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Phthalate pregnancy exposure and male offspring growth from the intra-uterine period to five years of age

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Abstract

Objective: To study associations between prenatal exposure to phthalates and fetal and postnatal growth up to age 5 years in male offspring.

Methods: Eleven phthalate metabolites were quantified in spot maternal urine samples collected during gestation among 520 women of the EDEN mother-child cohort who gave birth to a boy. Fetal growth was assessed from repeated ultrasound measurements and measurements at birth. We used repeated measures of weight and height in the first 5 years of life to model individual postnatal growth trajectories. We estimated adjusted variations in pre and postnatal growth

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Author contributions

MAC was the principal investigator (PI) of the EDEN cohort study and RS was especially involved in the environmental topics. RS was the PI of the project that also involved CP, MAC and JB. AC carried out the analytical measurements of phthalates at CDC. SC carried out postnatal growth modeling. JB analyzed the data and generated the tables and figures. All authors were involved in data interpretation, writing the paper and had final approval of the submitted and published versions.

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Conflicts of interest statement

The authors declare they have no actual or potential competing financial interests.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.08.033.

parameters associated with an interquartile range increase in ln-transformed phthalate metabolite concentrations.

Results: Monocarboxyisononyl phthalate (MCNP) was positively associated with femoral length during gestation and length at birth. High molecular weight phthalate metabolites were negatively associated with estimated fetal weight throughout pregnancy. Monoethyl phthalate (MEP) showed positive association with weight growth velocity from two to five years and with body mass index at five years (β=0.17 kg/m^2, 95% confidence interval, 0.04, 0.30).

Conclusions: We highlighted associations between gestational exposure to some phthalates and growth in boys. The positive association between MEP and postnatal growth in boys was also reported in several previous human studies.

Keywords

Body Mass Index; Endocrine Disruptors; Epidemiology; Fetal growth; Infant growth; Phthalates

1. Introduction

Pre- and post-natal growth patterns are associated with the risk of overweight or obesity later in life (Botton et al., 2008). In addition to factors such as maternal obesity or tobacco smoking, certain chemicals that exhibit affinity with nuclear receptors involved in lipid metabolism (Casals-Casas and Desvergne, 2011) have been suspected to affect growth and adiposity. This includes diesters of phthalic acid (phthalates). While three of them (di(2-ethylhexyl) phthalate, DEHP; dibutyl phthalate, DBP and butylbenzyl phthalate, BBzP) have been banned from a few products in Europe (e.g., in toys intended to be placed in the mouth by children under three years), phthalates are still used in many consumer products (Hauser and Calafat, 2005). Low molecular weight (LMW) phthalates are mainly used in personal care products (perfumes, lotions, cosmetics) or as coating for pharmaceutical products to provide timed releases; high molecular weight phthalates (HMW) are used as plasticizers in polyvinylchloride floor and wall covering, food packaging, and medical devices (Hauser and Calafat, 2005). Widespread exposure has been reported in French pregnant women (Philippat et al., 2012) and in many other countries.

Fetal life and infancy are potentially critical periods for the health effects of phthalates, in part because detoxification path-ways (e.g. glucuronidation) may not be fully mature during these periods (Gow et al., 2001).

In humans, some studies have investigated the associations between urinary concentrations of phthalate metabolites during pregnancy and offspring size at birth. Urinary concentration of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), a DEHP metabolite, was negatively associated with birth weight in a large cohort of 1250 term infants (Lenters and Portengen, 2015), while other studies did not highlight any association between urinary concentration of phthalate metabolite and offspring size at birth (Philippat et al., 2012; Suzuki et al., 2010; Wolff et al., 2008). Only one study looked at associations with intra-uterine growth assessed by repeated ultrasound during pregnancy; authors reported a positive association between urinary concentration of monobenzyl phthalate (MBzP) and femoral length and a negative

association between mono-n-butyl phthalate (MBP) and head circumference (Casas et al., 2015).

