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Full length article

# Analyzing the impact of phthalate and DINCH exposure on fetal growth in a cohort with repeated urine collection

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## ABSTRACT

**Background:** Most previous studies investigating the associations between prenatal exposure to phthalates and fetal growth relied on measurements of phthalate metabolites at a single time point. They also focused on weight at birth without assessing growth over pregnancy, preventing the identification of potential periods of fetal vulnerability. We examined the associations between pregnancy urinary phthalate metabolites and fetal growth outcomes measured twice during pregnancy and at birth.

**Methods:** For 484 pregnant women, we assessed 13 phthalate and two 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) metabolite concentrations from two within-subject weekly pools of up to 21 urine samples (median of 18 and 34 gestational weeks, respectively). Fetal biparietal diameter, femur length, head and abdominal circumferences were measured during two routine pregnancy follow-up ultrasonographies (median 22 and 32 gestational weeks, respectively) and estimated fetal weight (EFW) was calculated. Newborn weight, length, and head circumference were measured at birth. Associations between phthalate/DINCH metabolite and growth parameters were investigated using adjusted linear regression and Bayesian kernel machine regression models.

**Results:** Detection rates were above 99 % for all phthalate/DINCH metabolites. While no association was observed with birth measurements, mono-*iso*-butyl phthalate (MiBP) and mono-*n*-butyl phthalate (MnBP) were positively associated with most fetal growth parameters measured at the second trimester. Specifically, MiBP was positively associated with biparietal diameter, head and abdominal circumferences, while MnBP was positively associated with EFW, head and abdominal circumferences, with stronger associations among males. Pregnancy MnBP was positively associated with biparietal diameter and femur length at third trimester. Mixture of phthalate/DINCH metabolites was positively associated with EFW at second trimester.

**Abbreviations:** BMI, body mass index; BKMR, Bayesian kernel machine regression; CI, confidence interval; cx-MiNP, mono-4-methyl-7-carboxyoctyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DiBP, di-*iso*-butyl phthalate; DINCH, 1,2-cyclohexane dicarboxylic acid, diisononyl ester; DiNP, diisononyl phthalate; DnBP, di-*n*-butyl phthalate; HPLC-MS-MS, high-performance liquid chromatography coupled to mass spectrometry; LMP, last menstrual period; LOD, limit of detection; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-*iso*-butyl phthalate; MnBP, mono-*n*-butyl phthalate; MMCHP, mono-2-carboxymethyl hexyl phthalate; oh-MINCH, 2-(((hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic acid; oh-MiNP, mono-4-methyl-7-hydroxyoctyl phthalate; oh-MPHP, 6-hydroxy monopropylheptyl phthalate; oxo-MINCH, 2-(((4-methyl-7-oxooctyl)oxy)carbonyl)cyclohexanecarboxylic acid; oxo-MiNP, mono-4-methyl-7-oxooctyl phthalate; ΣDEHP, molar sum of DEHP metabolites (MECPP, MEHHP, MEHP, MEOHP, MMCHP); ΣDINCH, molar sum of DINCH metabolites (oh-MINCH, oxo-MINCH); ΣDiNP, molar sum of DiNP metabolites (cx-MiNP, oh-MiNP, oxo-MiNP).

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**Conclusions:** In this pregnancy cohort using repeated urine samples to assess exposure, MiBP and MnBP were associated with increased fetal growth parameters. Further investigation on the effects of phthalates on child health would be relevant for expanding current knowledge on their long-term effects.

## 1. Introduction

Phthalates are ubiquitous environmental contaminants used in various consumer products such as food packaging, toys, medical devices, and personal care products. Some are endocrine disrupting chemicals that can enter the body through ingestion, inhalation, and skin contact, and are quickly metabolized and excreted in urine. This widespread use in consumer products leads to ubiquitous exposure in the general population including pregnant women (Woodruff et al., 2011), that has been linked to adverse maternal health outcomes including pregnancy loss (Zhang et al., 2020), gestational diabetes (Yan et al., 2022), and preterm delivery (Wang et al., 2022; Welch et al., 2022). Regarding fetus health, a growing body of literature has investigated the associations between prenatal phthalate exposure and fetal growth, mostly measured at birth (19 studies reviewed by (Kamai et al., 2019) and followed up by others (Bloom et al., 2021; Cathey et al., 2022; Guo et al., 2022; Hu et al., 2021; Kalloo et al., 2020; Nidens et al., 2021; Qian et al., 2023)). However, results of these studies were overall inconsistent, reporting null, positive or negative associations depending of the phthalate-outcome pairs considered. For example, while Wolff and colleagues reported a positive association between monoethyl phthalate (MEP) and head circumference at birth, Bloom and colleagues reported a negative association (Bloom et al., 2021; Wolff et al., 2008). Studies also relied on ultrasound measurements to monitor fetal growth but again reporting inconsistent results, however with more null or negative than positive associations (Botton et al., 2016; Casas et al., 2016; Cowell et al., 2023; Ferguson et al., 2022, 2016; Goodrich et al., 2019; Ish et al., 2022; Li et al., 2021; Santos et al., 2021; Stevens et al., 2023, 2022; van den Dries et al., 2021). Furthermore, several studies have reported differences in associations related to infant's sex (Kamai et al., 2019).

Most studies investigating phthalate's and 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH)'s health effects used one or a few urine samples to measure their metabolite concentrations, leading to classical exposure measurement error and bias in dose-response functions (Perrier et al., 2016). Collection of repeated samples is key to reduce such bias (Perrier et al., 2016; Vernet et al., 2019) for chemicals with high within-subject temporal variability in urinary metabolite concentrations, as phthalates and DINCH (Casas et al., 2018; Silva et al., 2004).

Finally, data is scarce for new chemicals, such as DINCH, that has been introduced into the market in 2002 and used as replacement of high molecular weight phthalates (Schütze et al., 2014). Only one study, so far, has investigated the association between DINCH and fetal growth and reported no associations (N = 254 (Stevens et al., 2023)).

Our aim was to investigate the associations between prenatal exposure to phthalates and replacement compounds such as DINCH and fetal growth, as well as whether infant's sex serves as an effect modifier of these associations. To limit exposure measurement error, we relied on pools of repeated urine samples (up to 42 urine samples per pregnancy) and further applied measurement error models to correct the dose-response function for potential measurement error in the exposure.

