Eco-Environment & Health 2 (2023) 152–160

Contents lists available at ScienceDirect

Eco-Environment & Health

journal homepage: www.journals.elsevier.com/eco-environment-and-health

Original Research Article

Sex-specific effects of organophosphate ester exposure on child growth trajectories in the first two years

Hang Wang [a,b,1], Liyi Zhang [a,b,1], Jie Wu [c], Pengpeng Wang [a,b], Qiang Li [a,b], Xinyao Sui [a,b], Yaqi Xu [a,b], Yue Zhao [a,b], Yang Liu [a,b], Yunhui Zhang [a,b,*]

[a] Key Lab of Health Technology Assessment, National Health Commission of the People's Republic of China (Fudan University), Shanghai 200032, China
[b] Key Laboratory of Public Health Safety, Ministry of Education, School of Public Health, Fudan University, Shanghai 200032, China
[c] The Maternal and Child Healthcare Hospital of Songjiang District, Shanghai 201600, China

ARTICLE INFO

Keywords:
Organophosphate esters
Child growth trajectories
Sex-specific effects
Birth cohort

ABSTRACT

The connections between urinary organophosphate ester (OPE) metabolites and child growth have been identified in prior research, but there is currently a dearth of epidemiological evidence regarding the sex-specific impact of OPEs on child growth trajectories. This study enrolled 804 maternal–child pairs, and five OPE congeners were quantified in maternal serum during pregnancy. In this study, the impact of prenatal OPE exposure on child growth trajectories was assessed using linear mixed-effect models and a group-based trajectory model (GBTM), with consideration given to sex-specific effects. Fetuses were frequently exposed to OPEs in utero, and tris(2-butoxyethel) phosphate (TBEP) exhibited the highest concentration levels in maternal serum. Among male children, an increase of 2.72 ng/g lipid in TBEP concentration was associated with a 0.11-unit increase in head circumference-for-age z-score (HCAZ), and the effect was mainly concentrated at 1 and 2 months of age. Among female children, an increase of 2.72 ng/g lipid in tris(2-chloro-1-(chloromethyl) ethyl) phosphate (TDCPP) concentration was associated with a 0.15-unit increase in length-for-age z-score (LAZ) and a 0.14-unit increase in weight-for-age z-score (WAZ), and the effects were mainly concentrated at 9 months of age. For HCAZ trajectories, higher prenatal TBEP exposure was associated with higher odds for the fast growth group in male children. For the LAZ and WAZ trajectories, higher prenatal TDCPP exposure was associated with higher odds for the fast growth group in female children. The trajectory analysis approach provided insight into the complex associations between OPE exposure and child growth.

1. Introduction

The phasing out of brominated flame retardants (BFRs) in numerous countries has resulted in an increase in the usage and production of organophosphate esters (OPEs). The physical addition of OPEs to consumer products facilitates their escape and entry into the environment [1]. Consequently, OPEs can be found in different environmental media, such as surface water [2], indoor dust [3–5], and air [6], with a high frequency of occurrence. Human exposure to OPEs can occur through ingestion, inhalation, and epidermal adsorption, leading to their entry into the body [7–9]. In addition to being detected in serum, OPEs have been found in the placenta, uterine decidua, and amniotic fluid [2,10,11]. These chemicals have the ability to pass through the placental barrier and impact offspring growth, as indicated.

The first two years of life is a crucial time for individual growth and development, and is important for programming long-term health and disease [12–14]. Previous toxicological and epidemiological studies have suggested that prenatal OPE exposure may be associated with decreased birth outcomes and an increased risk of childhood overweight or adiposity [15–22]. One toxicological study revealed that rats exposed to triphenyl phosphate (TPHP) during pregnancy showed earlier onset of type 2 diabetes and increased fat accumulation [15]. Another study in the United States found that early-life exposure to OPEs in rats affected serum thyroxine levels and resulted in weight gain in female rats [16]. Evidence from the National Health and Nutrition Examination Survey

* Corresponding author.
E-mail address: yhzhang@shmu.edu.cn (Y. Zhang).
[1] These authors contribute to this work equally.

https://doi.org/10.1016/j.eehl.2023.07.003
Received 4 May 2023; Received in revised form 29 June 2023; Accepted 10 July 2023
Available online 15 July 2023

indicated that OPEs are related to adiposity indicators among children [17]. In China, a previous birth cohort study found that OPE exposure during pregnancy altered obesity markers, but the effect was attenuated if breastfeeding lasted for more than four months [19]. Yang et al. reported that prenatal OPE exposure was linked to increased z-scores for weight, length, and head circumference in all 4-week-old children [18]. However, most of the existing research on the correlation between OPE metabolites and child growth was predominantly reliant on urine samples or limited to a single measurement of OPEs taken in early pregnancy. It is challenging to identify and utilize typical urinary OPE metabolites as exposure biomarkers, given the expanding variety of OPEs and the possibility that each OPE may have multiple metabolites [23]. Therefore, the concentrations of OPEs in blood are better suited for representing patterns of exposure and transient changes in humans.

As a result of the OPEs' short half-life [24,25], a single measurement of OPEs during pregnancy may not be a precise indicator of the mother's average prenatal exposure to OPEs. Despite the considerable amount of research on the effects of prenatal OPE exposure on birth size or adiposity during infancy and later stages of childhood, the association between OPEs and physical development remains uncertain. Furthermore, previous investigations have predominantly relied on static anthropometric assessments, which fail to provide insights into dynamic patterns of growth. The diversity observed in the growth patterns during early life necessitates a more nuanced approach, where the variations are captured through the identification of multiple distinctive trajectories, rather than relying on a single average growth pattern. Various studies have suggested that environmental stress experienced during pregnancy affects the growth trajectories of children after birth and is not solely associated with developmental indicators at a particular age [26–28]. For instance, a study examined the effect of prenatal phthalate (PAE) exposure on body mass index (BMI) trajectories in children, and the results showed that distinct PAE congeners had differing associations with BMI growth trajectories in boys and girls [26]. Another study in China discovered that prenatal air pollution exposure affected child growth trajectories, with a greater impact on girls [27]. Therefore, to explore the influence of prenatal OPE exposure on child growth, it is necessary to consider the growth trajectory pattern.

The effects of OPEs on children's health may differ depending on sex. For instance, Luo et al. discovered that exposure to diphenyl phosphate (DPHP) increased the likelihood of low birth weight exclusively among female neonates [21], whereas another study did not reveal any sex-specific positive relationships between OPEs and birth weight [22]. Possible explanations include differences in the endocrine systems of males and females during early life, placental barriers, and maternal nutritional status [29,30]. While recent research has observed links between urinary OPE metabolites and child growth, there is relatively less epidemiological evidence regarding the effects of serum OPE concentrations, especially the sex-specific impacts, on evolving child growth trajectories.

We conducted a birth cohort study in China to evaluate serum OPE concentrations during pregnancy and to measure child growth parameters on a recurring basis from 1 to 24 months of age. Our objective was to examine the sex-specific relationships between OPE exposure during pregnancy and child growth, as well as to investigate its effects on child growth trajectories.

2. Materials and methods

2.1. Study population

The Shanghai Maternal–Child Pairs Cohort (MCPC) is a birth cohort study designed to explore the effects of environmental exposures, lifestyle factors, and psychological stress during pregnancy on the health outcomes of both mother and child.