Regarding postnatal growth, one prospective study reported negative associations between prenatal urinary concentrations of metabolites of HMW phthalates and body mass index (BMI) gain during childhood in boys (Valvi et al., 2015). In another study, prenatal concentrations of non-DEHP metabolites were associated with lower BMI in boys (Maresca et al., 2016) In a pooled analysis of 707 US children, Buckley et al. reported a sex-specific association between monoethyl phthalate (MEP) during pregnancy and BMI at 4–7 years, which was negative in girls and positive (although not statistically significant) in boys (Buckley et al., 2016). In the same population, a similar trend was observed with fat mass, although the interaction test with child sex was not significant (Buckley et al., 2015). Finally, a study relying on a multi-pollutants analysis did not find any association between prenatal phthalates exposure and BMI at 7 years (Agay-Shay et al., 2015).

Our aim was to study the relationship between exposure to phthalates during pregnancy and prospectively assessed growth in boys, from the intra-uterine period to five years of age.

2. Methods

2.1. Population

The selection of the study population has been described elsewhere (Philippat et al., 2014). Briefly, 520 mother-boy pairs included in the French EDEN mother–child cohort were selected among the 998 mothers who delivered a boy. Recruitment in the cohort took place in the maternity wards of Poitiers and Nancy University hospitals, before the end of the 24th gestational week from April 2003 through March 2006 (Heude et al., 2015). We focused on males because a first assessment of phthalate exposure has been performed in the framework of a study on male congenital anomalies (Chevrier et al., 2012). Because sex-specific associations in relation with growth were plausible for EDCs (Casals-Casas and Desvergne, 2011), including both genders would, for a given total sample size, have been less statistically powerful than focusing on one gender. We selected male births with complete data on growth (three ultrasound measures, birth parameters and at least three postnatal measurements).

The EDEN cohort received approval from the ethics committee of Kremlin-Bicêtre. Women gave written informed consent for themselves and their child. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

2.2. Outcomes

Biparietal diameter was assessed by ultrasonography three times during pregnancy at mean gestational weeks 12.6 (5th-95th centiles, 11.1–14.0), 22.5 (5–95th centiles, 20.7–24.4) and 32.6 (5th-95th centiles, 30.6–34.2); head circumference, abdominal circumference and femoral length were assessed during the two last ultrasound examinations. Fetal weight was estimated using Hadlock formula (Hadlock et al., 1985) from abdominal circumference, femoral length, biparietal diameter and head circumference. Weight and length at birth were

extracted from hospital maternity records. Because head circumference can be distorted during labor, we relied on measures performed by midwives a few days after birth during the maternity stay.

A Jenss-Bayley mixed effects growth modeling approach was used to assess individual growth trajectories using weight and length or height measured at one, three and five years during study-specific examinations along with measures recorded in the child health booklet by health care practitioners. This model (Botton et al., 2014 Carles et al., 2016) allowed predicting weight and height at the same ages for all children (6, 12, 24, 36 and 60 months). We predicted growth velocities at 3, 6, 12, 24 and 48 months by calculating the first derivative of the individual equation (Botton et al., 2014), attempting to explore the timing of occurrence of any effect on growth. BMI at five years was computed as weight (in kg) for height (in m) squared.

2.3. Exposure assessment

Women collected the first morning urine void at home before the study visit between 22 and 29 gestational weeks (mean=26; 5th-95th centiles, 24 −28); if they forgot, urine was collected during the study visit; exclusion of these mother-child pairs (n=61, 12%) from the main analyses had no substantial effect on the dose-response estimates (not detailed). Urine samples were stored at −80 °C. Creatinine, 11 phthalate metabolites (listed in Table 1) and nine phenols (including triclosan and parabens) were measured at CDC (Atlanta, Georgia, USA) at two periods (110 in 2008, 410 in 2012) using an enzymatic reaction (creatinine) and online solid-phase-extraction high-performance liquid chromatography-isotope dilution tandem mass spectrometry (phthalate metabolites (Silva et al., 2004), phenols (Philippat et al., 2014)).

