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ORIGINAL PAPER

Intrauterine Exposure to Phthalates and Child Growth in the First Year of Life: Results from the BiTwin Cohort

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Abstract

Phthalates are among the endocrine-disrupting compounds with higher widespread in daily life. Our objective was to assess the associations between maternal exposure to phthalates assessed by urinary phthalate metabolites and growth at birth and in the first year of life. The BiTwin cohort (479 single and 246 multiple pregnancies) was recruited as part of the HEALS project (2017–2019). Evaluations were conducted at birth, 4, 8, and 12 months after childbirth. To mitigate the dependency on twins, we randomly selected one child per family. Birth weight was abstracted from clinical files, and parameters for the first year were based on the child health book. The maternal urine was collected at birth, and phthalate metabolites were determined by liquid chromatography coupled to tandem mass spectrometry. The association between weight growth curves and phthalates was estimated by fixed regression coefficients and 95% confidence intervals calculated through linear mixed effects models. All models include a fixed effect for time and time square and a random intercept and slope by individual. For birth weight, after adjustment, overall, a negative association was found but only statistically significant for mono-n-butyl phthalate metabolite $\beta = -0.195$ (95% CI −0.372; −0.018). In general, the results are similar by sex, but for di(2ethylhexyl) phthalate and cyclohexane-1,2-dicarboxylate, we found associations in the opposite directions. Regarding growth trajectories for the first year of life, overall, no statistically significant associations were found. However, the sum of di(2ethylhexyl) phthalate metabolites presented a positive statistically significant association $\beta = 0.062$ (95%CI 0.002; 0.121) after further adjustment for breastfeeding duration. A positive association was also found for Mono-iso-butyl phthalate in males ($\beta = 0.236$ (95%CI 0.063; 0.409)). Higher maternal phthalate concentrations tended to be associated with lower birth weight, although they did not reach statistical significance. Regarding the first year of life, di(2ethylhexyl) phthalate presented a positive statistically significant association with growth.

Keywords Prenatal exposure · Phthalates · Growth trajectories

Introduction

The diesters of 1,2-benzene dicarboxylic acid (phthalic acid), commonly known as phthalates (PHA), are endocrine-disrupting chemicals (EDCs) that are present ubiquitously in the environment. Human exposure occurs through ingestion, inhalation, and dermal contact (Diamanti-Kandarakis et al. 2009; Kumar et al. 2020). Low-molecular-weight (LMW) PHA are mainly used in personal care products (perfumes, lotions, cosmetics) or as a coating for pharmaceutical products to provide timed releases and include dimethyl phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), and di-isobutyl phthalate (DiBP); high-molecular-weight (HMW) PHA are used as plasticizers in polyvinylchloride floor and wall, covering food packaging, and medical devices and include di(2ethylhexyl) phthalate (DEHP),

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di-n-octyl phthalate (DnOP), Di-iso-decyl phthalate (DiDP) and di-isononyl phthalate (DiNP) (Hauser and Calafat 2005, Phthalates 2008). Due to their impact on human health, the use of some PHA has been regulated (Wang and Qian 2021). Since 2007 the use of DEHP, dibutyl phthalate (DBP), and butyl benzyl phthalate (BBzP) has been forbidden in all polyvinyl chloride (PVC) products, plasticized toys, and childcare articles; DiNP, di-iso-decyl phthalate (DiDP), and DnOP for those products that can be placed in children's mouth (Wang and Qian 2021). More recently, in 2018, DiBP was included in this list of restricted PHA (Wang and Qian 2021). Despite these restrictions, PHA are still used in many consumer products (Hauser and Calafat 2005). New compounds, such as Di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), were used as substitutes for the forbidden PHA compounds, and their exposure is increasing, but knowledge about its effect is scarce (Dominguez-Romero et al. 2022).

Maternal exposure to PHA results in the exposure of the fetus and neonate during pregnancy and lactation (Stefanidou et al. 2009; Lucas et al. 2022). PHA have a short biological half-live, so they are rapidly metabolized and excreted in urine and feces (Diamanti-Kandarakis et al. 2009). PHA may not be persistent, but humans are continuously exposed to them, so, they can be considered "pseudo-persistent" (Tyler et al. 2018). Additionally, metabolites have also been detected in blood, saliva, amniotic fluid, and breast milk (Stojanoska et al. 2017). The lipophilic property of phthalates increases with the length of their chain. Thus, HMW PHA are more prone to be stored in adipose tissue than LMW PHA (van der Meer et al. 2021). Furthermore, both molecular groups have been detected in adipose tissue (van der Meer et al. 2021). A large body of evidence showed that exposure to PHA and their metabolites could pass through the placental barrier during gestation and impact fetal intrauterine growth and birth outcomes (Mose et al. 2007; Yang et al. 2019). This impact on growth and adiposity could be explained due to their affinity with nuclear receptors involved in lipid metabolism (Casals-Casas and Desvergne 2011).

Fetal and first year of life are potentially critical periods for the health effects of PHA. The current evidence on the association between phthalate exposure during these critical periods and child growth remains controversial. Both pre- and post-natal growth patterns have been associated with the risk of being overweight or obese later in life (Botton et al. 2008; Sutharsan et al. 2015; Matthews et al. 2017; Arisaka et al. 2020).