Pregnant women aged 20–44 years old (n = 6,782) were enrolled in the MCPC study between 2016 and 2018. To be eligible for inclusion in the study, women had to be aged 20 or older and have resided in Shanghai for a minimum of one year before pregnancy. The exclusion criteria for this study included preexisting chronic diseases such as hypertension, diabetes, and heart disease among women. Following the exclusion of individuals who were lost to follow-up or experienced pregnancy losses through miscarriage or stillbirth, a total of 6,599 pregnant women who successfully delivered live births were included in the study. The presence of multiple gestation (involving more than one fetus) and a maternal medical history of chronic conditions can significantly impact both prenatal and postnatal growth. Consequently, pregnant women diagnosed with multiple gestation, preexisting diabetes, or cardiovascular disorders prior to enrollment were omitted from the study, resulting in a final cohort of 6,154 individuals. Then, we used stratified random sampling in the study population, grouping the study population according to the time it entered the cohort, and sampling the same proportion in each group. Finally, 1,069 pregnant women were selected. We additionally excluded children who missed at least five follow-up visits, spanning from 1 to 24 months of age (n = 265, see flowchart in Fig. S1). We compared baseline data between the included population (804 mother–newborn pairs) and the total population (1,069 mother–newborn pairs), and the results showed that there was no significant difference in baseline characteristics (Table S1). A total of 2,304 maternal serum samples were collected during pregnancy, and follow-up visits were conducted to obtain anthropometric measurements from children at 1, 2, 4, 6, 9, 12, 18, and 24 months of age.

At recruitment and each follow-up visit, all participating mothers provided informed consent for themselves and their children. The ethics committee of Fudan University approved the study (IRB#2016-04-0587).

2.2. Assessment of OPE exposure

Samples of maternal serum were obtained at approximately 17.82 ± 4.67 weeks, 22.74 ± 1.62 weeks, and 32.76 ± 4.74 weeks of gestation, and subsequently stored at −80 °C until they were analyzed. In this study, we specifically chose to examine five commonly detected OPEs suspected of causing developmental toxicity and produced in high volumes by industry. These OPEs include tributyl phosphate (TBP), tris(2-butoxyethyl) phosphate (TBEP), 2-ethylhexyl diphenyl phosphate (EHDPP), tris(2-chloro-1-(chloromethyl) ethyl) phosphate (TDCPP), and tri-m-cresyl phosphate (TMCP).

Liquid–liquid extraction was used for sample preparation. In summary, our process involved extracting 100 μL of serum, which was previously thawed and mixed, and subsequently transferring it to a centrifuge tube. We then added 2 mL of buffer solution, 1 mL of 0.50 mol/L tetrabutylammonium hydrogen sulfate, and a solution of mixed internal standards to the extracted sample. The sources of the standard chemicals used in this study have been described previously [31]. After adding 8 mL of methyl tertiary butyl ether and shaking the mixture, it was centrifuged for 2 min at 4,500 rpm and 20 °C. The lipid supernatant obtained was then transferred to a fresh centrifuge tube and dried in a water bath at 40 °C under nitrogen gas. The process was carried out to remove any remaining solvent in the sample. The residue was dissolved in methanol before sonication. Finally, the mixture was subjected to centrifugation at 4,500 rpm and 20 °C for 1 min prior to instrumental analysis. Quantification of serum OPE concentrations was performed using ultra-performance liquid chromatography tandem mass spectrometry (UPLC–MS/MS) analysis. The ACQUITY UPLC I-Class system (Waters, Milford, MA, USA) equipped with a Betasil C18 column (2.1 mm × 100 mm, 3 μm, Waters) was used for the separation of the targeted compounds, including TBP, TBEP, EHDPP, TDCPP, and TMCP. Detection was carried out using a QTRAP 6500+ Triple Quadrupole mass spectrometer (Scientific Export, Redwood City, CA). As part of the quality control process, a blank control sample (100 μL ultra-pure water) was added to each group of 28 samples, and standards were added to the blank samples to minimize the impact of environmental or human

factors. No target chemicals were detected in procedural blanks above the limits of detection (LOD). The recovery rates of OPEs were 69.0%–118.9%. The LODs for the OPEs were: 0.020 ng/mL for TBP, 0.210 ng/mL for TBEP, 0.030 ng/mL for EHDPP, 0.070 ng/mL for TDCPP, and 0.010 ng/mL for TMCP. The concentrations below the LOD were replaced by half of the LOD.

For this study, we measured total cholesterol and triglycerides using commercial reagents (Boehringer Mannheim, Germany) and a Hitachi 911 Chemistry Analyzer. The total lipid contents were calculated, and OPE dilution was corrected [32]. Concentrations of OPEs were reported as measured concentrations (μg/L) and lipid-adjusted values (ng/g lipid).

2.3. Measurement of child growth parameters and child growth trajectories

Professional pediatricians measured the weight (in kilograms), body length (in centimeters), and head circumference (in centimeters) of the children at community hospitals during follow-up visits at 1, 2, 4, 6, 9, 12, 18, and 24 months of age. BMI was obtained by dividing the weight in kilograms by the square of the height in meters. The z scores of BMI for age (BMIZ), head circumference for age (HCAZ), length for age (LAZ), weight for age (WAZ) and weight for length (WLZ) were calculated using the WHO Child Growth Standards (https://www.who.int/toolkits/child-growth-standards/standards).

2.4. Covariates

Self-reported data on maternal or child characteristics and behaviors were obtained from the mothers during pregnancy or follow-up visits, including: maternal education (middle school and below, high school, college, university and above), annual household [<10 ten thousand Yuan/year, (10–30) ten thousand Yuan/year, >30 ten thousand Yuan/year], and passive smoking during pregnancy through first follow-up questionnaire (yes or no), breastfeeding through two-year-old children follow-up questionnaire (yes or no), and physical activity levels during pregnancy through International Physical Activity Questionnaire (mild, moderate, severe). Other important covariates were obtained from hospital medical records, including maternal and paternal age (continuous, years), parity (nulliparous, multiparous), preterm birth (yes or no), child sex (male, female), gestational weight gain (GWG, continuous, kg), gestational diabetes mellitus (GDM, yes or no), birth weight (continuous, g), and birth length (continuous, cm). Breastfeeding duration and follow-up time were documented at follow-up (1, 2, 4, 6, 9, 12, 18, and 24 months of age). The prepregnancy BMI was determined by utilizing the self-reported weight prior to pregnancy and the maternal height (measured by a stadiometer).

2.5. Statistical analysis

Demographic information was analyzed using descriptive statistics. Continuous variables are presented as the mean ± SD, while categorical variables are presented as n (%). Prenatal OPE exposure was assessed by the mean OPE concentrations in maternal serum collected during the three follow-up visits. Below LOD OPE concentrations were replaced by half of the LOD. All OPE concentrations were subjected to the Shapiro–Wilk test to assess normality, and were transformed using natural logarithm due to skewed distribution. The characteristics of participants and child growth parameters between male and female children were compared using the Mann–Whitney U test.

First, linear mixed effects models were employed to investigate the relationship between serum OPE concentrations and child growth parameters, taking into account the multiple measurements within the same individual. We conducted multivariable linear regression analyses to assess the cross-sectional relationships between OPE exposure and child growth parameters at 1, 2, 4, 6, 9, 12, 18, and 24 months of age.

Second, the group-based trajectory model (GBTM) was used to identify the child growth trajectories in the first two years of life [33]. GBTM, a semiparametric approach used in longitudinal studies [33], is a statistical method that focuses on the individual and models the heterogeneity of change over time, enabling the identification of distinct subgroups of people who exhibit similar patterns of growth trajectories. Model selection was assessed based on the Bayesian information criterion (BIC), and average posterior probabilities (AvePP). The number of trajectories was determined using BIC and AvePP [34,35]. Furthermore, the group should have a minimum sample size of 5% of the population. The lower BIC absolute values indicate a better model fit. An AvePP of ≥0.70 was defined as appropriate. Table S2 and Table S3 display the fits of the GBTM models, specifically the parameters. Then, we determined the trajectory shapes that best described the observed trajectories. Linear, quadratic, cubic, and quartic functions were all tried out. Finally, the cubic function was selected to describe the trajectory shape. Upon determining the optimal quantity of trajectory clusters and the appropriate shape for each cluster, we graphically displayed the trajectories corresponding to each measurement and identified the group demonstrating moderate growth as the reference category.