## 2. Population and methods

### 2.1. Study design and population

This study included mother-child pairs enrolled in the SEPAGES prospective parent-child cohort between 2014 and 2017 in Grenoble area (France) (Lyon-Caen et al., 2019). Inclusion criteria were 1) being pregnant (singleton pregnancy) by less than 19 gestational weeks at

inclusion, 2) at least 18 years of age, 3) to read and speak French fluently, 4) to be affiliated to the French national social security system, and 5) to plan to deliver in one of the four maternity clinics of the area. The exclusion criteria were being under guardianship or deprived of liberty. Out of the 484 study participants, 477 and 456 subjects had urine samples collected in the second and third pregnancy trimesters, respectively (Supplementary Figure 1). The final sample size depended on the availability of fetal growth measurements and ranged from 433 to 475. The mothers signed an informed consent form and both parents signed the infant's consent form prior to inclusion. The study was approved by the relevant ethical committees: Comité de Protection des Personnes Sud-Est V and Commission Nationale Informatique et des Libertés.

### 2.2. Urine samples collection

Pregnant women were instructed to collect three spot urine samples per day (morning, midday, evening) for seven consecutive days at median 18 (second trimester) and 34 (third trimester) weeks of pregnancy. After collection, individual urine samples were stored at  $-20^{\circ}\text{C}$  in the participant's personal freezer until SEPAGES fieldworkers picked them up at the end of the collection week and transported them to the biobank. The samples were then thawed at  $4^{\circ}\text{C}$  overnight and within-subject weekly pools were made by pooling equal volume of all the spot urine samples collected over the collection week (Perrier et al., 2016; Philippat and Calafat, 2021).

### 2.3. Assessment of prenatal exposure to phthalates

An aliquot of each weekly pool of urine was shipped on dry ice to the Norwegian Institute of Public Health (Oslo, Norway) for exposure biomarker assessment. Briefly, metabolite concentrations were measured in 300  $\mu\text{L}$  of urine, after deconjugating the glucuronides using enzyme beta-glucuronidase (*E. coli*) and incubating for 1.5 h at  $37^{\circ}\text{C}$ , using the high-performance liquid chromatography coupled to tandem mass spectrometer as described elsewhere (Philippat et al., 2021; Sabaredzovic et al., 2015). We assessed urinary concentrations of 13 phthalate metabolites and two DINCH metabolites (Supplementary Table 1). Procedural blanks, in-house quality controls, and standard reference material (SRM 3673) from National Institute of Standards and Technology (NIST) were analyzed along with the samples. The accuracy of the method ranged from 70 % to 125 % and the precision given as relative standard deviation was below 25 % (Sabaredzovic et al., 2015).

### 2.4. Standardization and transformation of phthalate metabolite concentrations

To account for between-samples variation related to urine processing and assay, we standardized concentrations of all metabolites but mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP) that was not affected by urine processing and assay conditions, using a two-step approach (Guilbert et al., 2021; Mortamais et al., 2012; Philippat et al., 2014). The considered conditions were sample transport time from participant's home to the biobank, individual samples thawing time at  $4^{\circ}\text{C}$  during the pooling procedure, and analytical batches. First, we estimated the associations between each biomarker concentration (ln-transformed) assessed in pools and the conditions mentioned above using linear regression adjusted for maternal age, education, pre-pregnancy body mass index, parity, specific gravity, date, and season of sample collection. We then used the estimated effects of processing/assay conditions

associated with the biomarker urine concentrations (Wald test  $p$ -value  $< 0.2$ ) to predict standardized concentrations (i.e., concentrations that would have been observed if all samples had been processed under the same conditions and assayed in the same batch) by subtracting the effect estimates associated with the conditions from the measured biomarker concentrations (Supplementary Table 2). Biomarker concentrations were not adjusted for specific gravity, since it has been observed that such correction, classically applied to account for urine dilution when relying on spot samples, was not necessary or even counter-productive for equal-volume pooled samples (Philippat and Calafat, 2021). Before further analyses, standardized phthalate concentrations were  $\ln$ -transformed to approach normality.

## 2.5. Assessment of fetal growth

We extracted abdominal circumference, biparietal diameter, femoral length, and head circumference from two ultrasound examinations. Fetal weight was estimated at each ultrasound using the Hadlock formula (Hadlock et al., 1985). French pregnant women usually undergo three ultrasound examinations as a part of the routine pregnancy follow-up. In order to match with the timing of exposure assessments, we used those corresponding to the second and third ultrasound examinations (median 22 and 32 gestational weeks, respectively). For women with multiple ultrasound measurements per trimester of pregnancy, we selected the examination that was performed at the gestational age closest to the median gestational age of women with only one ultrasound per trimester available. At birth, newborns' weight, length, and head circumference were extracted from the child health booklet.

## 2.6. Statistical analyses

### 2.6.1. Adjustment factors

The potential confounders were selected *a priori* and included: maternal height (continuous) and pre-pregnancy weight (continuous), maternal age (continuous), maternal active smoking during 2nd trimester of pregnancy (above one cigarette a day; no, yes), maternal education level (less than three years after high school, three to four years after high school, more than four years after high school), gestational age at measurement (continuous and quadratic term), parity (nulliparous, one, two or more children) and child's sex (female, male; except for models stratified by sex). Data on covariates were collected by self-administered questionnaires using an online platform and questionnaires administered by a fieldworker during a study visit.

### 2.6.2. Imputation of the missing data

Phthalate/DINCH metabolites concentration values below limit of detection (LOD) were singly imputed using the NADA (Lee, 2020) and *msm* (Jackson, 2011) R packages allowing to randomly draw values below the LOD from the estimated distribution of the compound (Helsel, 1990; Lubin et al., 2004). Missing values for continuous covariates were replaced by the median calculated for the studied population and for categorical variables they were replaced by mode.

### 2.6.3. Associations between individual phthalate/DINCH metabolite concentrations and growth outcomes

Molar sums of metabolites of the same parent compounds (Diisononyl phthalate [DiNP], Di(2-ethylhexyl) phthalate [DEHP], DINCH) were computed and expressed in  $\mu\text{mol/L}$  and used in all the analyses instead of concentrations of individual metabolites.

We used adjusted linear regression models to study the associations between individual biomarkers (individual metabolites or molar sum) and each growth measurement. Specifically, we studied the associations between growth outcomes assessed at the second trimester and second trimester phthalate/DINCH metabolite urinary concentrations while later growth measurements (third trimester and at birth) were associated to the mean of phthalate/DINCH concentrations measured in

second and third trimester urine pools (Supplementary Figure 1). To allow results comparisons across outcomes and across timing of measurements, results using standardized growth measurements were presented in figures. The standardization was done by dividing time-specific growth measurements by their standard deviation. Distributions of the non-standardized growth outcomes are available in the Supplementary Table 3.  $P$ -values  $< 0.05$  were considered as statistically significant. To explore sex-specific effects, we assessed interaction between each phthalate/DINCH metabolite and child's sex, then for interactions with  $p$ -value below 0.2 we further performed additional sex-stratified analyses.