We calculated:

1. The sum of molar concentrations of DEHP metabolites: mono(2-ethyl-5-carboxypentyl) phthalate [MECPP], MEHHP, mono(2-ethylhexyl) phthalate [MEHP], mono(2-ethyl-5-oxohexyl) phthalate [MEOHP],
2. The sum of total LMW phthalate metabolites: monoethyl phthalate [MEP], mono-n-butyl phthalate [MBP], mono-isobutyl phthalate [MiBP]),
3. The sum of total HMW phthalate metabolites (monobenzyl phthalate [MBzP], monocarboxyisononyl phthalate [MCNP], monocarboxyisooctyl phthalate [MCOP], mono(3-carboxypropyl) phthalate [MCPP], DEHP metabolites.

2.4. Statistical analysis

We used instrumental reading values even for metabolite concentrations below the limit of detection. Ln-transformed concentrations were standardized for collection conditions, creatinine concentrations and analysis period using a two-step standardization method based on regression residuals (Mortamais et al., 2012; Philippat et al., 2014).

Effect estimates (β) are reported for an increase by one interquartile range (IQR) of ln-transformed standardized phthalate metabolite concentrations. We present associations and

95% confidence intervals (CI) estimated at each considered ages; for each compound, we performed a global test for the effect of exposures on prenatal or postnatal growth separately. Statistical analyses were performed with SAS 9.3.

2.5. Associations with prenatal growth

We used the date of last menstrual period (LMP) to estimate the gestational age, except if the estimate by the obstetrician was different from the LMP-based estimate by more than two weeks (n=3 women). In that case, we used the gestational age assessed by the obstetrician. In the models using fetal measurements as outcomes, we coded gestational age with three terms (gestational age at the powers one, two and three). The associations between phthalate metabolite concentrations and prenatal growth measurements were characterized using linear mixed-effect models with random effects corresponding to the mother–child pair on intercept and on linear slope. To allow for the effect of exposures on growth to vary along pregnancy, we included interaction terms between the metabolites concentrations and gestational age. We tested the global effect of each phthalate metabolite concentration on fetal growth parameters using a maximum likelihood ratio test between nested models (i.e. with and without the exposure variable and the interaction terms involving the exposure variable). We used the SAS PROC MIXED to take account the repeated measurements within each fetus during pregnancy, with one model for each exposure-outcome combination and we predicted trimester-specific effect sizes (β) and 95% confidence intervals at the mean gestational age at which each of the three ultrasound measurements were conducted.

2.6. Associations with postnatal growth

Multiple linear regression models were used to study the relationship between the biomarker concentrations and observed birth weight or length (adjusting for gestational age) or BMI at five years (adjusting for exact age at measurement).

To study the associations between phthalate metabolite concentrations and model-predicted postnatal weight and height, we used repeated measurements models with an unstructured covariance structure between the exact time-points. To allow for the effect-measure of exposures to vary along infancy and early childhood, we included interaction terms between metabolite and the time-point dummy-variable.

In supplementary analyses, we explored the associations with measured weight and length or height at birth, one, three and five years (study examinations) instead of model-predicted values, and with head circumference as well. These models were additionally adjusted for child age at the examination.

2.7. Confounding factors and estimated effect size

Directed acyclic graphs (DAG) were used to define adjustment factors (Figs. S1 and S2). Models were adjusted for recruitment center, maternal height (continuous), BMI using self-reported prepregnancy weight (continuous), smoking during pregnancy (active, mean number of cigarettes per day over the pregnancy and passive, yes/no), education level (three categories), age (continuous), weight gain during pregnancy (continuous) and parity (no

previous birth, one, more than one). As paternal anthropometry is associated with postnatal growth (Regnault et al., 2010), postnatal models were additionally adjusted for paternal height (continuous) and BMI (continuous). As growth patterns differ according to gestational age at birth, models were also adjusted for this variable. As we selected the children with available postnatal growth data, there were very few missing values (see Supporting Information, Table S1, maximum number=7) and in the absence of any information, they were imputed using the modal value of the distribution.