Then, we obtained a new outcome variable through the GBTM model—the child growth trajectory group. We found that BMIZ, HAZ, LAZ, WAZ, and WLZ were the best fit into two categories (moderate growth and fast growth). Next, employing multivariable logistic regression models, we examined the correlation between prenatal OPE exposure and the various trajectory groups while accounting for potential confounding factors through adjustment. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Additionally, the concentrations of OPEs underwent a natural logarithm-transformed and were incorporated into the regression models as a continuous variable. Consequently, the estimated effect was interpreted as that a unit increase in prenatal OPE concentrations was associated with increasing the risk of fast growth group in children.

To conduct sensitivity analyses, we excluded pregnant women who delivered before 37 weeks of gestation and nonbreastfed children. We employed a Benjamini–Hochberg false discovery rate (FDR) correlation to address the issue of multiple comparisons. We considered the following covariates in our analyses: maternal age, prepregnancy BMI, breastfeeding (yes or no), breastfeeding duration, maternal education, annual household income, children's age at follow-up (months), preterm birth, birth weight, birth length, and parity. The GBTM was performed using the "traj" plugin in STATA. All other statistical analyses were performed using R software (version R 4.1.1).

3. Results

3.1. Participant characteristics and child growth parameters

This study enrolled 804 mother–child pairs, comprising 422 male children and 382 female children. Table 1 shows the baseline characteristics of male and female children. The two groups were closely matched on maternal age (29.07 ± 4.34 years in the male child group vs. 29.26 ± 4.29 years in the female child group). The mean pre-pregnancy BMI was 21.52 ± 3.05 kg/m^2 for the male child group and 21.46 ± 2.94 kg/m^2 for the female child group. There was no significant difference in maternal education level, annual household income, parity, birth length, or duration of breastfeeding. The Mann–Whitney U test showed that there were significant differences in preterm birth and birth weight. At 1, 2, 4, 6, and 12 months of age, male and female children exhibited significant differences in body length, body weight, and head circumference, as well as in BMIZ, WAZ, and WLZ (Table S4 and Table S5). The physical growth curve for children aged 1–24 months is presented in Figs. S2 and S3.

3.2. Serum concentrations of OPEs

Fig. S4 displays how the concentrations of OPEs were distributed across the first, second, and third follow-ups. Table 2 shows the

Table 1
Characteristics of participants (n = 804).

Participants characteristics	Total	Male children (n = 422)	Female children (n = 382)	*P value*
Age of delivery	29.16 ± 4.31	29.07 ± 4.34	29.26 ± 4.29	0.494
Paternal age	30.35 ± 4.80	30.38 ± 4.88	30.32 ± 4.72	0.991
Pre-pregnancy BMI (kg/m^2)	21.48 ± 2.98	21.52 ± 3.05	21.46 ± 2.94	0.976
Gestational weight gain (kg)	13.76 ± 5.34	13.95 ± 5.17	13.69 ± 5.44	0.482
Gestational diabetes mellitus				
Yes	143 (17.79%)	81 (19.19%)	62 (16.23%)	0.272
No	661 (82.21%)	341 (80.81%)	320 (83.77%)	
Maternal education level				
Middle school and below	46 (5.72%)	25 (5.92%)	21 (5.50%)	0.937
High school	112 (13.93%)	59 (13.98%)	53 (13.87%)	
College	293 (36.44%)	157 (37.20%)	136 (35.60%)	
University and above	353 (43.91%)	181 (42.90%)	172 (45.03%)	
Annual household income (ten thousand Yuan/year)				
<10	195 (24.25%)	98 (23.22%)	97 (25.39%)	0.700
10–30	539 (67.04%)	285 (67.54%)	254 (66.49%)	
>30	70 (8.71%)	39 (9.24%)	31 (8.12%)	
Passive smoking during pregnancy				
Yes	197 (24.50%)	97 (22.99%)	100 (26.18%)	0.293
No	607 (75.50%)	325 (77.01%)	282 (73.82%)	
Physical activity during pregnancy				
Mild	163 (20.27%)	89 (21.09%)	74 (19.37%)	0.780
Moderate	636 (79.01%)	330 (78.20%)	306 (80.10%)	
Severe	5 (0.62%)	3 (0.71%)	2 (0.53%)	
Parity				
1	469 (58.33%)	241 (57.11%)	228 (59.69%)	0.459
>1	335 (41.67%)	181 (42.89%)	154 (40.31%)	
Preterm birth (gestation age <37 weeks)				
Yes	32 (3.98%)	24 (5.69%)	8 (2.09%)	**0.009***
No	772 (96.02%)	398 (94.31%)	374 (97.91%)	
Birth weight (g)	3,327.66 ± 429.09	3,355.47 ± 435.80	3,296.94 ± 419.98	**0.014***
Birth length (cm)	49.97 ± 0.95	49.99 ± 0.91	49.94 ± 0.79	0.772
Duration of breastfeeding (month)	9.25 ± 4.87	9.31 ± 4.80	9.19 ± 4.95	0.818
Breastfeeding				
Yes	792 (98.51%)	415 (98.34%)	377 (98.69%)	0.683
No	12 (1.49%)	7 (1.66%)	5 (1.31%)	

BMI, body mass index.

distribution of lipid-adjusted concentrations of OPEs in the two groups. There was no significant difference in OPE concentrations between the male child group and the female child group. Among all participants, TBP was the most frequently detected OPE, followed closely by TBEP and TDCPP. TBEP had the highest median concentration (0.48 ng/g lipid) among all OPEs.

3.3. Sex-specific correlations between prenatal OPE exposure and child growth

Sex-specific impacts of OPE exposure on BMIZ, HCAZ, LAZ, WAZ, and WLZ are depicted in Figs. 1 and 2. The correlations between OPEs and child growth, as determined by linear mixed-effect models, are illustrated in Fig. 1. Among male children, an increase of 2.72 ng/g lipid in TBEP concentration was associated with a 0.11-unit increase in HCAZ. Among female children, an increase of 2.72 ng/g lipid in TDCPP concentration was associated with a 0.15-unit increase in LAZ and a 0.14-unit increase in WAZ.

Multivariable linear regression analyses were conducted to assess the relationships between OPE exposure and child growth parameters for male and female children (Fig. 2), and the results were consistent with the results of the longitudinal analysis shown in Fig. 1. For male children, serum TBEP concentration was positively related to HCAZ at 1 and 2 months of age, while TBP concentration was positively related to BMIZ and WAZ at 1 month of age. Serum TDCPP was positively associated with WAZ at 1 month of age, while serum TDCPP exposure was positively correlated with BMIZ, WAZ, and WLZ at 2 months of age. For female children, serum TDCPP concentration was positively related to LAZ and WAZ at 9 and 12 months of age. At 18 months of age, serum TBP exposure was positively associated with HCAZ. TBP was positively correlated with LAZ and WAZ at 24 months of age.

3.4. Estimated effects of prenatal OPE exposure and child growth trajectories

GBTM identified two trajectory groups for each anthropometric measure (BMIZ, HCAZ, LAZ, WAZ, and WLZ) in this study. The trajectories for each measure are presented in Fig. S5. Trajectories were labeled based on the low or high values observed at different time points. The two trajectory groups for each anthropometric measure were: moderate growth and fast growth. The moderate growth group was selected as the reference group for all measures. Table S2 and Table S3 present comprehensive definitions of trajectory groups, as well as the model selection criteria, including BIC and AvePP.

The association between prenatal OPE exposure and child growth trajectories, stratified by sex, is presented in Table 3. For HCAZ, an increase of 2.72 ng/g lipid in TBEP was associated with a 1.36-fold increase in the risk of fast-growth HCAZ trajectory. For LAZ and WAZ, an increase of 2.72 ng/g lipid in TDCPP was associated with a 1.64-fold increase in the risk of fast-growth LAZ trajectory and a 1.68-fold increase in the risk of fast-growth WAZ trajectory.

3.5. Sensitivity analysis

Positive effects of OPEs and child growth persisted even after excluding preterm birth (Figs. 3 and S6), but no association between TBEP and HCAZ was found in male children. For child growth trajectories (Fig. S7), Table S6 displays the impacts of prenatal OPE exposure and child growth

Table 2
Detection rates and concentration distribution of OPEs throughout the entire pregnancy.