Birth weight (BW) and preterm delivery are among the most commonly studied pregnancy outcomes in environmental epidemiology. BW is easily acquired through birth records, has a reliable recall, is less subject to measurement error than other pregnancy outcomes, and it is used as a proxy of fetal growth (Kamai et al. 2019). Previous studies evaluate the associations of maternal phthalate metabolite concentrations during pregnancy with fetal growth; some found a negative (Song et al. 2018; Kamai et al. 2019; Nidens et al. 2021, Santos et al. 2021) and others no (Philippat et al. 2012; Casas et al. 2016; Shoaff et al. 2016) association. Although several studies have been published to understand the role of prenatal exposures to PHA on child growth, only some of them have evaluated longitudinally early in life (de Cock et al. 2014, Valvi et al. 2015, Botton et al. 2016, Li et al. 2021, Gao et al. 2022, Lee et al. 2022). More than an absolute measurement, it is important to study individual growth trajectories. Currently, a limited number of studies have focused on the effects of prenatal phthalate exposure on post-natal children's growth trajectory (de Cock et al. 2014, Botton et al. 2016, Heggeseth and Aleman 2018; Yang et al. 2018; Heggeseth et al. 2019; Gao et al. 2022; Kupsco et al. 2022). Thus, this study aimed to assess the association of prenatal phthalate exposure with birth weight and growth during the first year of life.

Methods

Study Design and Population

This study was embedded in the BiTwin Cohort, a Portuguese birth cohort of singletons and twins. This cohort was assembled as part of the HEALS project (FP7-ENV-2013-603946) that aimed to collect and harmonize data to study associations between long-term and short-term exposures and children's health (http://www.heals-eu.eu/).

The recruitment for the BiTwin Cohort took place between February 2017 and May 2019 at all four public maternity units of the metropolitan area of Porto, Portugal (Centro Hospital de S. João, Centro Materno Infantil do Norte, Unidade Local de Saúde de Matosinhos, Centro Hospitalar de Vila Nova de Gaia/Espinho). Study protocols were approved by the ethics committee of all hospitals and the national commission for data protection. Written informed consent was obtained from all parents.

The twins were recruited during pregnancy, and singletons were recruited at birth. All mothers of multiple pregnancies followed in these four public maternities were invited to participate at a medical appointment during pregnancy (of 329 eligible mothers, 14.0% refused to participate). In each hospital, for each multiple pregnancy, two mothers of singletons were recruited at birth (of 604 eligible mothers, 18.9% refused to participate). The cohort comprises 725 families corresponding to 974 neonates 479 singletons, and 495 from multiple pregnancies (235 twin pairs, four twin deliveries that resulted in just one live birth and seven triplets) (Fig. 1).

For this study, the sample was restricted to singletons ($n = 479$) and one randomly selected twin ($n = 246$). Of

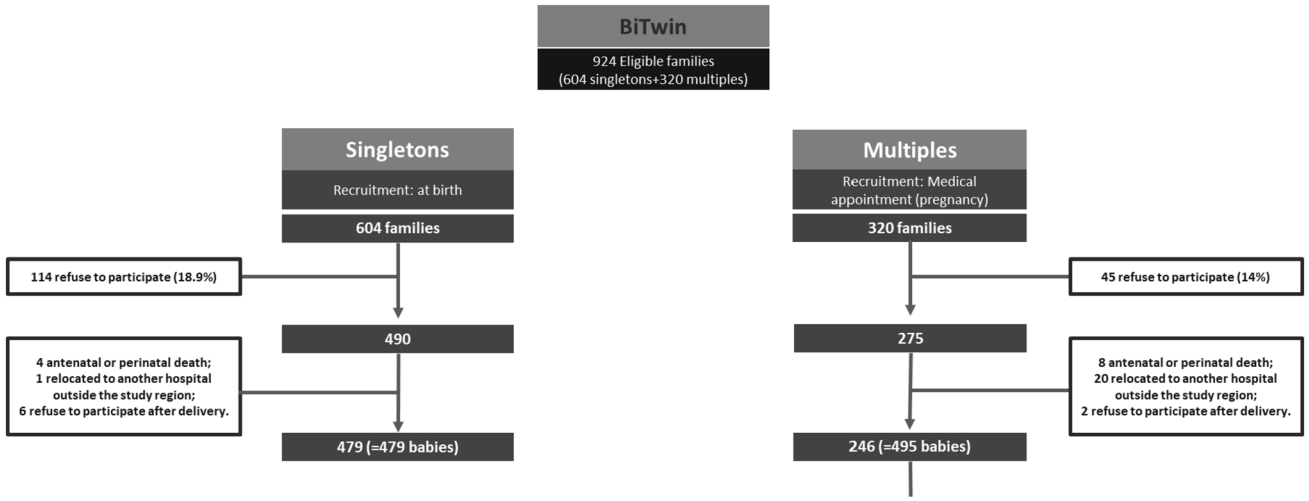

Fig. 1 Flowchart of participants

these 725 participants, 190 mothers did not provide urine samples and were excluded since it was not possible to measure PHA. Thus, our final sample comprises 535 mothers and the same number of children.

Data Collection

At baseline, data were collected through face-to-face interviews conducted by trained interviewers using structured questionnaires. Birth date, birth weight, sex, and gestational age (assessed through ultrasound), were abstracted from the clinical records. Information on family socio-demographic characteristics, maternal lifestyles, obstetric history, pregnancy intercurrences, and self-reported pre-pregnancy anthropometric parameters were collected.

Preterm birth was defined as the delivery before 37 weeks of gestation. Sex-specific weight-for-gestational age z-scores were determined according to Yunkin's growth chart.

During the first year, follow-up assessments were conducted at 4, 8, and 12 months through questionnaires applied to the family by telephone. During this first year, growth was monitored using weight measurements performed on health visits as part of the infant health surveillance program and was extracted from the National Health Service child health books. Breastfeeding duration was also accessed through follow-up evaluations. At 4, 8 and 12 months old, we asked the mother if she had ever breastfed her baby, and if she was currently feeding the baby any breast milk. In each follow-up, for infants who no longer breastfeed, we asked at what age the baby stopped breastfeeding.