### 2.6.4. Associations between phthalate/DINCH metabolites mixture and growth outcomes

We investigated the overall effect of the biomarkers mixture on each growth measurement using a Bayesian kernel machine regression (BKMR) model (Bobb et al., 2015). Similarly to individual biomarker analysis, we studied the associations between second trimester-measured growth outcomes and phthalate/DINCH metabolites mixture while later growth measurements (third trimester and at birth) were associated to the mixture of mean phthalate/DINCH concentrations at second and third trimesters. We performed 50,000 iteration and generate plots that illustrated the expected change in growth parameters for each 5 % increase in exposure, relative to no exposure.

### 2.6.5. Sensitivity analyses

To account for exposure measurement error, we applied a random-intercept model with 100 replications to calculate the variance of the estimated effects (Bartlett et al., 2009) using the *meqr* R package (Nab et al., 2021). This maximum likelihood-based method allows for correction of the dose-response function for measurement error occurring in the exposure (Carroll, 2006). It estimates the unobserved exposure  $X_i$  (real exposure measured without error) using  $k_i$  error-prone measurements ( $W_{i1}, \dots, W_{ik_i}$ ) of  $X_i$  and other covariates. Then we used the predicted values of  $X_i$  in the regression model.

Finally, to account for the effect of the exposure standardization on processing and assay conditions, we ran additional analysis using non-standardized biomarker concentrations.

## 3. Results

On average, women were 32.1 years old and delivered at 40.0 gestational weeks (Table 1). Detection rates were above 99 % for all phthalate and DINCH metabolites (Table 2). We observed moderate correlations between urinary phthalate/DINCH metabolite concentrations within the same time point (Spearman's correlation estimate  $\rho$  ranged between 0.12 and 0.64), and low to moderate correlation between trimesters ( $\rho$  ranged between 0.03 and 0.62) (Supplementary Figure 2).

### 3.1. Individual phthalate/DINCH metabolite concentrations and growth outcomes

Mono-*iso*-butyl phthalate (MiBP) concentrations were positively associated with all ultrasound measures at second trimester except for femur length (Fig. 1). Specifically, MiBP exposure at second trimester was associated with increased head circumference ( $\beta = 1.44$  mm, 95 % CI = 0.16 to 2.72 mm), abdominal circumference ( $\beta = 1.49$  mm, 95 % CI = 0.03 to 2.94 mm), and biparietal diameter ( $\beta = 0.46$  mm, 95 % CI = 0.03 to 0.89 mm) (Supplementary Table 4). While effect estimates were also positive for third trimester fetal growth measurements, confidence intervals were larger (Fig. 1).

Mono-*n*-butyl phthalate (MnBP) concentrations were positively associated with all growth outcomes measured at the second trimester ( $p$ -values ranged between 0.01 and 0.07, Supplementary Table 4). Positive associations were also observed at third trimester between

**Table 1**

Characteristics of the mother–child pairs included in SEPAGES couple-child cohort study (France, 2014–2017, n = 478).

Characteristic	Distribution	
	n (%)	Median [25th, 75th centiles]
<b>Maternal weight before pregnancy (kg)</b>		59.0 [54.0; 66.0]
Missing	0 (0.0)	
<b>Maternal height (cm)</b>		165 [161; 169]
Missing	4 (0.8)	
<b>Maternal age at conception (years)</b>		32.1 [29.9; 35.2]
Missing	0 (0.0)	
<b>Maternal education after high school (years)</b>		
< 3	82 (17.2)	
3–4	125 (26.2)	
> 4	268 (56.1)	
Missing	3 (0.6)	
<b>Maternal active smoking during trimester 2</b>		
≤ 1 cigarette/day	427 (89.3)	
> 1 cigarette/day	11 (2.3)	
Missing	40 (8.4)	
<b>Parity before the index pregnancy</b>		
Nulliparous	219 (45.8)	
1 child	211 (44.1)	
≥ 2 children	48 (10.0)	
Missing	0 (0.0)	
<b>Duration of gestation (weeks)<sup>a</sup></b>		40.0 [39.0; 40.7]
< 37 weeks	21 (4.4)	
≥ 37 weeks	455 (95.2)	
Missing	2 (0.4) <sup>b</sup>	
<b>Child's sex</b>		
Female	220 (46.0)	
Male	256 (53.6)	
Missing	2 (0.4) <sup>b</sup>	
<b>Weight at birth (g)</b>		3280 [3040; 3560]
< 2500 g	17 (3.6)	
≥ 2500 g and < 4000 g	422 (88.3)	
≥ 4000 g	36 (7.5)	
Missing	3 (0.6)	

Abbreviations: LMP: last menstrual period.

<sup>a</sup> Based on the date of the LMP or gestational duration assessed by the obstetrician if it differed from the LMP-based estimate by more than 2 weeks.

<sup>b</sup> Two recruited women had ultrasound data but dropped out of the study before delivery.

pregnancy MnBP concentrations and biparietal diameter ( $\beta = 0.66$  mm, 95 % CI = 0.07 to 1.25 mm) and femur length ( $\beta = 0.38$ , 95 % CI = 0.00 to 0.76 mm).

Other phthalates were not associated with any fetal growth outcome. Overall, there was no association with birth outcomes.

### 3.2. Sex-specific associations

We detected interactions with child's sex (p-value < 0.2) for several phthalates–growth outcome pairs, however, after stratification for child's sex, only the associations with MnBP were significant (Fig. 2). Specifically, the positive associations observed in our main analysis between MnBP, estimated fetal weight, and head and abdominal circumferences were observed in males ( $\beta = 0.32$  g, 95 % CI = 0.12 to 0.51 g,  $\beta = 2.99$  mm, 95 % CI = 0.94 to 5.04 mm and  $\beta = 3.19$  mm, 95 % CI = 0.95 to 5.43 mm, respectively) but not in females ( $\beta = 0.05$  g, 95 % CI = -0.12 to 0.23 g,  $\beta = 0.65$  mm, 95 % CI = -1.05 to 2.36 mm and  $\beta = 0.51$  mm, 95 % CI = -1.50 to 2.51 mm, respectively; Supplementary Table 5).

### 3.3. Phthalate/DINCH metabolites mixture and growth outcomes

Mixture of phthalate/DINCH metabolites was not associated with ultrasound parameters at second trimester, while it was positively associated with estimated fetal weight at the third trimester and showed a positive trend of association with abdominal circumference (Fig. 3). Specifically, fetuses exposed to the 75th percentile of the mixture showed, on average, a higher estimated fetal weight of 184.89 g (95 % CI, 52.28 to 317.50 g) and a longer abdominal circumference of 5.65 mm (95 % CI, -0.41 to 11.71 mm), compared to no exposure. Similarly to the individual biomarker analysis, there was no association with birth outcomes.