OPE congeners	Total		Male children		Female children		*P value*
	Detection rate (%)	OPE levels (ng/g)	Detection rate (%)	OPE levels (ng/g)	Detection rate (%)	OPE levels (ng/g)	
TBP	91.8	0.21 (0.15,0.28)	92.8	0.18 (0.10, 0.27)	89.4	0.18 (0.10, 0.27)	0.186
TBEP	66.8	0.48 (LOD,1.01)	65.9	0.47 (LOD, 1.04)	67.4	0.48 (LOD, 0.96)	0.343
EHDPP	62.1	0.06 (LOD,0.10)	60.8	0.06 (LOD, 0.11)	64.1	0.06 (LOD, 0.09)	0.348
TDCPP	66.4	0.35 (LOD,0.69)	66.7	0.32 (LOD, 0.62)	65.9	0.34 (LOD, 0.67)	0.178
TMCP	31.2	LOD (LOD,0.05)	31.6	LOD (LOD, 0.06)	30.7	LOD (LOD, 0.05)	0.193

OPE, organophosphate ester; TBP, tributyl phosphate; TBEP, tris(2-butoxyethyl) phosphate; EHDPP, 2-ethylhexyl diphenyl phosphate; TDCPP, tris(2-chloro-1-(chloromethyl) ethyl) phosphate; TMCP, tri-m-cresyl phosphate; LOD, limits of detection.

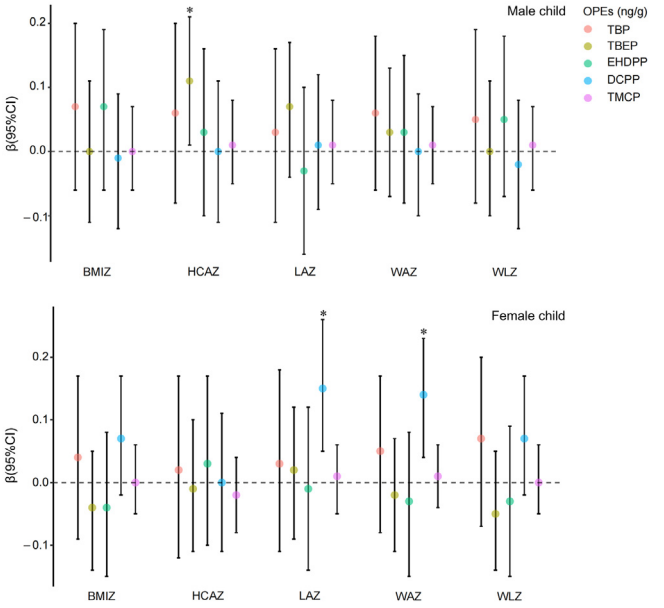

Fig. 1. Sex-specific associations between OPEs and child growth using linear mixed effects model. BMIZ, body mass index z-score; HCAZ, head circumference-for-age z-score; LAZ, length-for-age z-score; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score.

trajectories by sex after excluding preterm birth. TDCPP was associated with greater ORs for the fast-growth LAZ trajectories and fast-growth WAZ trajectories among female children but not male children.

Figs. S8 and S9 show the effects of OPEs and child growth after excluding nonbreastfed children, consistent with the results of the main analysis. For child growth trajectories (Fig. S10, Table S7), TBEP was associated with greater ORs for the fast growth HCAZ trajectories among male children. TDCPP was associated with greater ORs for the fast growth LAZ trajectories and fast growth WAZ trajectories among female children.

4. Discussion

This prospective cohort study was conducted to investigate the potential associations between five OPE concentrations during pregnancy and child growth patterns. Our results indicated that OPEs were related to increasing the speed of child growth, as shown by the increased BMIZ, HCAZ, LAZ, WAZ, and WLZ. Additionally, we observed significant positive effects of TBEP on HCAZ in male children. We also observed associations between TDCPP and LAZ or WAZ in female children. Specifically, prenatal OPE exposure had a discernible impact on the HCAZ trajectories in male children, and prenatal OPE exposure was associated with LAZ and WAZ trajectories in female children. Most of the findings remained consistent even after accounting for preterm births and nonbreasted children, except for the effect of TBEP exposure on HCAZ in male children.

OPEs are widely used as an alternative to BFRs. Identifying effective biomarkers for human exposure to OPEs is important due to their diverse sources. Prior research has utilized OPE metabolites in urine as biomarkers [20–22], but their accuracy in reflecting exposure status may be limited on account of the rapid metabolism of OPEs [24,25] and the existence of multiple metabolites for each type [24]. Concentrations of OPEs in the blood are more suitable for capturing changes and patterns of human exposure [36]. The detection rate for most OPEs in this study was above 60%, suggesting that pregnant women were generally exposed to OPEs in Shanghai. Another study in Beijing found that the detection rate of pregnant women was 100%, and the concentration of EHDPP was 5.96 ng/g [37], which was higher than that in this study (0.06 ng/g). Wang et al. reported that the TDCPP concentration during pregnancy was lower (0.24 μg/L) than that in this study (0.72 μg/L) [38], which may be due to differences in OPE application, usage and study population. However, previous investigations on the influence of OPE metabolites on child growth were mainly based on a single measurement of OPE taken at an early stage of pregnancy [19]. As OPEs have a short half-life in the body [24,25], a single OPE measurement during pregnancy may not accurately reflect the mother's overall prenatal OPE exposure. Therefore, this study collected multiple OPE measurements to address this issue.

Based on the Development Original of Health and Disease (DOHaD) theory, early life exposure to environmental factors, including OPEs, may impact children's health in later life. Similarly, OPE exposure during early life has been associated with adverse birth outcomes, allergic diseases, early growth and obesity, and neurodevelopmental disorders [17–19,39,40]. For example, one study conducted in Shanghai found that exposure to OPEs during pregnancy increased childhood adiposity indicators (WAZ, BMIZ, and arm circumference), particularly among those breastfed for less than four months [19]. Studies on toxicity have demonstrated that in rats, exposure to TPHP during pregnancy resulted in an earlier onset of type 2 diabetes and greater fat accumulation [15]. In this cohort study, we investigated the effects of OPEs on child growth by analyzing mixed effect growth trajectories with repeated measurements while taking into account the sex-specific differences. The findings of this study supported prior evidence that suggested a positive correlation between prenatal OPE exposure and obesity, as indicated by a positive correlation between OPEs and HCAZ in male children and LAZ or WAZ in female children.

In addition, our study continued to fit child growth trajectories using the GBTM and explored the impact of OPEs on child growth trajectories to verify the results of linear mixed-effect models and multivariable linear regression analyses. Our findings indicated that a higher prenatal TBEP concentration was related to greater odds of fast HCAZ trajectories in male children and that a higher TDCPP concentration was related to greater odds of faster LAZ or WAZ trajectories in female children, consistent with previous results. The majority of previous literature predominantly relied on fixed growth indicators, neglecting the dynamic nature of growth patterns. The conventional methodologies exhibit a cross-section framework, rendering them incapable of capturing the