Collection of Urine Samples and Assessment of Phthalate Metabolites

A spot urine sample was collected in phthalate-free containers immediately before the birth. Aliquots were stored at − 80 °C and sent to the Norwegian Institute of Public Health on dry ice to access the urinary concentrations of 13 PHA and two DINCH metabolites. The compounds concentration in maternal urine was determined by on-line column-switching liquid chromatography coupled to tandem mass spectrometry (HPLC-MS-MS) (Sabaredzovic et al. 2015). In brief, 300 µl of urine sample were taken and labelled internal standards and enzyme solution were added. After 1.5 h, the enzymatic reaction was stopped by adding formic acid. The samples were centrifuged, and the supernatant was injected into HPLC-MS-MS system. Both in-house control samples and standard reference materials (SRM 3673, a non-smokers urine) from National Institute of Standards and Technology (NIST) were analyzed along with each batch. The accuracy of the method ranged from 70 to 125% and the precision given as relative standard deviation was below 30%. The measurement comprises thirteen different phthalate metabolites: Monoethyl phthalate (MEP); Mono-iso-butyl phthalate (MiBP); Mono-n-butyl phthalate (MnBP); Monobenzyl phthalate (MBzP); Mono-n-pentyl phthalate (MnPeP), Mono-cyclo-hexyl phthalate (MCHP), Mono-n-octyl phthalate (MnOP), Mono-2-Ethylhexyl phthalate (MEHP); Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP); Mono-2-ethyl-5-oxoyhexyl phthalate (MEOHP); Mono-2-ethyl-5-carboxypentyl phthalate (MECPP); Mono-4-methyl-7-hydroxyoctyl phthalate (OH-MiNP); Mono-4- methyl-7oxooctyl phthalate (oxo-MiNP); Mono-4-methyl-7-carboxyheptyl phthalate (cx-MiNP); Mono-6-hydroxy-propylheptylphthalate (OH-MPHP);

2-(Hydroxyl-4-methyloctyl)oxy)carbonyl) cyclohexanecarboxylic acid (OH-MiNCH); 2-(4-Methyl-7-oxyoctyl) oxy)carbonyl) cyclohexanecarboxylic acid (oxo-MiNCH). Additionally, the molar concentrations of DEHP metabolites (MEHP, MECPP, MEOHP, and MEHHP), DiNP metabolites (OH-MiNP, oxo-MiNP, and cx-MiNP) and DINCH metabolites (OH-MiNCH, and oxo-MiNCH) were combined to estimate the parent compound exposure. The molar sum of DEHP (∑DEHP), DiNP(∑DINP) and DINCH (∑DINCH) metabolites were calculated by dividing each metabolite concentration by its molecular weight and then summing the metabolites that share a common parent compound.

For statistical analysis, urinary concentrations of PHA and DINCH below the limit of detection (LOD) were assigned a value equal to half the LOD. Phthalate metabolite concentrations for each participant were adjusted for specific gravity as previously described (Sabaredzovic et al. 2015) using the following formula: Adjusted Urine Concentration = Measured Urine Concentration (ng/mL) × (Mean SG-1)/(measured SG-1). The mean SG in the present study was 1.018. SG-corrected metabolites measures were natural log (ln)-transformed to normality before analysis.

Statistical Analysis

Descriptive statistics of maternal and child characteristics were computed using baseline data. Continuous variables are described as means and standard deviations (SD), or median and quartile and categorical variables are shown as counts and their corresponding percentages.

The evaluation of the association was not tested for metabolites that were detected in less than 1% of samples (MCHP, MnPeP, and MnOP). Spearman correlations were calculated between all the phthalate metabolites.

Association of Phthalates Compounds with Birth Weight

Gestational age is a possible intermediate step between prenatal phthalate exposure and birth weight.

In our sample, we found that higher exposure to MiBP, MnBP, MEHHP, MEOHP, MECPP, ∑DEHP, oxo-MINCH and ∑DINCH was associated with higher gestational ages (Supplementary Table 1). Thus, the final model for the birth weight did not consider gestational age as covariate. As covariates, we considered sex, gemelarity, maternal education, maternal age, and maternal weight before pregnancy.

Log-linear regression models were run to test the associations between concentrations of phthalate metabolites and birth weight z-score with the calculation of regression coefficients (β) and the corresponding 95% confidence intervals (95% CI).

Growth Curves

Measurements extracted from the child health book records at birth, 4, 6, 8, and 12 months to model growth curves were used to assess child growth. To model the growth curves, we use a linear mixed effects model (a two-degree polynomial curve with age was fitted). First, we tested age non-linearity using different degrees. One, two and three degrees were tested and visual inspection of the residuals against the fitted values was checked to assess the best degree and if the distribution was normal. Secondly, the random effects (random intercept and/or slope) were assessed. Respective fixed regression coefficients (β) and 95% confidence intervals (CI) were used to estimate the magnitude of the association. All models include fixed effect for age and age square and a random intercept and slope by individual. The total number of measurements from the 535 participants included in the analysis, a total of 2296 measurements of weight (4 measurements per subject per individual until the first year of age, on average) were analyzed. The third step was assessed if there was an interaction between age terms and all the compounds in the study. No significant interaction was found (data not shown).

We presented a final model for the growth curves considering the confounders identified in the directed acyclic graph (DAG). The following covariates were considered in constructing the DAG: maternal age, maternal education, maternal weight before pregnancy and gestational age, gestational age, breastfeeding duration, sex, and gemelarity (Fig. 2).