### 3.4. Sensitivity analyses

Results of the sensitivity analyses using an algorithm to account for measurement error in the exposure were overall similar to those of our main analysis. For the phthalate exposures identified as associated with growth outcomes in the main analysis (MiBP and MnBP), the corrected effect estimates were generally further away from zero compared to those of the main analysis, but the CIs were notably wider (Supplementary Table 6). However, this analysis accounting for exposure measurement error revealed one new isolated association at second trimester between  $\Sigma$ DINCH concentrations and increased abdominal circumference ( $\beta = 2.49$  mm, 95 % CI = 0.34 to 7.11 mm compared to  $\beta = 0.25$  mm, 95 % CI = -0.70 to 1.21 mm in main analysis).

Associations using non-standardized pregnancy phthalate metabolite concentrations gave overall similar results to those of our main analysis, with most of the associations observed between MiBP, MnBP and growth parameter at the second trimester (Supplementary Table 7). The analysis using the non-standardized exposure concentrations revealed one new isolated association at second trimester between  $\Sigma$ DINCH concentrations and increased biparietal diameter (p-value of 0.05 [ $\beta = 0.25$  mm, 95 % CI = 0.00 to 0.51 mm] compared to a p-value of 0.1 [ $\beta = 0.24$  mm, 95 % CI = -0.04 to 0.51 mm] in main analysis).

## 4. Discussion

Relying on collection of repeated within-subject urine samples over pregnancy, we identified positive associations between the mixture and estimated fetal weight at third trimester, as well as between two individual metabolites, MiBP and MnBP and most of the growth parameters measured during pregnancy, but not at birth. When interaction with child's sex was detected (MnBP and estimated fetal weight, head and abdominal circumferences), stronger associations were observed among males than females. MiBP and MnBP are metabolites of two dibutyl phthalates (di-*iso*-butyl phthalate [DiBP] and di-*n*-butyl phthalate [DnBP]), respectively that differ by their structural isomerism (Centers for Disease Control and Prevention, 2017; Koch et al., 2012). Both are used as industrial solvents or additives in personal care products and food (Kavlock et al., 2002) and in our study, their concentrations were highly correlated within trimesters (rho of 0.60 and 0.64 at second and third trimester, respectively), suggesting similar sources of exposure as also discussed by Koch and colleagues (Koch et al., 2013). Other phthalate metabolites were not associated with any growth outcome. Finally, sensitivity analysis accounting for exposure measurement error gave similar results overall, but revealed that in the second trimester DINCH was positively associated with abdominal circumference.

Most studies assessing maternal urinary concentration of MnBP and MiBP did not report associations with ultrasound measurements (Botton et al., 2016; Ferguson et al., 2016; Goodrich et al., 2019; Zhao et al., 2014), with few exceptions (Casas et al., 2016; Santos et al., 2021; Stevens et al., 2023). The lack of association reported in most studies for MnBP and MiBP, may result from low number of urine samples collected per woman (N ranged between 1 and 4) (Perrier et al., 2016). The reported intraclass correlation coefficients (ICC) ranged from 0.32 to 0.57



**Table 2**

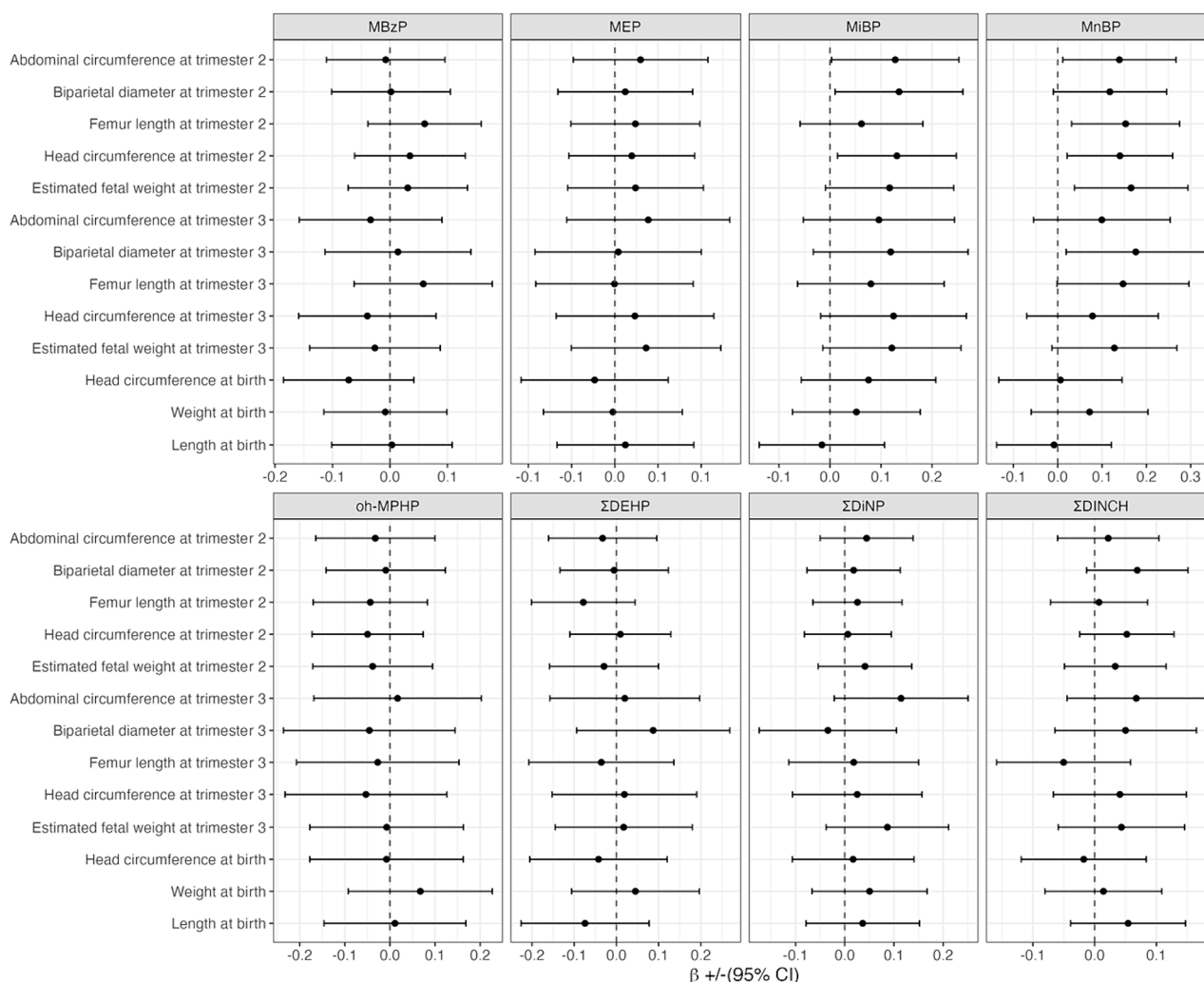
Average maternal urinary phthalate metabolite concentrations assessed in weekly pools collected in the second and third trimesters of pregnancy, without or with standardization on sampling and assay conditions (n = 478 pregnant women).