2.8. Sensitivity analyses

Pre- and postnatal weight growth models were adjusted for height or length measurements in the main analyses and not in the supplementary analyses. Within the same study population, maternal urinary concentration of the antibacterial agent triclosan has been negatively associated with fetal growth measurements late in pregnancy and parabens have been positively associated with weight at birth and until 36 months (Philippat et al., 2014). Because exposure to these chemicals and phthalates might co-occur, we adjusted the prenatal associations for triclosan concentration and the postnatal associations for the molar sum of paraben concentrations. We tested the impact of adjusting prenatal models for maternal total caloric intake and postnatal weight models for breastfeeding or child caloric intake at eight months (available for 78% of the 520 children), computed based on a three-day dietary record.

3. Results

Average maternal age was 29.7 years; 26% of women were overweight or obese (BMI ≥25 kg/m^2) and 5% developed gestational diabetes. Women in the present study were more educated and smoked less compared to the whole group of EDEN mothers who gave birth to a boy (Table S1). Other characteristics were similar.

Phthalate metabolites were detected in more than 97% of the samples (Table 1). MEP had the largest median (96 μg/L, IQR=51, 195). DEHP metabolites represented the largest proportion of HMW phthalates. Among non-DEHP HMW phthalates, MBzP had the highest median (18 μg/L, IQR=11, 33). Correlations among LMW phthalates were modest (Table S2, below 0.12 for MEP). MEP was the phthalate metabolite most strongly associated with triclosan (r=0.23) and with the sum of molar concentrations of parabens (r=0.25).

Maternal MCNP concentration was associated with increased fetal femoral length (Table 2, global adjusted p-value 0.04) at the second (β, 0.20 mm, 95% CI, 0.00, 0.39 for each IQR increment) and third trimesters of pregnancy (0.24 mm, 95% CI, 0.01, 0.47). This chemical was also associated with increased length at birth (0.19 cm, 95% CI, −0.01, 0.38). A similar trend was observed between MCPP and fetal femoral length (global adjusted p-value 0.07) but not birth length.

Six of the eight HMW phthalate metabolites (including the four DEHP metabolites) tended to be negatively associated with estimated fetal weight (Table 3, p-values from 0.04 to 0.13) and with biparietal diameter (Table S3) but not with birthweight. Changes associated with one IQR variation in the sum of HMW metabolites concentration were −3.3 g (95% CI,

−7.7, 1.2) and −13.6 g (95% CI, −35, 7.8) for EFW at the second and third trimesters, respectively (global p-value, 0.03), −14.1 g (95% CI, −44.8, 16.6) for birth weight and −0.45 mm (95% CI, −0.73, −0.17) and −2.3 mm (95% CI, −3.8, −0.68) for biparietal diameter at first and third trimester, respectively (global p-value, 0.01). Similar trends were observed for prenatal head circumference (Table S3). Adjusting for triclosan or maternal total caloric intake did not change these results (data not shown)

After birth, MBzP was positively associated with height in the two first years of life (Table 2, global *p*-value, 0.04, β at one year, 0.24 cm, 95% CI, 0.02, 0.45). We observed a positive association between MBzP, MiBP and height growth velocity at three months (Table S5), consistent with their association with length at one year.

After adjustment for height, we did not observe any strong global association between any phthalate metabolite concentration and postnatal weight (Table 3, *p*-values >0.15). When specific time points were considered, a positive association between MEP and weight adjusted for height was observed at three (132 g, 95% CI, −9, 273) and five years (234 g, 95% CI, 21, 446). MEP was positively associated with BMI at the 5-year clinical examination (Fig. 1, 0.17 kg/m^2, 95% CI, 0.04, 0.30). A positive association between MEP and weight growth velocity was observed at two and four years (β, 4.2 g/month, 95% CI, 0.6, 7.6, global *p*-value=0.35). Positive associations were observed between MBzP and weight at earlier ages (e.g. 126 g, 95% CI, 19, 234 at 2 years). MBzP tended to be positively associated with weight growth velocity (Table 4, global p-value=0.07), especially at early ages (e.g. β at three months, 11.7 g/month, 95% CI, 2.6, 20.8). Postnatal head circumference was not significantly associated with any phthalate metabolite (Table S3).