For the analyses of the association between compounds and growth during the first year, we corrected age for gestational age by adding the gestational age in months to chronological age (month) and subtracting six months (younger children have 6 months) applieit d to all children.

The lme4 package (Bates et al. 2015) from R 4.2.1 was used to fit the linear mixed effects models.

Results

The included participants had lower maternal age, lower education, fewer multiple births, and presented higher birthweight and gestational age than non-included participants (Table 1). Most of the compounds were detected in more than 90% of the samples, except for MnOP, MnPeP, and MCHP metabolites, with less than 1% detection (Table 2). MEP had the largest median concentration (39.4 µg/L), followed by the MiBP (13.2 µg/L), MnBP (12.9 µg/L), and the cx-MiNP (11.5 µg/L). Spearman's correlation analysis between the individual metabolites is presented in supplementary Table 2. Most phthalate metabolites were somewhat positively correlated. As expected, correlations were mostly between metabolites deriving from the same parent

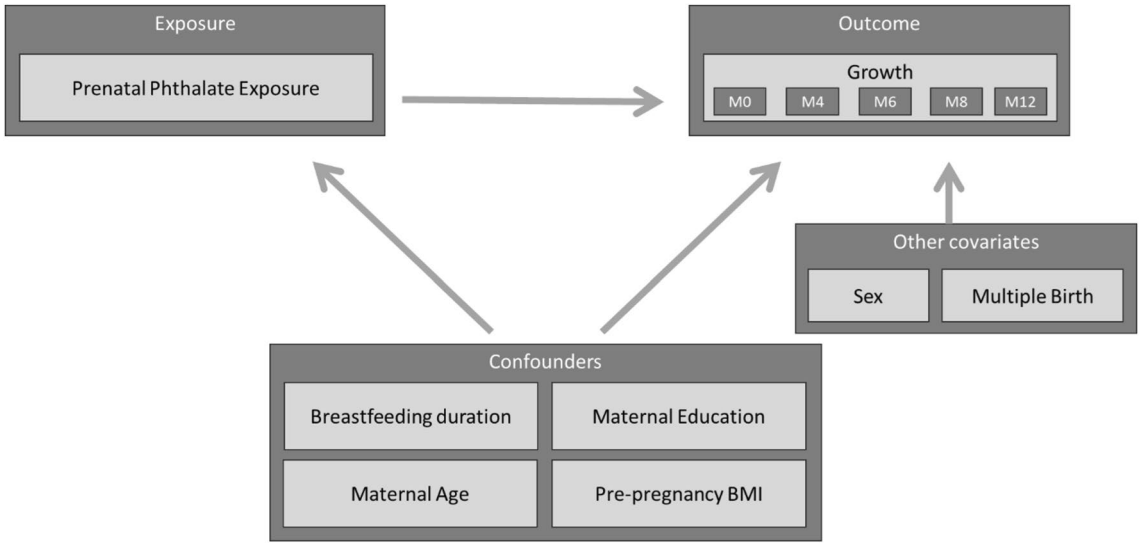

Fig. 2 Directed acyclic graph generated to assess the impact of intrauterine phthalate exposure on child growth during the first year of life. Y0: birth weight; M4: first anthropometric measurement (about 4 months of age); M6: second weight measurement (about 6 months of age); M8: third weight measurement (about 8 months of age); M12: fourth weight measurement (about 12 months of age)

Table 1 Comparison between participants and non-participants

		Included participants	Non-included participants	*p*
Maternal and pregnancy characteristics		***n* = 535**	***n* = 190**	
Maternal education (years), mean (SD)		13.0 (3.0)	14.0 (2.4)	< 0.001
Maternal age (years), mean (SD)		31.6 (5.5)	32.2 (4.7)	0.130
Pre-pregnancy weight (kg), mean (SD)		65.6 (13.6)	64.6 (11.7)	0.349
Gestational age (weeks), mean (SD)		38.1 (2.3)	36.5 (3.1)	< 0.001
Newborn characteristics				
Gemelarity, *n* (%)				
	Singleton	391 (73.1)	88 (46.3)	< 0.001
	Multiples	144 (26.9)	102 (53.7)	
Sex, *n* (%)				
	Male	283 (52.9)	109 (57.4)	0.310
	Female	252 (47.1)	81 (42.6)	
Birth weight (g), mean (SD)		2974.4 (634.8)	2581.4 (743.7)	< 0.001
Birth weight-for-gestational age, Z-score, mean (SD)		− 0.31 (0.96)	− 0.59 (0.99)	< 0.001

Bold: *p*-value less than 0.05

compound. LMW PHA metabolites, including MEP, MiBP, and MnBP, presented significant positive correlations ($r = 0.142–0.588$). For PHA metabolites with HMW, including MBzP, MEHP, MEHHP, MEOHP, MECPP, MEHHP, OH-MiNP, oxo-MiNP, cx-MiNP, and OH-MPHP, the significant correlation coefficients ranged from 0.096 to 0.961. (Supplementary Table 2).

Table 3 shows the association between intrauterine phthalate and DINCH metabolites concentrations and birth weight z-score. In the crude model, the MnBP, MECPP, and OH-MPHP metabolites presented a negative statistically significant association on the birth weight z-score. Nevertheless, only the metabolite of DnBP (MnBP) reached statistical significance after adjusting for confounders ($\beta = -0.195$ (95% CI −0.372; −0.018)). Sex-specific effects have been tested, and in general, after adjustments, the results were similar between sex. It was only observed differences in the metabolites of the DEHP parent compound, where they showed a positive association in males and a negative association in females (supplementary Table 3).