Phthalate/DINCH metabolite	LOD (µg/L)	Raw concentrations									Standardized <sup>a</sup> concentrations								
		Trimester 2 urine pool						Trimester 3 urine pool			Trimester 2 urine pool						Trimester 3 urine pool		
		>LOD (%)		Percentiles				>LOD (%)		Percentiles	>LOD (%)		Percentiles				>LOD (%)		Percentiles
		5th	50th	95th	5th	50th	95th	5th	50th	95th	5th	50th	95th	5th	50th	95th	5th	50th	95th
MBzP	0.07	100	1.5	4.8	17.3	100	1.6	4.4	18.1	100	1.7	4.8	17.3	100	1.5	4.6	18.4		
MEP	0.2	100	6.4	24.8	146.4	100	5.0	21.6	139.7	100	6.4	24	136.9	100	4.9	20.8	131.3		
MiBP	0.2	100	6.6	18.1	53.8	100	5.9	18.2	67.3	100	6.6	15.8	46.5	100	5.5	15.8	53.3		
MnBP	0.2	100	5.4	12.6	40.5	100	4.7	13.1	38.9	100	4.8	11.2	33.6	100	4.1	11.8	33.6		
oh-MPHP	0.07	100	0.4	0.9	2.7	100	0.3	0.8	2.2	100	0.5	0.9	2.6	100	0.5	0.8	2.4		
MECPP	0.7	100	5.4	10.5	29.0	100	4.9	10.3	31.3	100	5.1	9.8	26.3	100	5.1	10.1	26.6		
MEHHP	0.2	100	3.2	7.0	23.5	100	2.6	7.0	20.9	100	3.2	6.9	24.1	100	2.8	7.2	21.3		
MEHP	0.2	100	0.7	2.3	8.0	99.8	0.5	1.9	7.0	100	0.8	2.4	8.3	100	0.5	1.9	6.8		
MEOHP	0.2	100	2.2	5.2	17.2	100	2.1	5.4	16.5	100	2.3	5.0	16.6	100	2.0	5.3	15.1		
MMCHP	0.7	99.4	5.0	9.4	25.2	99.6	4.5	9.3	24.4	99.4	4.2	7.6	19.8	99.6	4.1	7.6	19.7		
ΣDEHP*	/	/	0.1	0.1	0.3	/	0.1	0.1	0.3	/	/	/	/	/	/	/	/		
cx-MiNP	0.4	100	2.5	4.6	27.1	100	2.3	4.4	18.2	100	2.6	4.6	26.0	100	2.4	4.4	15.5		
oh-MiNP	0.1	100	1.7	4.9	28.7	100	1.5	4.5	29.3	/	/	/	/	/	/	/	/		
oxo-MiNP	0.1	100	0.8	2.2	17.2	100	0.8	2.2	14.4	100	0.8	2.1	14.5	100	0.7	2.0	11.9		
ΣDiNP*	/	/	0.0	0.0	0.2	/	0.0	0.0	0.2	/	/	/	/	/	/	/	/		
oh-MINCH	0.07	100	0.5	1.5	13.6	100	0.4	1.3	9.2	100	0.7	1.7	15.1	100	0.6	1.6	11.0		
oxo-MINCH	0.07	99.8	0.4	1.1	8.9	99.8	0.4	1.1	7	99.8	0.6	1.4	10.1	100	0.5	1.4	9.2		
ΣDINCH*	/	/	0.0	0.0	0.1	/	0.0	0.0	0.1	/	/	/	/	/	/	/	/		

Note: Units are in µg/L except for molar sums (ΣDEHP, ΣDiNP and ΣDINCH) that are displayed in µmol/L.

Abbreviations: cx-MiNP: mono-4-methyl-7-carboxyoctyl phthalate, DEHP: di(2-ethylhexyl) phthalate, DINCH: 1,2-cyclohexane dicarboxylic acid, diisononyl ester, DiNP: diisononyl phthalate, LOD: limit of detection, MBzP: monobenzyl phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEP: monoethyl phthalate, MiBP: mono-*iso*-butyl phthalate, MnBP: mono-*n*-butyl phthalate, MMCHP: mono-2-carboxymethyl hexyl phthalate, oh-MINCH: 2-(((hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic acid, oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate, oh-MPHP: 6-hydroxy monopropylheptyl phthalate, oxo-MINCH: 2-(((4-methyl-7-oxooctyl)oxy)carbonyl)cyclohexanecarboxylic acid, oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate, \*ΣDEHP: molar sum (µmol/L) of DEHP metabolites (MECPP, MEHHP, MEHP, MEOHP, MMCHP), \*ΣDINCH: molar sum (µmol/L) of DINCH metabolites (oh-MINCH, oxo-MINCH), \*ΣDiNP: molar sum (µmol/L) of DiNP metabolites (cx-MiNP, oh-MiNP, oxoMiNP).

<sup>a</sup> Raw concentrations were standardized on sampling and assay conditions (Guilbert et al., 2021; Mortamais et al., 2012; Philippat et al., 2014). oh-MiNP concentrations were not standardized either as none of the considered conditions was associated with this phthalate.

