. Conclusions

We found limited evidence of associations between gestational exposure to the OPEs assessed in this study and childhood obesity risk. Associations also varied in direction, as gestational exposure to DBUP/DIBP was associated with an increased obesity risk, whereas gestational exposure to BDCPP showed an inverse association with obesity risk in middle childhood. Overall, our findings suggest a complex interplay between gestational OPE exposure and childhood obesity. Future research should aim to assess a broader range of OPE metabolites, employ mixture analyses, and focus on populations with known elevated exposures. It should also include greater coverage of exposure across gestation, repeated measurements during pregnancy, and mechanistic animal studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The authors do not have permission to share data.

Abbreviations:

OPEs	Organophosphate esters
PBDEs	polybrominated diphenyl ethers
EDCs	Endocrine-disrupting chemicals
HIPAA	Health Insurance Portability and Accountability Act
ECHO	Environmental influences on Child Health Outcomes
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
DPHP	Bis-(2-propylheptyl)-phthalate
DPRP	dipropyl phosphate
DBUP/DIBP	composite of dibutyl phosphate and di-isobutyl phosphate
LOD	limit of detection
MICE	multiple imputation by chained equations
BKMR	Bayesian kernel machine regression
BMI	Body mass index

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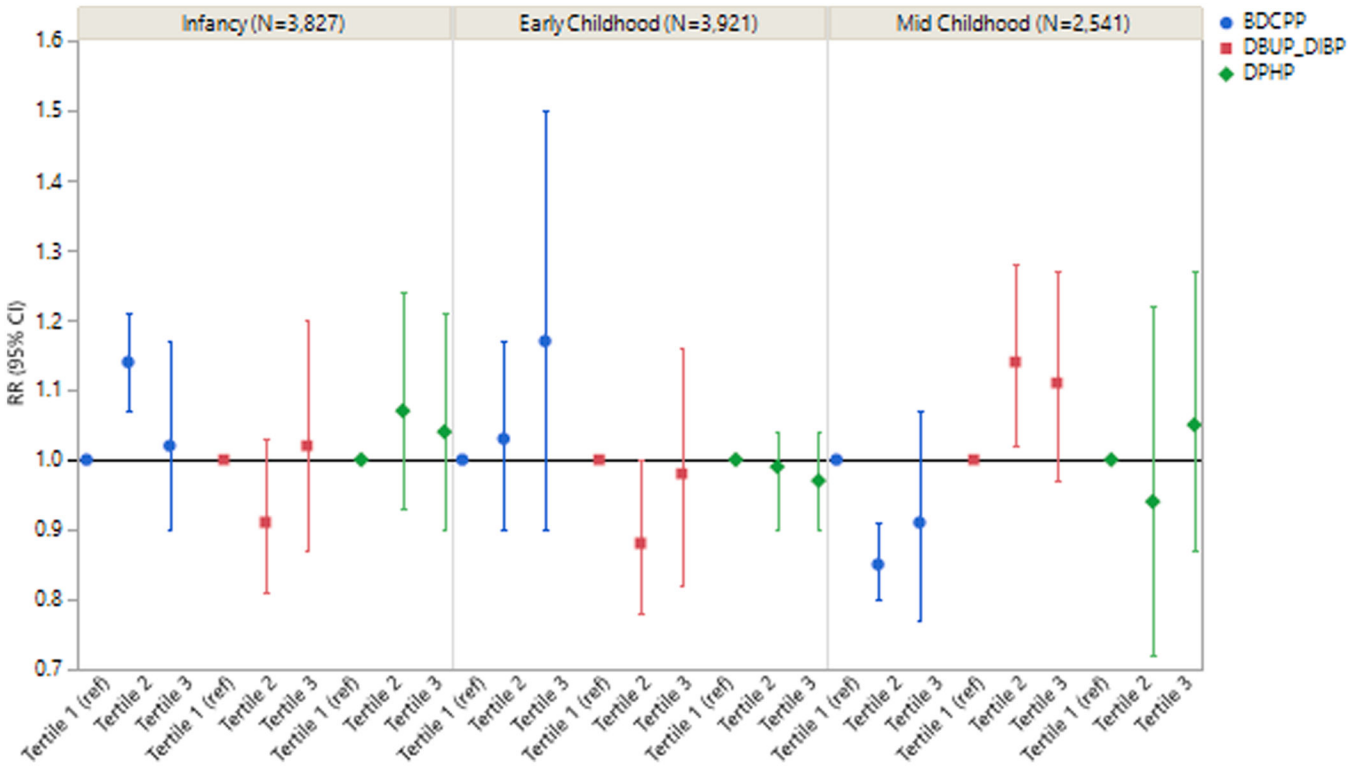

Fig. 1.