The relation between intrauterine exposure to PHA and child growth during the first year of life is presented

Table 2 Parent compounds and respective PHA and DINCH metabolite concentrations (µg/L) in urine samples

Parent compound	Metabolite measured (SG-adjusted)	LOD (µg/L)	LOQ (µg/L)	*N* (%)	Min	25th percentile	Median (µg/L)	75th percentile	Max
Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)	0.2	0.5	515 (96.3)	2.03	20.4	39.4	84.7	7173
Di-iso-butyl phthalate (DiBP)	Mono-iso-butyl phthalate (MiBP)	0.2	0.5	534 (99.8)	1.44	7.84	13.2	23.3	283
Di-n-butyl phthalate (DnBP)	Mono-n-butyl phthalate (MnBP)	0.2	0.5	535 (100)	1.15	8.12	12.9	24.5	414
Benzylbutyl phthalate (BBzP)	Monobenzyl phthalate (MBzP)	0.07	0.2	510 (95.3)	0.12	0.77	1.33	2.37	552
Di-n-pentyl phthalate (DnPeP)	Mono-n-pentyl phthalate (MnPeP)	0.2	0.5	9 (0.02)	0.28	0.43	0.57	0.89	1.61
DCHP (di-cyclohexyl phtalate)	Mono-cyclohexyl phthalate (MCHP)	0.2	0.5	4 (0.04)	0.48	0.50	0.81	2.64	3.16
DnOP (di-n-octyl phthalate)	Mono-n-octyl phthalate (MnOP)	0.5	1.5	54 (0.1)	0.41	0.67	0.90	1.32	3.75
Di (2-ethylhexyl) phthalate (DEHP)	Mono-2-ethylhexyl phthalate (MEHP)	0.2	0.5	433 (80.9)	0.14	1.06	3.91	15.4	143
	Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP)	0.2	0.5	534 (99.8)	0.54	2.47	3.75	5.79	80.4
	Mono-2-ethyl-5oxohexyl phthalate (MEOHP)	0.2	0.5	532 (99.4)	0.35	1.92	2.92	4.63	47.8
	Mono-2-ethyl-5-carboxypentyl phthalate (MECPP)	0.7	2	535 (100)	2.27	6.87	9.64	13.9	99.3
Di-isononyl phthalate (DiNP)	Mono-4-methyl-7-hydroxyoctyl phthalate (OH-MiNP)	0.2	0.5	535 (100)	0.54	2.81	4.91	8.35	195
	Mono-4-methyl-7-oxooctyl phthalate (oxo-MiNP)	0.2	0.5	511 (95.5)	0.19	1.55	2.79	5.60	199
	Mono-4-methyl-7-carboxyoctyl phthalate (cx-MiNP)	0.7	2	535 (100)	1.58	7.73	11.49	20.0	337
Bis(2-propylheptyl) phthalate (DPHP)	Mono-6-hydroxy-propylheptyl phthalatephthalate (OH-MPHP)	0.2	0.5	478 (89.3)	0.16	0.70	1.09	1.80	39.3

Table 2 (continued)

Parent compound	Metabolite measured (SG-adjusted)	LOD (µg/L)	LOQ (µg/L)	*N* (%)	Min	25th percentile	Median (µg/L)	75th percentile	Max
1,2-Cyclohexane dicarboxylic acid, diisononyl ester (DINCH)	2-(((Hydroxy-4-methyloctyl) oxy) carbonyl) cyclohexanecarboxylic acidacid (OH-MINCH)	0.2	0.5	524 (97.9)	0.31	0.83	1.22	1.93	595
	2-(((4-Methyl-7-oxooctyl) oxy) carbonyl) cyclohexanecarboxylic acidacid (oxo-MINCH)	0.2	0.5	505 (94.3)	0.21	0.66	0.99	1.66	324

Table 3 Birthweight Z score (*g*) in relation to log-specific gravity-adjusted prenatal phthalate exposure

(ln)-transformed SG-corrected metabolites	*N*	Crude β (95%CI)	Adjusted model[a] β (95%CI)
MEP	515	−0.173 (−0.324; 0.023)	0.006 (−0.130; 0.142)
MiBP	534	0.050 (−0.163; 0.264)	0.017 (−0.171; 0.205)
MnBP	535	**−0.240 (−0.438; −0.042)**	**−0.195 (−0.372; −0.018)**
MBzP	535	−0.045 (−0.204; 0.114)	−0.018 (−0.158; 0.121)
MEHP	535	0.039 (−0.057; 0.135)	0.004 (−0.080; 0.088)
MEHHP	535	−0.163 (−0.429; 0.103)	0.001 (−0.234; 0.235)
MEOHP	535	−0.129 (−0.385; 0.127)	0.004(−0.221; 0.230)
MECPP	535	**−0.347 (−0.676; −0.018)**	0.052 (−0.242; 0.347)
∑DEHP	535	−0.046 (−0.161; 0.068)	0.013 (−0.088; 0.114)
OH-MiNP	535	−0.052 (−0.261; 0.156)	−0.074 (−0.256; 0.108)
Oxo-MiNP	535	−0.155 (−0.311; 0.002)	−0.069 (−0.207; 0.069)
cx-MiNP	535	−0.263 (−0.492; −0.034)	−0.097 (−0.299; 0.105)
∑DINP	535	−0.086 (−0.183; 0.012)	−0.042 (−0,128; 0.044)
OH-MPHP	535	**−0.353 (−0.553; −0.153)**	−0.152 (−0.331; 0.028)
OH-MINCH	535	−0.126 (−0.341; 0.089)	−0.020 (−0.209; 0.169)
Oxo-MINCH	535	−0.149 (−0.352; 0.054)	−0.053 (−0.231; 0.126)
∑DINCH	535	−0.065 (−0.162; 0.032)	−0.015 (−0.101; 0.070)