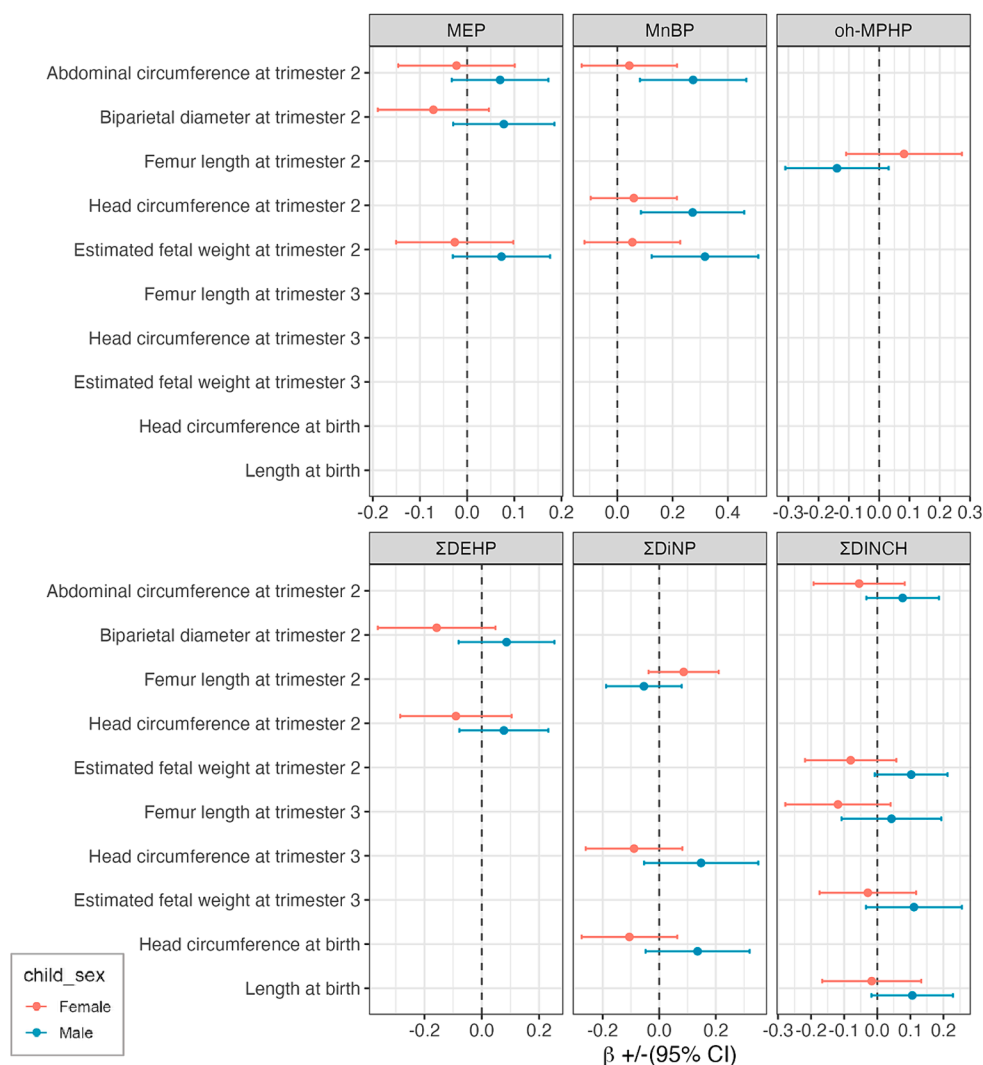


**Fig. 1.** Adjusted associations between pregnancy phthalate/DINCH metabolite concentrations and standard deviation of growth outcomes *in utero* (trimesters 2 and 3) and at birth.  $\beta$  regression estimates correspond to the change in standard deviation of the considered growth outcome associated with a 1-unit increase in standardized ln-transformed urinary phthalate/DINCH metabolite concentration. Trimester 2 outcomes were related to trimester 2 exposures while trimester 3 and birth outcomes were related to trimesters 2 and 3 averaged exposures. Regression models were adjusted for maternal height, maternal pre-pregnancy weight, maternal age, maternal active smoking during trimester 2, maternal education level, gestational age at measurement, child's sex, and parity.  $\beta$  regression estimates correspond to the change in standard deviation of the considered growth outcome associated with a 1-unit increase in standardized ln-transformed urinary phthalate/DINCH metabolite concentration. For the original units of growth measurements refer to the [Supplementary Table 3](#).  $\beta$  regression estimates corresponding to the change in millimeter or gram of the considered growth outcome are provided in [Supplementary Table 4](#). Abbreviations: cx-MiNP: mono-4-methyl-7-carboxyoctyl phthalate, MBzP: monobenzyl phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEP: monoethyl phthalate, MiBP: mono-*iso*-butyl phthalate, MnBP: mono-*n*-butyl phthalate, MMCHP: mono-2-carboxymethyl hexyl phthalate, oh-MINCH: 2-(((hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic acid, oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate, oh-MPHP: 6-hydroxy monopropylheptyl phthalate, oxo-MINCH: 2-(((4-methyl-7-oxooctyl)oxy)carbonyl)cyclohexanecarboxylic acid, oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate,  $\Sigma$ DEHP: molar sum of DEHP metabolites (MECPP, MEHHP, MEHP, MEOHP, MMCHP),  $\Sigma$ DINCH: molar sum of DINCH metabolites (oh-MINCH, oxo-MINCH),  $\Sigma$ DiNP: molar sum of DiNP metabolites (cx-MiNP, oh-MiNP, oxo-MiNP).

for MnBP and from 0.34 to 0.58 for MiBP (reviewed by (Casas et al., 2018)), suggesting moderate temporal variability for these compounds. In our study relying on pooled biospecimens, the ICC of MnBP and MiBP in pregnant women were 0.58 and 0.60, respectively (Philippat et al., 2021). Among the few studies suggesting association for these two compounds, MnBP has been negatively associated with fetal length at third trimester (Santos et al., 2021) and head circumference during the second trimester (Casas et al., 2016), which is not consistent with our results suggesting positive associations with these outcomes. Results for abdominal circumference and estimated fetal weight were mixed. One study, in line with our results, reported positive association with MnBP at third trimester in males but not in girls (Casas et al., 2016), while another reported negative association with abdominal circumference for metabolites of both DnBP and DiBP (Stevens et al., 2023). Overall, our

results on a positive association between MnBP and MiBP are inconsistent with most of the previously published studies investigating prenatal exposure to MnBP and MiBP.