We generally observed similar patterns of associations using observed measures of length or height and weight (Table S4) instead of the model-predicted growth parameters. Adjusting postnatal growth models for parabens concentrations did not change the results (data not shown). The models were robust to the adjustment for breastfeeding and child caloric intake at eight months.

4. Discussion

In our population of boys followed from intra-uterine life onwards, maternal urinary concentrations of metabolites of HMW phthalates were negatively associated with EFW and biparietal diameter assessed during pregnancy, but not with birthweight. MCNP, a metabolite of di-isodecyl phthalate, was positively associated with prenatal femoral length and birth length. MEP, the main diethyl phthalate metabolite, was positively associated with weight growth velocity from two years onwards, with weight at 3 and 5 years and BMI at five years. MBzP, a metabolite of BBzP, tended to be positively associated with both weight and height growth velocities before one year.

Our study is the first to explore the effects of early life exposure to phthalates on growth during both the prenatal and postnatal periods. We relied on repeated measurements of growth during fetal and early postnatal life in a relatively large sample size of boys. The prospective design allowed exposure to be assessed during a toxicologically-relevant

window, the fetal period, although repeated urine collection would have provided more accurate exposure estimates. Sex-specific effects have been reported for phthalates and we chose to focus on boys to maximize statistical power, in a context where total sample size was limited.

Phthalate metabolites were measured in one spot urine sample at 26 weeks of gestation on average, which is after the first assessment of biparietal diameter, and concurrently or before the other fetal growth measurements. Depending on the toxicologically-relevant exposure window (which is unknown), the bias in the dose-response function may be larger for the growth parameter assessed before the time of urine collection. The model allowed associations between metabolite concentrations and each outcome to change with the time of the assessment of the growth parameter. Moreover, due to the phthalates short half-life and to the likely episodic nature of the exposures, reliance on a single urine sample to assess exposure leads to exposure misclassification (Adibi et al., 2008; Cantonwine et al., 2014; Perrier et al., 2016). Assuming a classical-type error structure and a monotonous association, the resulting bias in the dose-response function is expected to correspond to attenuation (Perrier et al., 2016), although we cannot exclude sampling fluctuation leading to significant associations by chance. Intraclass correlation coefficients (ICC) were generally low for MCNP (ICC=0.05–0.09) and DEHP metabolites (ICC=0.08–0.36), and slightly higher for MBzP (ICC=0.25–0.65) and MEP (ICC=0.30–0.56) (Adibi et al., 2008; Braun et al., 2012; Cantonwine et al., 2014; Dewalque et al., 2015), suggesting that exposure misclassification would be higher for MCNP and DEHP metabolites, compared to MBzP and MEP. Finally, we cannot exclude a residual bias in the associations due to unmeasured confounders. Note that, as we collected the first morning voids, this could have favored some sources of exposure (e.g. diet on the previous evening compared to cosmetic use on the morning).

MBzP was positively associated with birth length (Wolff et al., 2008) and femoral length in a study using ultrasound measurements during pregnancy (Casas et al., 2015), a result we did not confirm. In our population, this is MCNP, another HMW phthalate metabolite not considered in these studies, which was positively associated with fetal femoral length and birth length. The positive trend between MCNP and birth length had already been described in a study including part of our population sample (Philippat et al., 2012). Note that this metabolite has the lowest ICC among the ones studied (Cantonwine et al., 2014). No other phthalate metabolite was associated with birth length in our study. We observed negative associations between HMW metabolites and prenatal biparietal diameter and EFW.

Birth weight has been considered in a few previous studies (Casas et al., 2015; Lenters and Portengen, 2015; Philippat et al., 2012; Wolff et al., 2008). No phthalate metabolite was clearly associated with birth weight adjusted for birth length in our study. Two birth cohort studies, including ours (Philippat et al., 2012; Wolff et al., 2008), did not find any statistically significant association with birth weight (n=404 and 287 mother-newborn pairs), but DEHP metabolites concentration was associated with lower birth weight in a study of 1250 term singleton infants from three studies (Lenters and Portengen, 2015) and prenatal MBzP was positively associated with birth weight in boys (Casas et al., 2015).