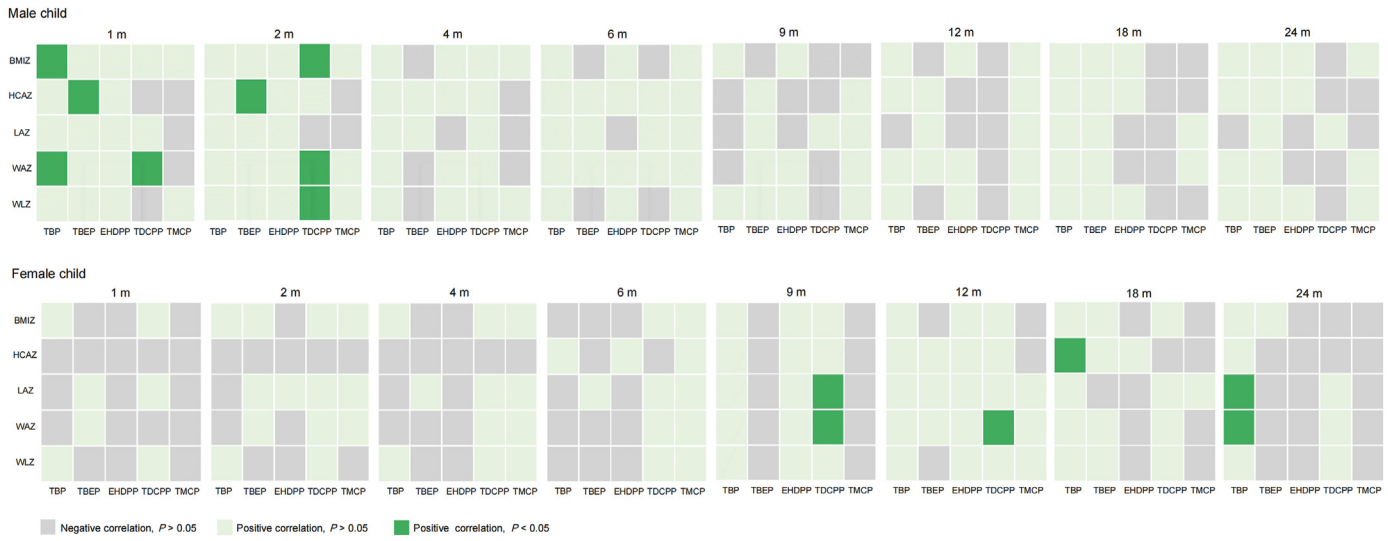

Fig. 2. Sex-specific associations of the OPE levels (ng/g) with child growth characteristics using multivariable linear regression analyses.

Table 3
The correlations between prenatal OPE exposure (ng/g) on child growth trajectory group by sex.

	BMIZ		HCAZ		LAZ		WAZ		WLZ	
	OR (95%CI)	*P value*	OR (95%CI)	*P value*	OR (95%CI)	*P value*	OR (95%CI)	*P value*	OR (95%CI)	*P value*
	Fast growth vs. Moderate growth									
Male children										
TBP	1.17 (0.78,1.78)	0.448	1.13 (0.75,1.72)	0.561	1.55 (1.00,2.46)	0.054	1.53 (0.99,2.39)	0.059	1.08 (0.72,1.62)	0.708
TBEP	0.96 (0.69,1.33)	0.785	1.36(1.01,1.92)	0.041*	1.17 (0.83,1.68)	0.371	1.21 (0.86,1.70)	0.285	0.92 (0.67,1.28)	0.624
EHDPP	1.21 (0.83,1.78)	0.330	1.18 (0.80,1.75)	0.403	0.89 (0.59,1.34)	0.573	1.16 (0.78,1.73)	0.460	1.12 (0.77,1.64)	0.553
TDCPP	0.96 (0.71,1.31)	0.803	1.09 (0.79,1.50)	0.592	1.13 (0.81,1.57)	0.472	1.12 (0.82,1.55)	0.475	0.94 (0.69,1.27)	0.674
TMCP	0.90 (0.74,1.10)	0.303	1.02 (0.84,1.25)	0.824	0.93 (0.75,1.15)	0.502	1.04 (0.84,1.27)	0.732	0.92 (0.76,1.12)	0.425
Female children										
TBP	0.95 (0.61,1.49)	0.833	0.86 (0.55,1.33)	0.495	1.16 (0.73,1.85)	0.542	1.08 (0.67,1.73)	0.759	1.03 (0.66,1.61)	0.902
TBEP	0.88 (0.63,1.22)	0.432	0.83 (0.60,1.15)	0.257	1.15 (0.81,1.62)	0.436	0.88 (0.62,1.24)	0.452	0.85 (0.61,1.17)	0.319
EHDPP	0.79 (0.52,1.18)	0.247	1.14 (0.77,1.72)	0.512	0.88 (0.58,1.34)	0.557	0.97 (0.63,1.49)	0.880	0.78 (0.51,1.17)	0.227
TDCPP	1.12 (0.81,1.56)	0.504	0.94 (0.67,1.29)	0.687	1.64(1.16,2.35)	0.005*	1.68(1.18,2.40)	0.004*	1.15 (0.83,1.60)	0.399
TMCP	1.01 (0.84,1.21)	0.924	0.95 (0.79,1.13)	0.539	1.07 (0.89,1.30)	0.463	1.08 (0.90,1.31)	0.408	1.05 (0.88,1.26)	0.591

Data were presented as estimated values and 95% confidence intervals (CI).
*$P < 0.05$, adjusted by false discovery rate (FDR), models were adjusted for maternal age, pre-pregnancy BMI, parity, maternal education, annual household income, preterm birth, birth weight, birth length, breast-feeding (yes or no), breastfeeding duration, follow-up period, and OPE concentrations in breast milk.
OR, odds ratio.

dynamic nature and inherent variability of growth patterns. Growth trajectories provide a dynamic view of child growth patterns, and the impact of differences in early life growth trajectories can persist into childhood, adolescence, and adulthood.

While research on the correlation between prenatal OPE exposure and child growth trajectories remains limited, relevant studies have explored the relationships between other environmental pollutants and child growth trajectories. For example, one birth cohort study explored BMI trajectories for exposure to bisphenol A (BPA) and PAEs [26]. The findings indicated that exposure to PAEs was associated with the highest predicted BMI trajectories in children, whereas no correlations were found between BPA exposure and children's growth trajectories [26]. One study did not detect any variances in BMI trajectories related to prenatal persistent organic pollutant (POP) levels [41], while another study found that prenatal perfluorooctanoic acid (PFOA) was related to alterations in BMI trajectories during the first 12 years of life [42]. Our study did not find any impact of OPEs on BMI trajectories. The reason for the inconsistency with the previous study's results may be due to differences in the types of pollutants and study population. Previous research has not reported the impact of OPEs on child growth trajectories. Therefore, it is essential for future studies to focus on further exploration of OPEs and child growth trajectories.

This study also found that different OPE congeners had different effects on child growth, among which TBP, TBEP, and TDCPP had greater effects. This may be attributed to different transplacental transfer efficiencies and different concentrations of various substances. First, previous studies by our team have found that the C:M ratios (expressed as cord blood to maternal blood concentration ratios) of TBP, TBEP, and TDCPP are higher than 1 [43], indicating that they easily pass the placental barrier and influence fetal development. Second, due to the low concentrations of EHDPP and TMCP in our study population, no effect on child growth was found.

Additionally, our study indicated that prenatal exposure to OPEs had varying impacts on child growth depending on the sex of the child. This phenomenon has been identified in previous studies as well, e.g., one birth cohort study showed that prenatal OPE exposure was positively related to child anthropometric measures, such as weight, height, and head circumference z-scores in 4-week-old children [18]. The associations with bis(2-chloroethyl) phosphate (BCEP), di-n-butyl phosphate (DNBP), and DPHP were typically stronger among males, while associations with bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) were stronger among females [18]. Moreover, early-life exposure to OPEs affected serum thyroid hormone levels and caused weight gain in female rats [16], consistent with our findings. Furthermore, this study found that

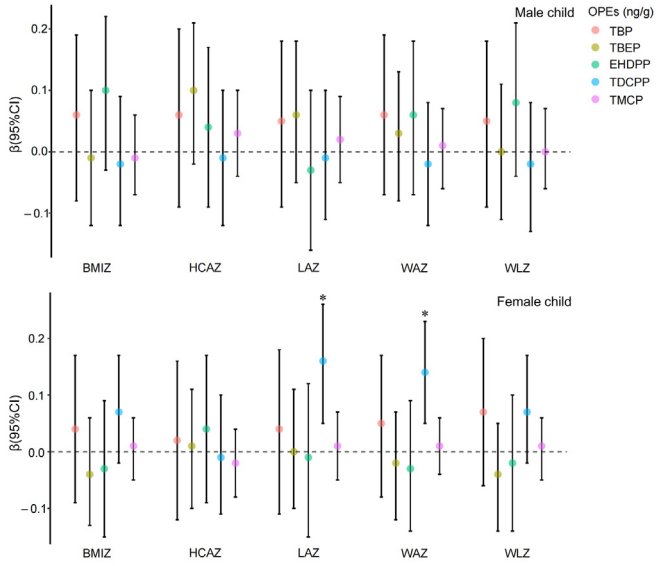

Fig. 3. Sex-specific associations between OPEs and child growth using linear mixed effects model (exclude preterm birth).