[a]Adjusted model for sex and gemelarity, maternal education, maternal age, and maternal weight before pregnancy

MEP Monoethyl phthalate, *MiBP* Mono-iso-butyl phthalate, *MnBP* Mono-n-butyl phthalate, *MBzP* Monobenzyl phthalate, *MnPeP* Mono-n-pentyl phthalate, *MCHP* Mono-cyclo-hexyl phthalate, *MnOP* Mono-n-octyl phthalate, *MEHP* Mono-2-Ethylhexyl phthalate, *MEHHP* Mono-2-ethyl-5-hydroxyhexyl phthalate, *MEOHP* Mono-2-ethyl-5-oxoyhexyl phthalate, *MECPP* Mono-2-ethyl-5-carboxypentyl phthalate, ∑*DEHP* molar sum of DEHP metabolites, *OH-MiNP* Mono-4-methyl-7-hydroxyoctyl phthalate, *oxo-MiNP* Mono-4- methyl-7oxooctyl phthalate, *cx-MiNP* ∑*DINP* molar sum of DINP metabolites, Mono-4-methyl-7-carboxyheptyl phthalate, *OH-MPHP* Mono-6-hydroxy-propylheptylphthalate, *OH-MiNCH* 2-(Hydroxyl-4-methyloctyl)oxy)carbonyl) cyclohexanecarboxylic acid, *oxo-MiNCH* 2-(4-Methyl-7-oxyoctyl)oxy)carbonyl) cyclohexanecarboxylic acid, ∑*DINCH* molar sum of DINCH metabolites. Bold: *p*-value less than 0.05

in Table 4. The results are similar to those found for birth weight, and no statistically significant association was found between prenatal exposure to PHA and child growth during the first year. We also tested a model including breastfeeding duration. In general, the results are similar or attenuated, but for MiBP and DEHP, an increase in the association was found. A positive statistically significant association after adjusted for breastfeeding duration were found when we used the sum of DEHP metabolites $\beta = 0.062$ (95% CI 0.002; 0.121). Sex-specific effects have been tested, and only

Table 4 Child weight growth in the first year of life (kg) in relation to log-specific gravity-adjusted intrauterine phthalate exposure

(ln)-transformed SG-corrected metabolites	Model 0 β (95%CI)	Adjusted Model 1 β (95%CI)	Adjusted Model 2 β (95%CI)
MEP	−0.011 (−0.079; 0.057)	0.041 (−0.025; 0.106)	0.046 (−0.032; 0.123)
MiBP	0.071 (−0.027; 0.169)	0.059 (−0.033; 0.151)	0.122 (0.007; 0.237)
MnBP	−0.041 (−0.133; 0.051)	−0.032 −0.120; 0.056)	0.028 (−0.085; 0.142)
MBzP	0.004 (−0.070; 0.079)	0.003 (−0.066; 0.074)	0.030 (−0.060; 0.119)
MEHP	0.040 (−0.003; 0.083)	0.031 (−0.009; 0.072)	0.060 (0.010; 0.110)
MEHHP	−0.017 (−0.137; 0.103)	0.035 (−0.078; 0.148)	0.112 (−0.025; 0.250)
MEOHP	0.001 (−0.115; 0.116)	0.048 (−0.061; 0.156)	0.125(−0.005; 0.256)
MECPP	−0.115 (−0.264; 0.033)	−0.001 (−0.143; 0.142)	0.068 (−0.101; 0.238)
∑DEHP	0.013 (−0.039; 0.065)	0.030 (−0.019; 0.079)	**0.062 (0.002; 0.121)**
OH-MiNP	−0.026 (−0.121; 0.069)	−0.039 (−0.128; 0.050)	0.007(−0.104; 0.117)
Oxo-MiNP	−0.042 (−0.113; 0.030)	−0.029 (−0.097; 0.038)	0.002 (−0.059; 0.108)
cx-MiNP	−0.084 (−0.188; 0.021)	−0.048 (−0.147; 0.050)	0.014 (−0.107; 0.137)
∑DINP	−0.030 (−0.075; 0.015)	−0.022 (−0.064; 0.020)	0.006 (−0.046; 0.058)
OH-MPHP	−0.117 (−0.209; −0.026)	−0.073 (−0.161; 0.015)	−0.005(−0.161; 0.059)
OH-MINCH	−0.059 (−0.160; 0.042)	−0.040 (−0.135; 0.056)	−0.039 (−0.162; 0.083)
Oxo-MINCH	−0.083 (−0.178; 0.012	−0.667 (−0.157; 0.023)	0.082 (−0.200; 0.036)
∑DINCH	−0.035 (−0.081; 0.011)	−0.026 (−0.070; 0.017)	−0.031 (−0.089; 0.026)

Adjusted Model 0: Age and age^2 (time)

Adjusted Model 1: Model 0 plus sex and gemelarity, maternal education, maternal age, and maternal weight before pregnancy