Several epidemiological studies considered the effect of prenatal phthalate exposure assessed using urinary biomarkers on postnatal weight growth or child overweight (Agay-Shay et al., 2015; Buckley et al., 2016, 2015; Maresca et al., 2016; Valvi et al., 2015). Overall, there were generally few statistically significant associations, and effect modifications by sex have been highlighted. One of our results that was the most consistent with the literature was the one observed between prenatal MEP, the metabolite of the most prevalent LMW phthalate, and postnatal growth. Although this association did not appear as significant in all the studies, a positive trend in boys was observed in several of them (Buckley et al., 2016; Valvi et al., 2015), as well as in our study. Buckley et al. observed a heterogeneity by sex with a negative association in girls and a positive trend in boys (β, 0.07, 95% CI, −0.07, 0.21). Valvi et al. (2015) reported a positive trend between prenatal urinary concentrations of LMW phthalate metabolites and BMI z-score (Valvi et al., 2015) among 205 seven years old Spanish boys from INMA cohort (β, 0.21, 95% CI, −0.08, 0.50). In this study, they also found a negative association in boys between prenatal urinary HMW phthalate concentration and weight gain in the first six months (Valvi et al., 2015). In our study, MBzP, but not the sum of HMW metabolites, was positively associated with infant height and weight growth velocity in the first year. Maresca et al. (Maresca et al., 2016) showed a negative association in boys between non-DEHP metabolites (factor including LMW and HMW phthalates) measured prenatally and BMI at five and seven years in a minority cohort in New York City (β=−0.30, 95% CI: −0.50, −0.10, n=156), but not with MEP (Maresca et al., 2016). Finally, Agay-Shay et al. did not find any association between prenatal phthalate metabolites concentrations (analyzed by a multi-pollutant approach) and weight at 7 years (Agay-Shay et al., 2015); in that study as there was no significant interaction by sex the results were pooled and can therefore not be compared to our results obtained specifically in boys.

Several mechanisms could explain an effect of prenatal exposure to select phthalates on human growth. Phthalates can stimulate adipogenesis in vitro (Taxvig et al., 2012). For instance, MEHP activates peroxisome proliferator-activated receptor (PPAR) α and PPARγ nuclear receptors, which are implied in lipid metabolism; MEHP induces adipocyte differentiation and lipid accumulation (Taxvig et al., 2012). Another possible mechanism is an action of phthalates through thyroid metabolism. Thyroid hormones, which are involved in early growth regulation, have been associated with phthalate metabolite concentrations in children (Boas et al., 2010). Epigenetic modulation induced by a suboptimal fetal environment has also been hypothesized to explain the relationship between intra-uterine exposure to EDCs and the later risk of obesity (LaRocca et al., 2014; Zhao et al., 2014). First trimester exposure to LMW phthalates in humans was associated with methylation level of IGF2 paternally expressed and H19 maternally expressed non-coding genes, which play major roles in embryonic and placental growth (Zhao et al., 2014).

Anti-androgenic associations of postnatal urinary concentrations of several phthalate metabolites (including MEP, MBP and MEHP) with serum testosterone have been described in a cross-sectional study of 8–15 year-old boys (Xie et al., 2015). There is a gender-specific association between 3-month weight growth velocity and adolescent fat-free mass (Botton et al., 2008) that previously led us to postulate that the peak of testosterone in early infancy in boys might be implicated in that relationship. As testosterone is known to induce lipolysis,

this might explain the positive associations observed between MBzP and/or MEP and postnatal weight growth.