different OPE congeners had different effects between male children and female children. For example, TBEP mainly affected HCAZ in male children, and TDCPP mainly affected LAZ or WAZ in female children. One plausible explanation is prenatal OPE exposure caused fetal growth restriction, which has been confirmed by our study and others (prenatal exposure affects head circumference in male fetus and birth weight or birth length in female fetus) [18,31,44]. The growth-restricted newborns were more likely to experience rapid postnatal weight gain during the first two years of life to compensate for intrauterine restraint [13]. Then, toxicological studies have shown that TDCPP only interferes with the expression of Hypothalamic-pituitary-thyroid axis (HPT)-related genes in female zebrafish, thus interfering with its development [45], as is consistent with the results of our study. Last, TBEP is an alkyl OPE, and TDCPP is a chlorinated OPE. We speculated that the difference in structure may be the cause of gender differences. Additionally, this study also found that OPE exposure affected male children and female children at different ages, mainly affecting male children at 1 month of age and female children at 9 months of age. It has been suggested that the catch-up growth time of head circumference was earlier than that of body length and body weight, and it started at 1 month of age [46]. Studies have shown that the developmental milestones of male children are achieved earlier after birth than those of female children [47]. Subsequently, the growth rate of female children gradually increased faster than that of male children [48], and reached its peak within 12 months of age. It should be noted that exposure to OPEs during pregnancy can accelerate the height growth of female children, which may have adverse effects on subsequent life. Previous research has suggested that accelerated growth during infancy may increase the risk of obesity and metabolic disorders later in life [49]. For instance, Taveras et al. found that a 2 percentile increase in child height during the first six months of life was associated with a higher risk of obesity 5–10 years later [50]. In a study conducted across several low- and middle-income countries, faster height growth during infancy was linked to a higher likelihood of overweight and hypertension [51]. Thus, rapid body length growth during infancy may have unfavorable implications for future health outcomes, and future attention needs to be focused on OPE exposure status in early life.

Emerging evidence has gradually indicated gender disparities regarding the impact of environmental substances on maternal well-being and children's health. However, the precise mechanisms underlying these differences have not yet been fully elucidated. Significant variances based on gender have been detected in the relationship between DNA methylation of genes associated with thyroid hormone regulation and the presence of POPs [52]. Sex disparities could arise from variances in genetics, reactions to environmental elements, and disparities in interactions between genetics and the environment. Acting as a pivotal intermediary between the maternal environment during pregnancy and the developing fetus, the placenta plays a prominent role in mediating the manifestation and adjustment of stressful parental pre-pregnancy conditions [53]. Differences in gene expression between sex have been observed in te placental tissue of both humans and animals [54]. The levels of maternal hormones and the presence of environmental chemical exposure during pregnancy may exert sex-specific effects on placental development. These factors have the capacity to modify genetic and epigenetic programming in the fetus, thereby influencing the epigenetic responses of male and female fetuses to adverse intrauterine conditions. Consequently, these influences can have enduring implications [55]. Moreover, research has indicated the presence of sexual dimorphism in the expression of membrane proteins responsible for thyroid hormones (TH) transport in placental tissue. This discrepancy in protein expression serves as an additional potential factor contributing to the divergent impact of environmental pollutant exposure on human development based on sex [56]. In a separate investigation, it was discovered that TDCPP disrupted the expression of genes related to the HPT and altered receptor transcription, exhibiting a sex-specific pattern of disturbance. Female zebrafish exposed to TDCPP exhibited significant decreases in plasma concentrations of triiodothyronine (T3) and thyroxine (T4), accompanied by notable downregulation of corticotropin-releasing hormone (CRH) and thyroid stimulating hormone (TSH) transcripts [45]. Disrupted inflammatory responses are regarded as a potential mechanism through which OPE exposure gives rise to risks for maternal and fetal well-being, particularly due to their affinity for peroxisome proliferator-activated receptors (PPARs) [57]. One research demonstrated distinct sexual dimorphism in the expression patterns of PPARα under fasting and feeding states [58]. We speculate that sex-specific mechanisms may be involved in placental inflammation induced by exposure to OPEs.

This study has several advantages. Based on the prospective design and repeated measurements of child growth parameters from 1 to 24 months of age, this study can explore the impacts of prenatal OPE exposure on child growth by sex. We measured five child growth parameters in this study, including BMIZ, HCAZ, LAZ, WAZ, and WLZ, which could identify changes in child growth from different perspectives. Then, this study applied the GBTM to fit child growth trajectories and evaluated the impact of OPEs on child growth trajectories. Overall, these results further supported our findings in the linear mixed-effect models. These findings enhance our comprehension of the negative effects that OPEs can have on child growth. Last, serum OPE exposure may better identify OPE prototypes that had an impact on physical development. However, there were some limitations to this study. First, unmeasured confounding factors, such as maternal dietary status, could have had an impact on the results. Second, as this study only measured five specific OPE congeners, it was not possible to evaluate the potential impacts of other congeners on child growth. Last, this study could not rule out the effects of postnatal exposure. For indirect exposure (breastfeeding), we analyzed the effects of OPE exposure on the child growth trajectory in a subset of the population and corrected for OPE concentrations in breast milk, and the findings remained consistent (data not shown). But we cannot rule out direct exposure, and future studies are needed to consider these effects.

5. Conclusion

In summary, our findings suggested that there may be a correlation between prenatal OPE exposure and altered child growth during the first 24 months of life, particularly in specific exposure windows and among female children. For instance, we observed significant positive effects of TBEP on HCAZ in male children, and associations between TDCPP and

LAZ or WAZ in female children. Finally, the impact of OPEs on child growth trajectories verified the above results. These findings remained consistent even after accounting for preterm births and nonbreastfed children.

Author contributions

H.W.: methodology, investigation, formal analysis, software, visualization, writing–original draft, writing–review & editing. L.Y.Z.: methodology, investigation. J.W.: investigation, software. P.P.W.: investigation, supervision. Q.L., X.Y·S., Y.Q.X., Y.Z. and Y.L.: methodology. Y.H.Z.: conceptualization, funding acquisition, project administration, resources, supervision, writing–review & editing.

Data availability

The authors do not have permission to share data.

Ethics approval and consent to participate

The research protocol was approved by the ethics committee of Fudan University (IRB#2016-04-0587), and all participants or their respondents provided written informed consent.

Declaration of competing interests

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.

Acknowledgment

This work was supported by the National Key Research and Development Program of China (Grant No. 2022YFC2705004), the National Natural Science Foundation of China (Grant No. 82273585), and Key Project on Science and Technology Program of Fujian Health Commission (Gran No. 2021ZD01002).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eehl.2023.07.003.