Adjusted Model 2: Model 1 plus breastfeeding duration

MEP Monoethyl phthalate, *MiBP* Mono-iso-butyl phthalate, *MnBP* Mono-n-butyl phthalate, *MBzP* Monobenzyl phthalate, *MnPeP* Mono-n-pentyl phthalate, *MCHP* Mono-cyclo-hexyl phthalate, *MnOP* Mono-n-octyl phthalate, *MEHP* Mono-2-Ethylhexyl phthalate, *MEHHP* Mono-2-ethyl-5-hydroxyhexyl phthalate, *MEOHP* Mono-2-ethyl-5-oxoyhexyl phthalate, *MECPP* Mono-2-ethyl-5-carboxypentyl phthalate, ∑*DEHP* molar sum of DEHP metabolites, *OH-MiNP* Mono-4-methyl-7-hydroxyoctyl phthalate, *oxo-MiNP* Mono-4- methyl-7oxooctyl phthalate, *cx-MiNP* ∑*DINP* molar sum of DINP metabolites, Mono-4-methyl-7-carboxyheptyl phthalate, *OH-MPHP* Mono-6-hydroxy-propylheptylphthalate, *OH-MiNCH* 2-(Hydroxyl-4-methyloctyl)oxy)carbonyl) cyclohexanecarboxylic acid, *oxo-MiNCH* 2-(4-Methyl-7-oxyoctyl)oxy)carbonyl) cyclohexanecarboxylic acid, ∑*DINCH* molar sum of DINCH metabolites; Bold: *p*-value less than 0.05

a statistically significant association was found for males regarding MiBP metabolite (Supplementary table 4). After adjustments for the final model (including breastfeeding duration), each incremental unit of ln transformed MiBP intrauterine concentration increased by 0.236 kg (95% CI 0.063; 0.409) of child weight. Table 5 shows the relation between intrauterine exposure to PHA and child length growth in the first year of life.

Discussion

In this study, we analyzed the association between prenatal exposure to PHA and DINCH with birth weight and child growth in the first year of life. Although, higher maternal PHA concentrations tended to be associated with lower birth weight, no statistically significant association was found. The sum of DEHP metabolites presented a positive statistically significant association with growth curves in the first year of life.

Only 3 phthalate metabolites (MCHP, MnPeP, and MnOP) were found in less than 1% of the sample. For the other compounds, urinary phthalate metabolite levels of pregnant women in our study population presented a wide range of individual exposures since they ranged from below LOD to several-fold higher, which is important to have power for identified associations. However, our cohort showed lower phthalate metabolites levels than other European studies with pregnant women using the same methodologic approach (Sabaredzovic et al. 2015; Haug et al. 2018), which may have contributed to the lack of associations. Nevertheless, it is important to note that other studies reported smaller sample sizes and included older studies, and the differences observed could be explained by the globally decreasing of PHA due to European regulations.

We found that PHA metabolites from the same parent compound followed the same association trend for birth

Table 5 Child length in the first year of life (kg) in relation to log-specific gravity-adjusted intrauterine phthalate exposure

(ln)-transformed SG-corrected metabolites	Model 0 β (95%CI)	Adjusted model 1 β (95%CI)	Adjusted model 2 β (95%CI)
MEP	−0.046 (−0.374; 0.281)	0.230 (−0.077; 0.537)	0.236 (−0.127; 0.598)
MiBP	0.227 (−0.241; 0.696)	0.228 (−0.201; 0.657)	0.304 (−0.228; 0.837)
MnBP	−0.350 (−0.788; 0.089)	−0.239 (−0.646;0.168)	−0.104 (−0.626; 0.419)
MBzP	0.131 (−0.226; 0.487)	0.157 (−0.167; 0.481)	0.251 (−0.157; 0.659)
MEHP	0.149 (−0.073; 0.304)	0.098 (−0.091; 0.287)	**0.252 (0.019; 0.485)**
MEHHP	0.040 (−0.533; 0.612)	0.379 (−0.142; 0.900)	0.498 (−0.137; 1.123)
MEOHP	0.142 (−0.115; 0.116)	0.458 (−0.041; 0.968)	0.546(−0.056; 1.148)
MECPP	−0.247 (−0.958; 0.465)	0.450 (−0.206; 0.107)	0.526 (−0.253; 1.305)
∑DEHP	0.150 (−0.074; 0.375)	0.137 (−0.088; 0.362)	0.249 (−0.026; 0.524)
OH-MiNP	−0.006 (−0.461; 0.448)	−0.065 (−0.477; 0.347)	−0.061(−0.568; 0.446)
Oxo-MiNP	−0.084 (−0.429; 0.260)	0.004 (−0.309; 0.318)	0.093 (−0.291; 0.476)
cx-MiNP	−0.338 (−0.841; 0.163)	−0.118 (−0.576; 0.341)	0.051 (−0.512; 0.614)
∑DiNP	−0.092 (−0.306; 0.122)	−0.037 (−0.232; 0.157)	0.013 (−0.228; 0.253)
OH-MPHP	**−0.474 (−0.911; −0.035)**	−0.157 (−0.565; 0.251)	−0.012(−0.520; 0.496)
OH-MINCH	−0.113 (−0.596; 0.371)	−0.006 (−0.448; 0.437)	−0.126 (−0.691; 0.439)
Oxo-MINCH	−0.181 (−0.638; 0.276)	−0.096 (−0.515; 0.323)	−0.239 (−0.783; 0.304)
∑DINCH	−0.058 (−0.278; 0.162)	−0.014 (−0.216; 0.187)	−0.074 (−0.338; 0.190)

Adjusted Model 0 Age and age^2 (time)

Adjusted Model 1 Model 0 plus sex and gemelarity, maternal education, maternal age, and maternal weight before pregnancy