Adjusted associations of gestational BDCPP, DBUP/DIBP, and DPHP tertiles with childhood obesity in infancy, early childhood and middle childhood. Note: Regression models reflect multiple imputation by chained equations (MICE) for covariates and were adjusted for urinary dilution, ECHO site, maternal age at birth, maternal race/ethnicity, maternal educational attainment, pre-pregnancy BMI, maternal smoking in pregnancy, parity, and child's year of birth. Infancy 0.5–1.9 years, Early Childhood 2.0–4.9 years, Middle Childhood 5.0–10.0 years. Obesity defined ≥ 95th percentile. DPHP, diphenyl phosphate; DBUP/DIBP, composite of dibutyl phosphate and di-isobutyl phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate.

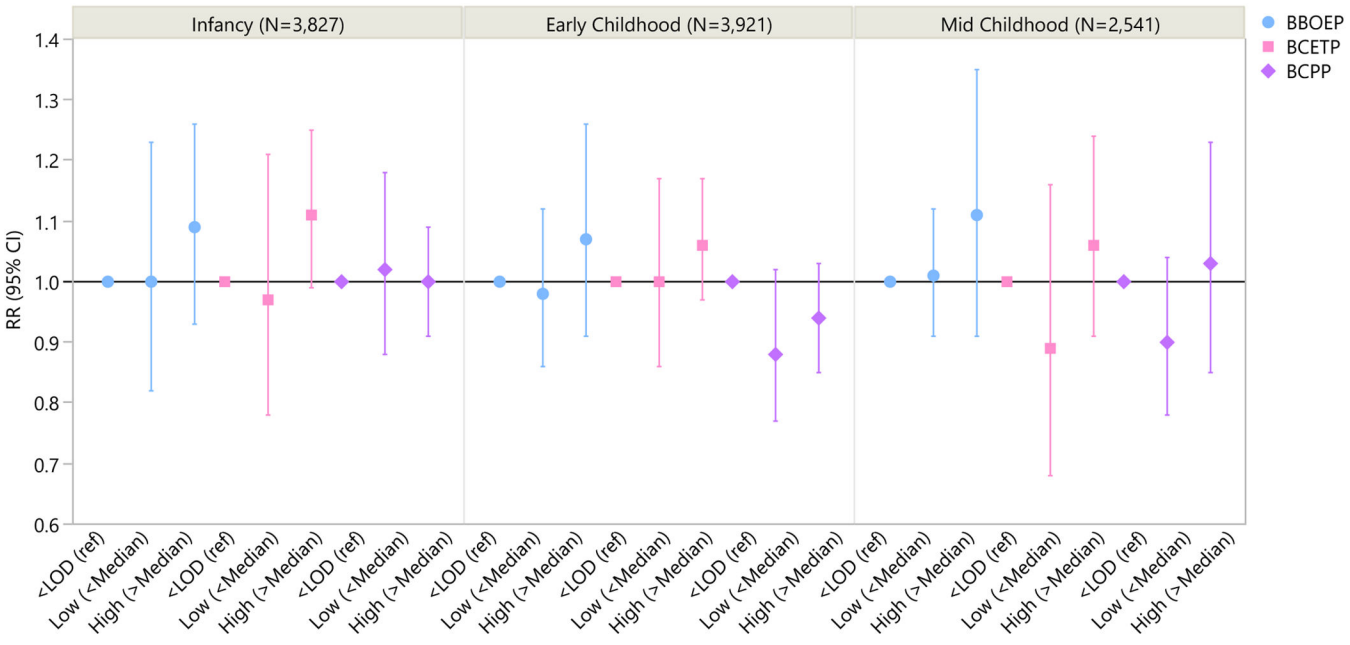

Fig. 2.

Adjusted associations of gestational BBOEP, BCETP, and BCPP with childhood obesity in infancy, early childhood and middle childhood. Note: Regression models reflect multiple imputation by chained equation (MICE) for covariates and were adjusted for urinary dilution, ECHO site, maternal age at birth, maternal race/ethnicity, maternal educational attainment, pre-pregnancy BMI, maternal smoking during pregnancy, parity, and child's year of birth. Infancy 0.5–1.9 years, Early Childhood 2.0–4.9 years, Middle Childhood 5.0–10.0 years. Obesity defined ≥ 95th percentile. BCETP, bis(2-chloroethyl) phosphate; BBOEP, bis(butoxyethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; LOD Limit of Detection. <LOD (value not detected), Low Exposure (Detected but less than median), High Exposure (Median and above).