We did not find any association with birth measurements. This highlighted the distinctions between evaluations of growth during pregnancy (ultrasound measurements) and measurements at birth, and suggested that birth measurements may be an inadequate proxy for fetal growth, as they do not distinguish constitutionally small fetuses from growth-restricted ones. In line with our results, others investigating either individual metabolites (Botton et al., 2016; Chiu et al., 2018; Philippat et al., 2019; Shoaff et al., 2016; Woods et al., 2017) or mixture (Hu et al., 2021; Kalloo et al., 2020) did not report associations with birth outcomes. However, several others studies have reported associations with anthropometric measurements at birth, with the sign of the



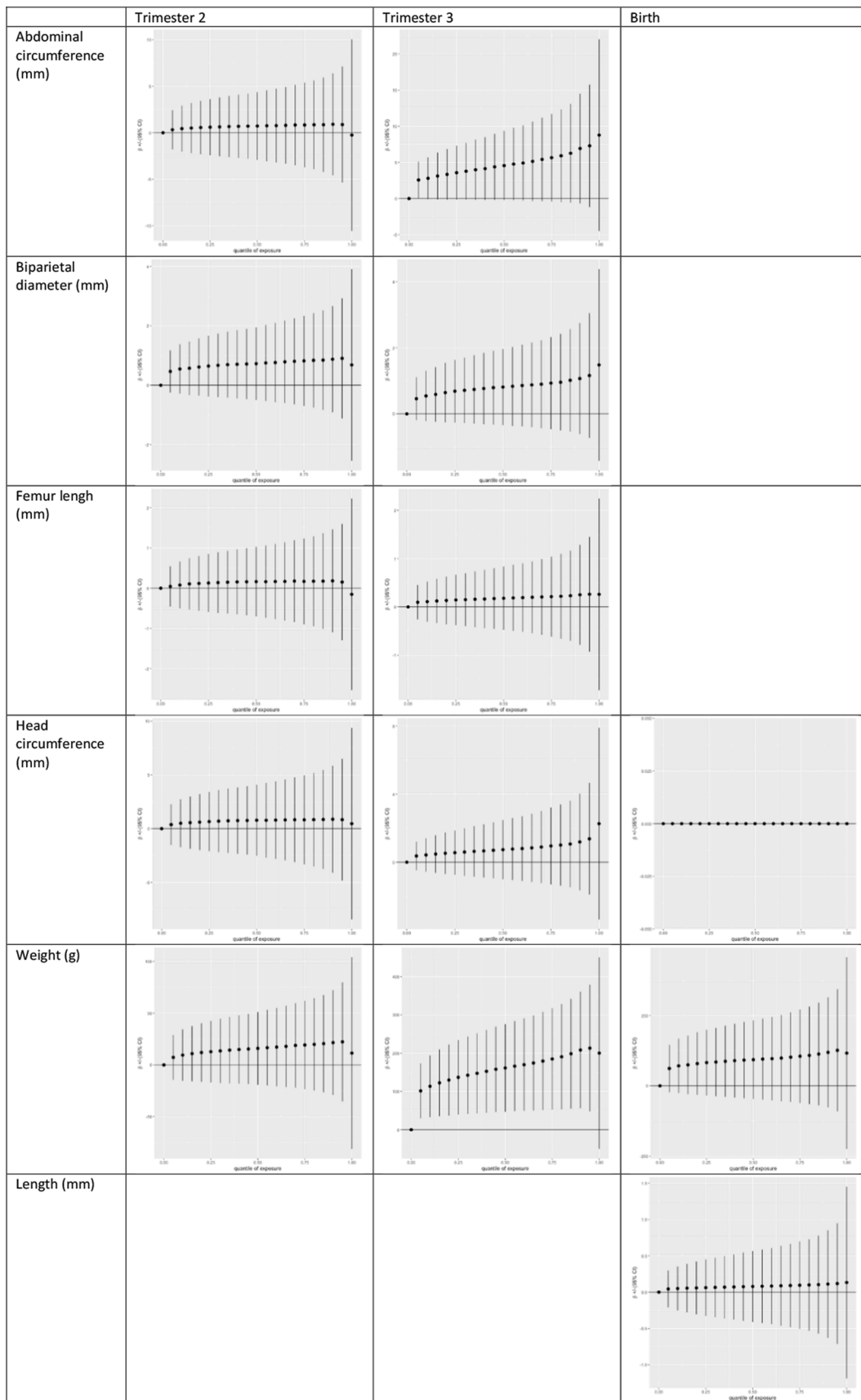
**Fig. 2.** Adjusted associations between pregnancy phthalate/DINCH metabolite concentrations and standard deviation of growth outcomes *in utero* (at trimester 2 and 3) and at birth in a sex-stratified analysis. Only phthalate/DINCH metabolites showing p-values for interaction with child's sex < 0.2 are displayed. For MBzP and MiBP no interactions with child's sex were detected. Trimester 2 outcomes were related to trimester 2 exposures while trimester 3 and birth outcomes were related to trimesters 2 and 3 averaged exposures. Regression models were adjusted for maternal height, maternal pre-pregnancy weight, maternal age, maternal active smoking during trimester 2, maternal education level, gestational age at measurement, and parity.  $\beta$  regression estimates correspond to the change in standard deviation of the considered growth outcome associated with a 1-unit increase in standardized ln-transformed urinary phthalate/DINCH metabolite concentration. For the original units of growth measurements refer to the [Supplementary Table 3](#). Results for sex-stratified analysis with  $\beta$  regression estimates corresponding to the change in millimeter or gram of the considered growth outcome are provided in [Supplementary Table 5](#). Abbreviations: cx-MiNP: mono-4-methyl-7-carboxyoctyl phthalate, DEHP: di(2-ethylhexyl) phthalate, DINCH: 1,2-cyclohexane dicarboxylic acid, diisononyl ester, DiNP: diisononyl phthalate, MBzP: monobenzyl phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEP: monoethyl phthalate, MiBP: mono-*iso*-butyl phthalate, MnBP: mono-*n*-butyl phthalate, MMCHP: mono-2-carboxymethyl hexyl phthalate, oh-MINCH: 2-(((hydroxy-4-methylloctyl)oxy)carbonyl)cyclohexanecarboxylic acid, oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate, oh-MPHP: 6-hydroxy monopropylheptyl phthalate, oxo-MINCH: 2-(((4-methyl-7-oxoocetyl)oxy)carbonyl)cyclohexanecarboxylic acid, oxo-MiNP: mono-4-methyl-7-oxoocetyl phthalate,  $\Sigma$ DEHP: molar sum of DEHP metabolites (MECPP, MEHHP, MEHP, MEOHP, MMCHP),  $\Sigma$ DINCH: molar sum of DINCH metabolites (oh-MINCH, oxo-MINCH),  $\Sigma$ DiNP: molar sum of DiNP metabolites (cx-MiNP, oh-MiNP, oxo-MiNP).

effect depending on the phthalate-outcome pair studied (Ferguson et al., 2022; Kamai et al., 2019; Nidens et al., 2021; Qian et al., 2023; Santos et al., 2021). When specifically considering exposure to MiBP and MnBP (or their parent compounds DiBP and DnBP, respectively), while some studies have reported no associations (Bloom et al., 2021; Chiu et al., 2018; Gao et al., 2017; Goodrich et al., 2019; Shoaff et al., 2016; Stevens et al., 2022; van den Dries et al., 2021; Woods et al., 2017), both positive (Guo et al., 2020, 2022; Messerlian et al., 2017; Watkins et al., 2016; Zhang et al., 2018) and negative associations have been observed with birth measurements (Ferguson et al., 2022; Qian et al., 2023; Santos et al., 2021; Stevens et al., 2023).