Adjusted Model 2 Model 1 plus breastfeeding duration

MEP Monoethyl phthalate, *MiBP* Mono-iso-butyl phthalate, *MnBP* Mono-n-butyl phthalate, *MBzP* Monobenzyl phthalate, *MnPeP* Mono-n-pentyl phthalate, *MCHP* Mono-cyclo-hexyl phthalate, *MnOP* Mono-n-octyl phthalate, *MEHP* Mono-2-Ethylhexyl phthalate, *MEHHP* Mono-2-ethyl-5-hydroxyhexyl phthalate, *MEOHP* Mono-2-ethyl-5-oxoyhexyl phthalate, *MECPP* Mono-2-ethyl-5-carboxypentyl phthalate, *∑DEHP* molar sum of DEHP metabolites, *OH-MiNP* Mono-4-methyl-7-hydroxyoctyl phthalate, *oxo-MiNP* Mono-4- methyl-7oxooctyl phthalate, *cx-MiNP* *∑DINP* molar sum of DINP metabolites, Mono-4-methyl-7-carboxyheptyl phthalate, *OH-MPHP* Mono-6-hydroxy-propylheptylphthalate, *OH-MiNCH* 2-(Hydroxyl-4-methyloctyl)oxy)carbonyl) cyclohexanecarboxylic acid, *oxo-MiNCH* 2-(4-Methyl-7-oxyoctyl)oxy)carbonyl) cyclohexanecarboxylic acid, *∑DINCH* molar sum of DINCH metabolites. Bold: *p*-value less than 0.05

weight and child growth. This clustering results supports the association with the general family. However, we cannot exclude the hypothesis that this clustering results may represent a common effect since the similarity of chemical structure of the different compounds leads to the same result in the analysis or, since these metabolites have been driven from the same parent compound, they represent a simultaneously exposure to similar compounds.

In the present study, higher maternal phthalate concentrations tended to be associated with lower birth weight. The MnBP, MECPP, and OH-MPHP metabolites presented a negative statistically significant association on the birth weight z-score in the crude model; nonetheless, after covariate adjustment, most of the results lost statistical significance or were attenuated, indicating that there was confounding by these factors. In the final model, only statistical significance was found for MnBP, which was inversely associated with birth weight. No statistically significant differences were found after stratifying by sex.

In line with our results, Chang et al. 2022 showed that pregnant women exposed to MnBP are at risk for delivering LBW and SGA male neonates, despite not finding a significant association between maternal MnBP exposure levels and birth weight z scores (Chang et al. 2022). Conversely, a Spanish study showed that MnBP was associated with higher birth weight in boys, but not in girls (Casas et al. 2016). Previous studies evaluating the overall study population have reported statistically significant negative results for MMP, MEP, MEHP, and MEOPH (Gao et al. 2017; Zhang et al. 2018; Zhu et al. 2018) or non-significant results (Wolff et al. 2008; Suzuki et al. 2010; Casas et al. 2016; Polanska et al. 2016; Shoaff et al. 2016; Huang et al. 2017; Zhu et al. 2018) in the associations between phthalate metabolites and size at birth.

No phthalate or DINCH metabolites were significantly associated with growth curves in the adjusted model, even for compounds with high concentration levels. From the studies that evaluated growth trajectories longitudinally

early in life (de Cock et al. 2014, Valvi et al. 2015, Botton et al. 2016, Li et al. 2021, Nidens et al. 2021) with inconsistent results, our results align with Nidens et al., which found no association between prenatal phthalate exposure and weight gain in the first two years of life (Nidens et al. 2021). The remaining three studies are discrepant from our findings. Valvi et al. 2015 reported that prenatal exposure to ΣHMW PHA was significantly associated with a lower weight gain Z-score in the first six months of age among boys (Valvi et al. 2015). Also, Li et al. 2021 showed significant negative associations between prenatal exposure to DEHP with weight z-scores at six months in female infants (Li et al. 2021). Nevertheless, DEHP levels were associated with higher growth in the first 12 months of age among all infants (de Cock et al. 2014; Li et al. 2021). Bottom (2016) shows that MBzP tended to be positively associated with predicted weight growth velocity, especially at early ages in male offspring (Botton et al. 2016).

After further adjusting for breastfeeding duration, the results remain similar or attenuated, but an increase in the association was found for MiBP, MBzP and DEHP metabolites. A statistically significant association was found for males regarding MiBP metabolite after stratifying for sex. The lower urine concentrations of phthalate metabolites in our population comparing with other studies might have complicated the detection of associations. The increase in the association measure found for MiBP, MBzP and DEHP metabolites after adjusting for breastfeeding duration can be explained by the lipophilic properties of PHA that increasingly fat soluble depending on how long their chain is (Giuliani et al. 2020; Lucas et al. 2022). ∑DEHP where the only one with a positive statistical significance association, this could be explained since HMW PHA are more liposoluble than LMW PHA (van der Meer et al. 2021). So, they have more probability have been accumulated in the adipose tissue before pregnancy and transfer to infants upon breastfeeding (Stefanidou et al. 2009; Lehmann et al. 2014). The transference of PHA from body lipids into breast milk is due to its high lipid content. Subsequently, breast milk produced by exposed mothers may have a significant burden of PHA, and breastfed infants may be exposed to these chemicals (Lehmann et al. 2014).

The main strength of this study includes its longitudinal design with information on multiple time points for the same child during the first year of life. Furthermore, we included the phthalate substitute DINCH to assess their effects on child growth since their use in different consumer products is increasing in European countries (Dominguez-Romero et al. 2022).

Our findings may also highlight the limitation of using spot urine samples to reflect chronic exposure to PHA since maternal spot urine samples are only indicative of recent exposure (Hoppin et al. 2002). Nonetheless, it was shown that a single measure moderately predicts exposure over some months (Hoppin et al. 2002; Hauser et al. 2004) with moderate to high sensitivity to allocate individuals into higher ranges of exposures.

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Data Availability The data that support the findings of this study are available from the corresponding author, CR, upon reasonable request.

Declarations

Conflict of interest There are no conflicts of interest to disclose.

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