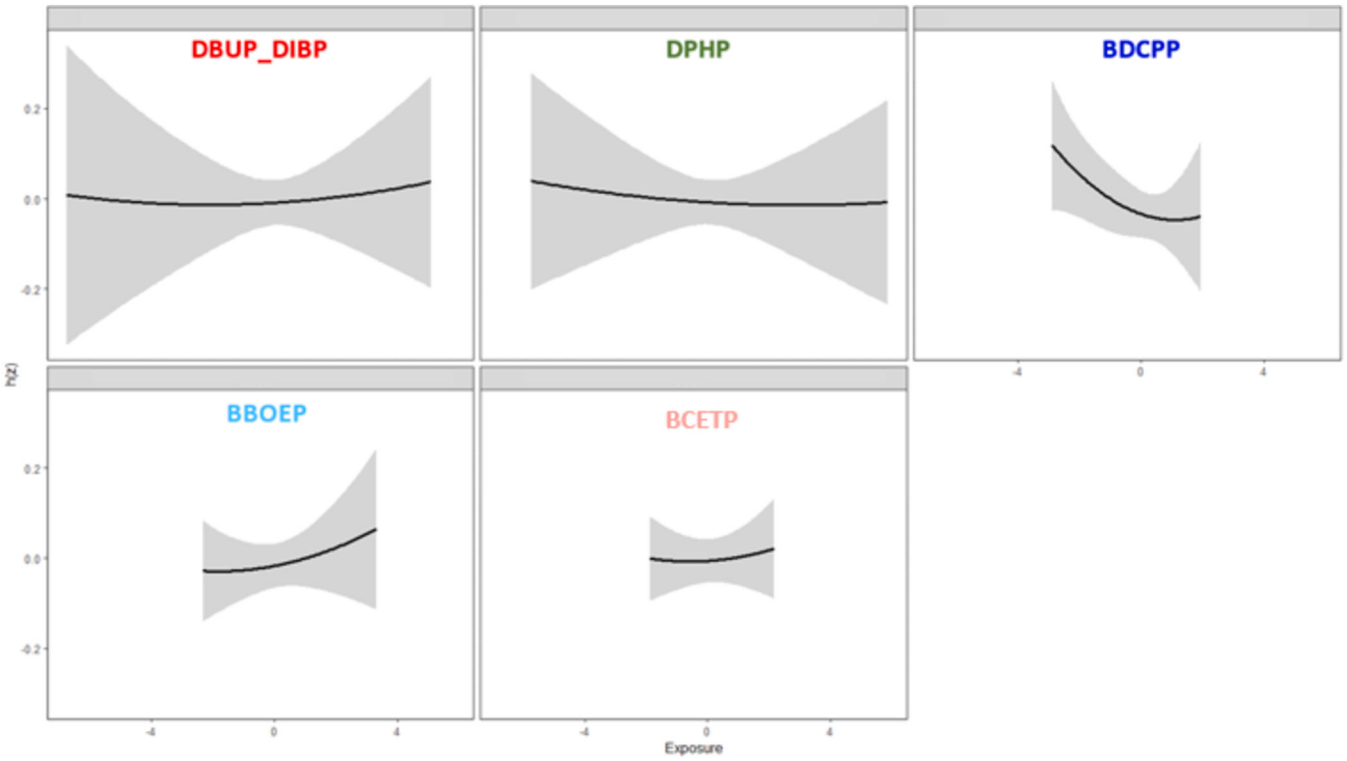

Fig. 3.

Exposure response function for each organophosphate esters (OPE) from Bayesian kernel machine regression models in middle childhood.