In the sensitivity analyses, the regression coefficient estimates

obtained after accounting for exposure measurement error may reflect the real effect estimates more accurately than the uncorrected ones, however their CIs usually show larger variances than CIs of classical linear regression (Perrier et al., 2016), and thus should be interpreted with caution. Interestingly, both sensitivity analyses (after accounting for exposure measurement error and using non-standardized pregnancy phthalate metabolite concentrations), identified positive associations between DINCH concentrations and abdominal circumference and biparietal diameter at the second trimester. DINCH is a new compound replacing the high molecular weight phthalates, such as DEHP. The literature on prenatal exposure to this compound is scarce. To our knowledge, only one study investigated the association between this





**Fig. 3.** Change for each 5% increase in exposure to the mixture of phthalate/DINCH metabolite concentrations and growth outcomes *in utero* (at trimester 2 and 3) and at birth. Trimester 2 outcomes were related to trimester 2 exposures while trimester 3 and birth outcomes were related to trimesters 2 and 3 averaged exposures. BKMR models were adjusted for maternal height, maternal pre-pregnancy weight, maternal age, maternal active smoking during trimester 2, maternal education level, gestational age at measurement, child sex and parity. Abbreviations: BKMR: Bayesian kernel machine regression

compound and fetal growth assessed in 254 pregnant women recruited between 2017 and 2020, and reported no associations (Stevens et al., 2023). Additionally, one study has measured prenatal DINCH concentration, but investigated post-natal weight trajectory among 1118 mother–child pairs in Sweden (Svensson et al., 2021). Studies on rodent models and *in vitro* on human cells reported that DINCH was associated with an activation of the peroxisome proliferator-activated receptors (PPARs) (Campioli et al., 2019; Engel et al., 2018).

Most associations reported in this study were positive, suggesting increased fetal growth to be associated with increased phthalate exposure. Similarly to undergrowth, fetal overgrowth can also lead to perinatal complication for the fetus or the mother, such as preterm birth (Elenis et al., 2020; Pedersen et al., 2008). Fetal overgrowth has also been associated with higher risk to develop obesity, diabetes, and cardiovascular disease in childhood and later in life (Lai et al., 2019; Skilton et al., 2014).

Regarding mechanisms by which phthalates can affect growth and metabolism, these may also be pro-inflammatory effects through upregulation of the PPARs, and specifically PPAR-gamma which contributes to adipocyte differentiation and insulin sensitization, as shown for non-phthalate plasticizers (i.e., DINCH) (Campioli et al., 2019; Engel et al., 2018). In addition to the well-known effect on androgen receptors (anti-androgenic effect) some phthalates can also target the thyroid hormone pathway; of interest, MnBP has been positively associated with 3'-triiodothyronine during pregnancy among women with normal iodine concentration from the SEPAGES cohort (Nakiwala et al., 2022). While DiBP has been less studied, the transplacental passage of DnBP metabolites has been demonstrated in rats, with its predominant metabolite, MnBP, largely responsible for the observed embryotoxic effects (Sailenfait, 1998). Oral exposure to DnBP in mice has been associated with delayed ossification and decreased fetal weight of the litter (Ema et al., 1993; Shiota et al., 1980; Shiota and Nishimura, 1982).

Furthermore, phthalates can affect the aryl hydrocarbon receptor (Mankidy et al., 2013) known to be involved in the regulation of lipogenesis and glucose homeostasis (Sato et al., 2008; Thackaberry et al., 2003). Finally, in our study, for associations modified by child's sex, they were overall stronger among males. Sex-specific associations may result from the disruption of the androgen-signaling pathway in males through interaction between phthalates and nuclear androgen receptors (Swedenborg et al., 2009), or may be explained by sexually dimorphic placental response (Sood et al., 2017). For example, DnBP shows an anti-androgenic activity, with a decrease in testosterone production being the most commonly described effect (Czubacka et al., 2021), comforting the plausibility of the stronger effect that we observed among males. However, our sex-specific results should be interpreted cautiously since our sample size was limited (256 males and 220 females).

Our study is not without limitations. First, the sample size of our study was modest and might not allow for the detection of small effects. However, the unique urine collection scheme applied in our study (up to 42 urine samples per participant during pregnancy) should better represent prenatal exposure during the second and third trimester, decrease bias in the effect estimates (Perrier et al., 2016), and thus increase power compared to studies of similar sample size but relying on a single urine sample. Second, we were not able to assess exposure at first trimester. Finally, we cannot rule out residual confounding by additional unmeasured factors, such as maternal diet, which could be associated with phthalate exposure (Serrano et al., 2014) and fetal growth (Lu et al., 2016). Nevertheless, one study reported no relationship between diet and DiBP and DnBP metabolite concentrations (Koch et al., 2013), suggesting that, for those metabolites, our results are unlikely to be confounded by maternal diet.

In conclusion, results reported for this prospective pregnancy cohort revealed that prenatal concentrations of MiBP and MnBP were associated with increased fetal growth parameters, with stronger associations observed among males. The mixture of phthalates/DINCH metabolites was also associated with increased estimated fetal weight at third

trimester. The sensitivity analyses revealed additional positive associations between  $\Sigma$ DINCH at second trimester and abdominal circumference and biparietal diameter, highlighting the need for investigation of this overlooked compound. Further investigation on the effects of phthalates on child health would be relevant to expand current knowledge on their long-term effects.

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## CRedit authorship contribution statement

**Marion Ouidir:** Formal analysis, Writing – original draft. **Paulina Jedynak:** Data curation, Formal analysis, Writing – original draft. **Mathieu Rolland:** Data curation, Formal analysis, Writing – review & editing. **Sarah Lyon-Caen:** Project administration, Writing – review & editing. **Cathrine Thomsen:** Resources, Writing – review & editing. **Amrit K. Sakhi:** Resources, Writing – review & editing. **Azemira Sabaredzovic:** Resources, Writing – review & editing. **Sam Bayat:** Investigation, Writing – review & editing. **Rémy Slama:** Funding acquisition, Supervision, Writing – review & editing. **Claire Philippat:** Funding acquisition, Supervision, Writing – review & editing.

## Declaration of competing interest

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

## Data availability

Data will be made available on request.

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Morin (Clinique des Cedres, Echirolles), A. Morlot (Clinique Belledonne, Saint-Martin d'Herès), J. Lepeule, S. Lyon-Caen, C. Philippat, I. Pin, J. Quentin, V. Siroux, R. Slama (Inserm, CNRS, University Grenoble Alpes IAB research center).

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108584>.

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