References

[1] J. Yang, Y. Zhao, M. Li, M. Du, X. Li, Y. Li, A review of a class of emerging contaminants: the classification, distribution, intensity of consumption, synthesis routes, environmental effects and expectation of pollution abatement to organophosphate flame retardants (OPFRs), Int. J. Mol. Sci. 20 (12) (2019).
[2] J. Ding, X. Shen, W. Liu, A. Covaci, F. Yang, Occurrence and risk assessment of organophosphate esters in drinking water from Eastern China, Sci. Total Environ. 538 (2015) 959–965.
[3] N. Ali, A.C. Dirtu, N. Van den Eede, E. Goosey, S. Harrad, H. Neels, A. t Mannetje, J. Coakley, J. Douwes, A. Covaci, Occurrence of alternative flame retardants in indoor dust from New Zealand: indoor sources and human exposure assessment, Chemosphere 88 (11) (2012) 1276–1282.
[4] M.A. Abdallah, A. Covaci, Organophosphate flame retardants in indoor dust from Egypt: implications for human exposure, Environ. Sci. Technol. 48 (9) (2014) 4782–4789.
[5] X. Zheng, F. Xu, K. Chen, Y. Zeng, X. Luo, S. Chen, B. Mai, A. Covaci, Flame retardants and organochlorines in indoor dust from several e-waste recycling sites in South China: composition variations and implications for human exposure, Environ. Int. 78 (2015) 1–7.
[6] F. Xu, G. Giovanoulis, S. van Waes, J.A. Padilla-Sanchez, E. Papadopoulou, J. Magnér, L.S. Haug, H. Neels, A. Covaci, Comprehensive study of human external exposure to organophosphate flame retardants via air, dust, and hand wipes: the importance of sampling and assessment strategy, Environ. Sci. Technol. 50 (14) (2016) 7752–7760.
[7] M.F. Hughes, B.C. Edwards, C.T. Mitchell, B. Bhooshan, In vitro dermal absorption of flame retardant chemicals, Food Chem. Toxicol. 39 (12) (2001) 1263–1270.
[8] M.S. Mäkinen, M.R. Mäkinen, J.T. Koistinen, A.L. Pasanen, P.O. Pasanen, P.J. Kalliokoski, A.M. Korpi, Respiratory and dermal exposure to organophosphorus flame retardants and tetrabromobisphenol A at five work environments, Environ. Sci. Technol. 43 (3) (2009) 941–947.
[9] J.D. Meeker, H.M. Stapleton, House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters, Environ. Health Perspect. 118 (3) (2010) 318–323.
[10] O.B. Jonsson, E. Dyremark, U.L. Nilsson, Development of a microporous membrane liquid-liquid extractor for organophosphate esters in human blood plasma: identification of triphenyl phosphate and octyl diphenyl phosphate in donor plasma, J. Chromatogr. B Biomed. Sci. Appl. 755 (1–2) (2001) 157–164.
[11] X.Y. Bai, S.Y. Lu, L. Xie, B. Zhang, S.M. Song, Y. He, J.P. Ouyang, T. Zhang, A pilot study of metabolites of organophosphorus flame retardants in paired maternal urine and amniotic fluid samples: potential exposure risks of tributyl phosphate to pregnant women, Environ Sci Process Impacts 21 (1) (2019) 124–132.
[12] R.E. Black, C.G. Victora, S.P. Walker, Z.A. Bhutta, P. Christian, M. de Onis, M. Ezzati, S. Grantham-McGregor, J. Katz, R. Martorell, et al., Maternal and child undernutrition and overweight in low-income and middle-income countries, Lancet 382 (9890) (2013) 427–451.
[13] K.K. Ong, M.L. Ahmed, P.M. Emmett, M.A. Preece, D.B. Dunger, Association between postnatal catch-up growth and obesity in childhood: prospective cohort study, BMJ 320 (7240) (2000) 967–971.
[14] L.E. Pryor, R.E. Tremblay, M. Boivin, E. Touchette, L. Dubois, C. Genolini, X. Liu, B. Falissard, S.M. Côté, Developmental trajectories of body mass index in early childhood and their risk factors: an 8-year longitudinal study, Arch. Pediatr. Adolesc. Med. 165 (10) (2011) 906–912.
[15] A.J. Green, J.L. Graham, E.A. Gonzalez, M.R. La Frano, S.E. Petropoulou, J.S. Park, J.W. Newman, K.L. Stanhope, P.J. Havel, M.A. La Merrill, Perinatal triphenyl phosphate exposure accelerates type 2 diabetes onset and increases adipose accumulation in UCD-type 2 diabetes mellitus rats, Reprod. Toxicol. 68 (2017) 119–129.
[16] H.B. Patisaul, S.C. Roberts, N. Mabrey, K.A. McCaffrey, R.B. Gear, J. Braun, S.M. Belcher, H.M. Stapleton, Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster® 550 in rats: an exploratory assessment, J. Biochem. Mol. Toxicol. 27 (2) (2013) 124–136.
[17] M. Boyle, J.P. Buckley, L. Quirós-Alcalá, Associations between urinary organophosphate ester metabolites and measures of adiposity among U.S. children and adults: nhanes 2013-2014, Environ. Int. 127 (2019) 754–763.
[18] W. Yang, J.M. Braun, A.M. Vuong, Z. Percy, Y. Xu, C. Xie, R. Deka, A.M. Calafat, M. Ospina, H.H. Burris, et al., Gestational exposure to organophosphate esters and infant anthropometric measures in the first 4 weeks after birth, Sci. Total Environ. 857 (Pt 1) (2023) 159322.
[19] Y. Chen, X. Zhang, Z. Wang, Z. Yuan, M. Luan, W. Yuan, H. Liang, H. Chen, D. Chen, Y. Yang, et al., Gestational exposure to organophosphate esters and adiposity measures of children up to 6 years: effect modification by breastfeeding, Int. J. Hyg Environ. Health 248 (2023) 114089.
[20] D. Luo, W. Liu, W. Wu, Y. Tao, L. Hu, L. Wang, M. Yu, A. Zhou, A. Covaci, W. Xia, et al., Trimester-specific effects of maternal exposure to organophosphate flame retardants on offspring size at birth: a prospective cohort study in China, J. Hazard Mater. 406 (2021) 124754.
[21] D. Luo, W. Liu, Y. Tao, L. Wang, M. Yu, L. Hu, A. Zhou, A. Covaci, W. Xia, Y. Li, et al., Prenatal exposure to organophosphate flame retardants and the risk of low birth weight: a nested case-control study in China, Environ. Sci. Technol. 54 (6) (2020) 3375–3385.
[22] K. Hoffman, H.M. Stapleton, A. Lorenzo, C.M. Butt, L. Adair, A.H. Herring, J.L. Daniels, Prenatal exposure to organophosphates and associations with birthweight and gestational length, Environ. Int. 116 (2018) 248–254.
[23] M. Hou, Y. Shi, Q. Jin, Y. Cai, Organophosphate esters and their metabolites in paired human whole blood, serum, and urine as biomarkers of exposure, Environ. Int. 139 (2020) 105698.
[24] J. Shen, Y. Zhang, N. Yu, D. Crump, J. Li, H. Su, R.J. Letcher, G. Su, Organophosphate ester, 2-ethylhexyl diphenyl phosphate (EHDPP), elicits cytotoxic and transcriptomic effects in chicken embryonic hepatocytes and its biotransformation profile compared to humans, Environ. Sci. Technol. 53 (4) (2019) 2151–2160.
[25] A. Ballesteros-Gómez, C.A. Erratico, N.V. Eede, A.C. Ionas, P.E. Leonards, A. Covaci, In vitro metabolism of 2-ethylhexyldiphenyl phosphate (EHDPHP) by human liver microsomes, Toxicol. Lett. 232 (1) (2015) 203–212.
[26] T.C. Yang, K.E. Peterson, J.D. Meeker, B.N. Sánchez, Z. Zhang, A. Cantoral, M. Solano, M.M. Tellez-Rojo, Exposure to Bisphenol A and phthalates metabolites in the third trimester of pregnancy and BMI trajectories, Pediatr Obes 13 (9) (2018) 550–557.
[27] Y. Tan, J. Liao, B. Zhang, H. Mei, A. Peng, J. Zhao, Y. Zhang, S. Yang, M. He, Prenatal exposure to air pollutants and early childhood growth trajectories: a population-based prospective birth cohort study, Environ. Res. 194 (2021) 110627.
[28] M. Ding, C. Yuan, A.J. Gaskins, A.E. Field, S.A. Missmer, K.B. Michels, F. Hu, C. Zhang, M.W. Gillman, J. Chavarro, Smoking during pregnancy in relation to grandchild birth weight and BMI trajectories, PLoS One 12 (7) (2017) e0179368.
[29] J.W. Porter, J.L. Barnas, R. Welly, N. Spencer, J. Pitt, V.J. Vieira-Potter, J.A. Kanaley, Age, sex, and depot-specific differences in adipose-tissue estrogen receptors in individuals with obesity, Obesity 28 (9) (2020) 1698–1707.
[30] C. Leonetti, C.M. Butt, K. Hoffman, S.C. Hammel, M.L. Miranda, H.M. Stapleton, Brominated flame retardants in placental tissues: associations with infant sex and thyroid hormone endpoints, Environ. Health 15 (1) (2016) 113.
[31] H. Wang, P. Wang, Q. Li, J. Li, L. Zhang, H. Shi, J. Li, Y. Zhang, Prenatal exposure of organophosphate esters and its trimester-specific and gender-specific effects on fetal growth, Environ. Sci. Technol. 56 (23) (2022) 17018–17028.