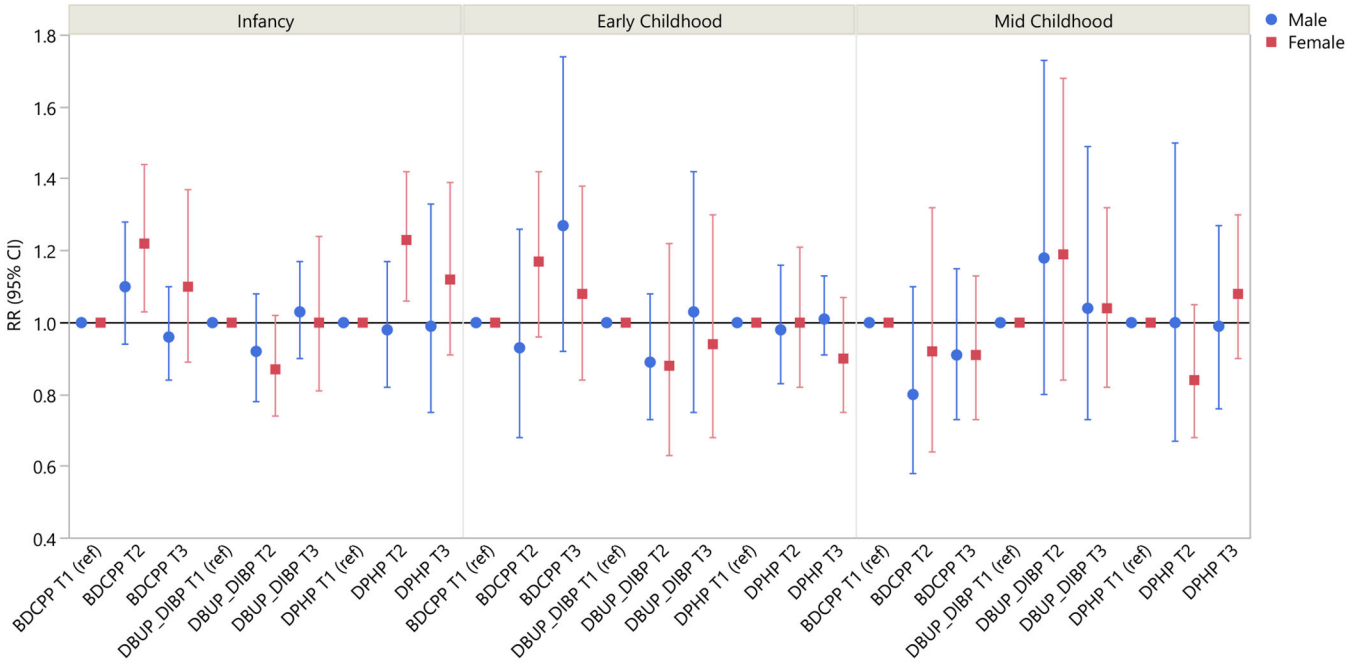

Fig. 4.

Adjusted associations of gestational BDCPP, DBUP/DIBP, and DPHP tertiles with childhood obesity in infancy, early childhood and middle childhood by child sex. Note: Regression models reflect multiple imputation by chained equations (MICE) for covariates and were adjusted for urinary dilution, ECHO site, maternal age at birth, maternal race/ethnicity, maternal educational attainment, pre-pregnancy BMI, maternal smoking in pregnancy, parity, and child's year of birth. Infancy 0.5–1.9 years, Early Childhood 2.0–4.9 years, Middle Childhood 5.0–10.0 years. Obesity defined ≥ 95th percentile. DPHP, diphenyl phosphate; DBUP/DIBP, composite of dibutyl phosphate and di-isobutyl phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate. T = Tertile.

Table 1

Characteristics of 5,087 mother–child pairs participating in the Environmental influences on Child Health Outcomes (ECHO) program in the full sample and by age groups.

Characteristic	Full Sample N = 5,087 n(%)	Infancy 0.5–1.9 yrs N = 3,827 n (%)	Early Childhood 2.0–4.9 yrs N = 3,921 n (%)	Mid Childhood 5.0–10.0 yrs N = 2,541 n (%)
Maternal age, years				
Mean (SD)	30.2 (5.7)	30.1 (5.7)	30.2 (5.6)	30.1 (5.6)
<25	912 (17.9)	676 (17.7)	693 (17.7)	437 (17.2)
25–29	1266 (24.9)	994 (26.0)	992 (25.3)	674 (26.5)
30–34	1694 (33.3)	1282 (33.5)	1328 (33.9)	860 (33.8)
>=35	1215 (23.9)	875 (22.9)	908 (23.2)	570 (22.4)
Maternal education				
High school degree, GED, or equivalent or lower	1490 (29.3)	1163 (30.4)	1150 (29.3)	619 (24.4)
Some college, no degree	821 (16.1)	606 (15.8)	603 (15.4)	402 (15.8)
Bachelor's	1324 (26.0)	998 (26.1)	1032 (26.3)	741 (29.2)
Master's and above	1155 (22.7)	794 (20.7)	915 (23.3)	598 (23.5)
Missing	297 (5.8)	266 (7.0)	221 (5.6)	181 (7.1)
Maternal race and ethnicity				
Non-Hispanic Asian	264 (5.2)	208 (5.4)	227 (5.8)	114 (4.5)
Non-Hispanic Black	1030 (20.2)	816 (21.3)	894 (22.8)	581 (22.9)
Hispanic All	970 (19.1)	744 (19.4)	600 (15.3)	230 (9.1)
Non-Hispanic Multiple Race	153 (3.0)	111 (2.9)	129 (3.3)	101 (4.0)
Non-Hispanic Other	40 (0.8)	19 (0.5)	33 (0.8)	21 (0.8)
Non-Hispanic White	2606 (51.2)	1908 (49.9)	2029 (51.7)	1484 (58.4)
Missing	24 (0.5)	21 (0.5)	9 (0.2)	10 (0.4)
Pre-pregnancy body mass index, kg/m^2				
Mean (SD)	26.9 (6.7)	27.1 (6.9)	27.0 (6.8)	27.1 (6.9)
Underweight, < 18.5	151 (3.0)	122 (3.2)	123 (3.1)	74 (2.9)
Normal Weight, 18.5–24.9	2185 (43.0)	1619 (42.3)	1678 (42.8)	1106 (43.5)
Overweight, 25.0–29.9	1264 (24.8)	929 (24.3)	976 (24.9)	640 (25.2)
Obese ≥ 30.0	1255 (24.7)	992 (25.9)	987 (25.2)	663 (26.1)
Missing	232 (4.6)	165 (4.3)	157 (4.0)	58 (2.3)
Parity				
Nulliparous	2226 (43.8)	1661 (43.4)	1735 (44.2)	113 (44.6)
Multiparous	2713 (53.3)	2055 (53.7)	2115 (53.9)	1391 (54.7)
Missing	148 (2.9)	110 (2.9)	71 (1.8)	17 (0.7)
Any tobacco use during pregnancy				
No	4383 (86.2)	3249 (84.9)	3380 (86.2)	2296 (90.4)
Yes	350 (6.9)	279 (7.3)	289 (7.4)	239 (9.4)
Missing	354 (7.0)	300 (7.8)	252 (6.4)	6 (0.2)
Infant sex				

Characteristic	Full Sample N = 5,087 n(%)	Infancy 0.5–1.9 yrs N = 3,827 n (%)	Early Childhood 2.0–4.9 yrs N = 3,921 n (%)	Mid Childhood 5.0–10.0 yrs N = 2,541 n (%)
Female	2490 (48.9)	1786 (46.7)	1935 (49.3)	1264 (49.7)
Male	2597 (51.1)	2041 (53.3)	1986 (50.7)	1277 (50.3)
Year of birth				
Median (IQR)	2012 (2010–2016)	2012 (2010–2016)	2012 (2010–2015)	2011 (2010–2013)
2006–2010	1466 (28.8)	1255 (32.8)	1272 (32.4)	924 (36.4)
2011–2015	2310 (45.4)	1441 (37.7)	1845 (47.1)	1495 (58.8)
2015–2020	1311 (25.8)	1131 (29.6)	804 (20.5)	122 (4.8)
Child mean age, years	N/A	1.0 (0.3)	3.2 (1.0)	7.5 (1.5)
Child BMI				
Underweight	N/A	76 (2.0)	111 (2.8)	46 (1.8)
Normal	N/A	2304 (60.2)	2591 (66.1)	1656 (65.2)
Overweight	N/A	661 (17.3)	607 (15.5)	397 (15.6)
Obese	N/A	786 (20.5)	612 (15.6)	442 (17.4)

Note: Weight distributions and age cannot be provided for the entire sample as some children may be represented in only certain age groups or in all age groups of outcome assessment. If > 1 BMI was available, the highest after cleaning was used for analysis. Child BMI: Underweight less than 5th percentile, Normal Weight 5th percentile to less than the 85th percentile, Overweight 85th percentile to less than the 95th percentile, Obesity 95th percentile or greater.

Table 2

Organophosphate esters (OPEs) limit of detection and urinary concentrations of OPEs across percentiles among 5,087 pregnant women in the Environmental influences on Child Health Outcomes (ECHO) consortium.

Analyte	LOD µg/L	Percent above LOD	5th µg/L	25th µg/L	50th µg/L	75th µg/L	95th µg/L
DBUP_DIBP	0.04	95.7	0.07	0.12	0.19	0.3	0.87
DPHP	0.03	99.5	0.26	0.55	0.92	1.82	8.51
BDCPP	0.02	86.9	ND	0.34	0.89	1.75	5.31
BCPP	0.02	51.6	ND	ND	0.08	0.74	3.34
BCETP	0.02	68.9	ND	ND	0.52	1.66	9.04
BBOEP	0.02	66.1	ND	ND	0.05	0.09	0.25
BMPP	0.01	35.5	ND	0.01	ND	0.03	0.13
BEHP	0.02	29.8	ND	ND	ND	0.04	0.54
DPRP	0.03	25.6	ND	ND	ND	0.03	0.33

ND = Not Detected, LOD = Limit of Detection