[32] E.F. Schisterman, B.W. Whitcomb, G.M. Louis, T.A. Louis, Lipid adjustment in the analysis of environmental contaminants and human health risks, Environ. Health Perspect. 113 (7) (2005) 853–857.
[33] D.S. Nagin, R.E. Tremblay, Analyzing developmental trajectories of distinct but related behaviors: a group-based method, Psychol. Methods 6 (1) (2001) 18–34.
[34] J. Twisk, T. Hoekstra, Classifying developmental trajectories over time should be done with great caution: a comparison between methods, J. Clin. Epidemiol. 65 (10) (2012) 1078–1087.
[35] D.S. Nagin, C.L. Odgers, Group-based trajectory modeling in clinical research, Annu. Rev. Clin. Psychol. 6 (2010) 109–138.
[36] A. Alves, A. Kucharska, C. Erratico, F. Xu, E. Den Hond, G. Koppen, G. Vanermen, A. Covaci, S. Voorspoels, Human biomonitoring of emerging pollutants through non-invasive matrices: state of the art and future potential, Anal. Bioanal. Chem. 406 (17) (2014) 4063–4088.
[37] F. Zhao, M. Chen, F. Gao, H. Shen, J. Hu, Organophosphorus flame retardants in pregnant women and their transfer to chorionic villi, Environ. Sci. Technol. 51 (11) (2017) 6489–6497.
[38] X. Wang, P. Chen, L. Zhao, L. Zhu, F. Wu, Transplacental behaviors of organophosphate tri- and diesters based on paired human maternal and cord whole blood: efficiencies and impact factors, Environ. Sci. Technol. 55 (5) (2021) 3091–3100.
[39] R. Castorina, A. Bradman, H.M. Stapleton, C. Butt, D. Avery, K.G. Harley, R.B. Gunier, N. Holland, B. Eskenazi, Current-use flame retardants: maternal exposure and neurodevelopment in children of the CHAMACOS cohort, Chemosphere 189 (2017) 574–580.
[40] A. Araki, M. Bastiaensen, Y. Ait Bamai, N. Van den Eede, T. Kawai, T. Tsuboi, R.M. Ketema, A. Covaci, R. Kishi, Associations between allergic symptoms and phosphate flame retardants in dust and their urinary metabolites among school children, Environ. Int. 119 (2018) 438–446.
[41] A. Cai, L. Portengen, E. Govarts, L.R. Martin, G. Schoeters, J. Legler, R. Vermeulen, V. Lenters, S. Remy, Prenatal exposure to persistent organic pollutants and changes in infant growth and childhood growth trajectories, Chemosphere 314 (2023) 137695.
[42] J.M. Braun, M. Eliot, G.D. Papandonatos, J.P. Buckley, K.M. Cecil, H.J. Kalkwarf, A. Chen, C.B. Eaton, K. Kelsey, B.P. Lanphear, et al., Gestational perfluoroalkyl substance exposure and body mass index trajectories over the first 12 years of life, Int. J. Obes. 45 (1) (2021) 25–35.
[43] J. Li, Assessment of Exposure to Per- and Polyfluoroalkyl Substances and Organophosphorus Flame Retardants in Early Life and Infant Health Risk Evaluation, Fudan University, 2022. Master.
[44] W. Yang, J.M. Braun, A.M. Vuong, Z. Percy, Y. Xu, C. Xie, R. Deka, A.M. Calafat, M. Ospina, H.H. Burris, et al., Associations of gestational exposure to organophosphate esters with gestational age and neonatal anthropometric measures: the HOME study, Environ. Pollut. 316 (Pt 1) (2023) 120516.
[45] X. Liu, Y. Cai, Y. Wang, S. Xu, K. Ji, K. Choi, Effects of tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and triphenyl phosphate (TPP) on sex-dependent alterations of thyroid hormones in adult zebrafish, Ecotoxicol. Environ. Saf. 170 (2019) 25–32.
[46] S. Chen, S. He, S. Meng, S. Wang, Z. Liao, Study on Physical development and neuropsychological development of premature small of gestational age infants, Maternal and Child Health Care of China 34 (23) (2019) 5416–5419.
[47] E. Bjarnadóttir, J. Stokholm, B. Chawes, J. Thorsen, A.C. Mora-Jensen, M. Deleuran, K. Bønnelykke, L. Lauritzen, H. Bisgaard, Determinants of neurodevelopment in early childhood–results from the Copenhagen prospective studies on asthma in childhood (COPSAC(2010)) mother-child cohort, Acta Paediatr. 108 (9) (2019) 1632–1641.
[48] L. Xiao, The boy crisis phenomenon attributable and countermeasures research, Hunan University, 2012. Master.
[49] P.O. Monteiro, C.G. Victora, Rapid growth in infancy and childhood and obesity in later life–a systematic review, Obes. Rev. 6 (2) (2005) 143–154.
[50] E.M. Taveras, S.L. Rifas-Shiman, B. Sherry, E. Oken, J. Haines, K. Kleinman, J.W. Rich-Edwards, M.W. Gillman, Crossing growth percentiles in infancy and risk of obesity in childhood, Arch. Pediatr. Adolesc. Med. 165 (11) (2011) 993–998.
[51] L.S. Adair, C.H. Fall, C. Osmond, A.D. Stein, R. Martorell, M. Ramirez-Zea, H.S. Sachdev, D.L. Dahly, I. Bas, S.A. Norris, et al., Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies, Lancet 382 (9891) (2013) 525–534.
[52] S. Kim, Y.H. Cho, S. Won, J.L. Ku, H.B. Moon, J. Park, G. Choi, S. Kim, K. Choi, Maternal exposures to persistent organic pollutants are associated with DNA methylation of thyroid hormone-related genes in placenta differently by infant sex, Environ. Int. 130 (2019) 104956.
[53] A. Gabory, T.J. Roseboom, T. Moore, L.G. Moore, C. Junien, Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics, Biol. Sex Differ. 4 (1) (2013) 5.
[54] C.S. Rosenfeld, Sex-specific placental responses in fetal development, Endocrinology 156 (10) (2015) 3422–3434.
[55] S. Pérez-Cerezales, P. Ramos-Ibeas, D. Rizos, P. Lonergan, P. Bermejo-Alvarez, A. Gutiérrez-Adán, Early sex-dependent differences in response to environmental stress, Reproduction 155 (1) (2018) R39–r51.
[56] C. Prouillac, S. Lecoeur, The role of the placenta in fetal exposure to xenobiotics: importance of membrane transporters and human models for transfer studies, Drug Metab. Dispos. 38 (10) (2010) 1623–1635.
[57] A.S. Young, T. Zoeller, R. Hauser, T. James-Todd, B.A. Coull, P.A. Behnisch, A. Brouwer, H. Zhu, K. Kannan, J.G. Allen, Assessing indoor dust interference with human nuclear hormone receptors in cell-based luciferase reporter assays, Environ. Health Perspect. 129 (4) (2021) 47010.
[58] N. Wege, A. Schutkowski, M. Boenn, J. Bialek, A. Schlitt, F. Noack, I. Grosse, G.I. Stangl, Men and women differ in their diurnal expression of monocyte peroxisome proliferator-activated receptor-α in the fed but not in the fasted state, Faseb. J. 29 (7) (2015) 2905–2911.