5. Conclusion

Our study is among the first and the largest to relate pregnancy urinary concentrations of a large range of phthalate metabolites to pre- and postnatal growth. Under certain hypotheses, the reliance on spot urine samples to assess exposure could have led to an underestimation of any association with growth (Perrier et al., 2016). Future studies should rely on repeated urine samples (possibly pooled within subjects) to limit bias and increase power, in particular for the compounds with the largest intra-individual variability. The association we report between exposure to diethylphthalate, the precursor of MEP, with postnatal weight and BMI was robust to adjustment for maternal weight and postnatal caloric intake and is consistent with the literature. Early exposure to this highly prevalent chemical might contribute, among many other factors, to the development of childhood overweight among boys.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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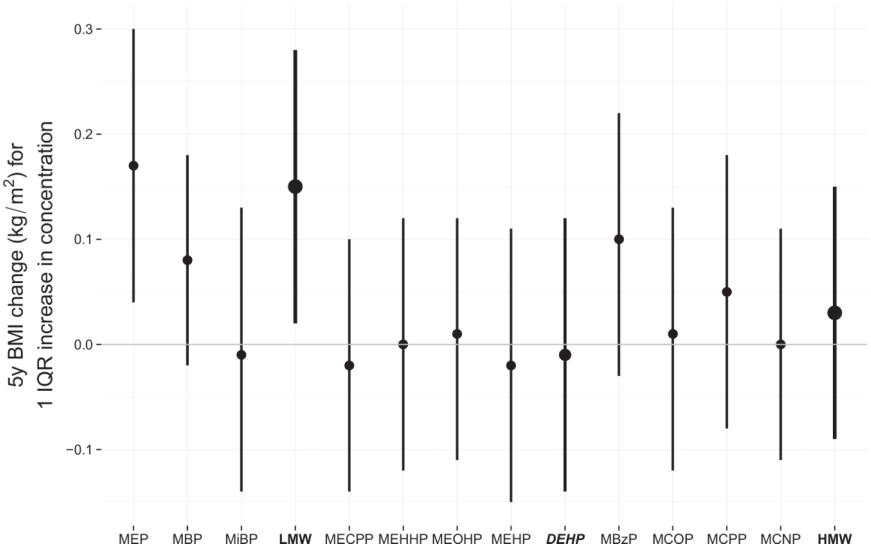

Fig. 1.

Associations between ln-transformed phthalate metabolite urinary concentrations and offspring's BMI at 5 years. Results are expressed as beta regression coefficient and 95% confidence interval for one interquartile range increase in exposure variable adjusted for maternal and paternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age at birth, weight gain during pregnancy and parity. LMW, low molecular weight; HMW, high molecular weight; DEHP, molar sum of DEHP metabolites.

Table 1

Maternal urinary concentrations of phthalate metabolites in 520 mothers of the EDEN mother-child cohort study who gave birth to a boy.

				Standardized concentrations[a,b], percentiles					Non standardized concentrations[a] 5th-50th-95th
Phthalate metabolites	**Abbrev.**	**LOD (µg/L)**	**% > LOD**	**5th**	**25th**	**50th**	**75th**	**95th**	
Monoethyl phthalate (µg/L)	MEP	0.6	100	21	51	96	195	714	20–112–1055
Mono-n-butyl phthalate (µg/L)	MBP	0.2	100	12	28	43	73	438	8–51–513
Mono-isobutyl phthalate (µg/L)	MiBP	0.2	100	12	25	39	69	166	9–44–215
Sum of LMW metabolite concentrations (µM)	Σ*LMW*	–	–	*0.38*	*0.69*	*1.09*	*1.99*	*6.76*	*0.29–1.32–9.06*
Mono(2-ethyl – 5-carboxypentyl) phthalate (µg/L)	MECPP	0.2	100	12	25	38	62	160	11–43–196
Mono(2-ethyl – 5-hydroxyhexyl) phthalate (µg/L)	MEHHP	0.2	100	6.8	16	27	44	103	5.9–30–125
Mono(2-ethyl – 5-oxohexyl) phthalate (µg/L)	MEOHP	0.2	99.7	5.6	14	23	36	84	4.5–25–106
Mono(2-ethylhexyl) phthalate (µg/L)	MEHP	0.5	98	1.6	4.4	7.7	15	35	1.2–8.9–43
Sum of DEHP concentrations (µM)	Σ*DEHP*	–	–	*0.09*	*0.20*	*0.32*	*0.53*	*1.24*	*0.07–0.36–1.56*
Monobenzyl phthalate (µg/L)	MBzP	0.3	100	4.5	11	18	33	104	2.9–20–133
Monocarboxy-isooctyl phthalate (µg/L)	MCOP	0.2	99	1.2	2.4	3.9	6.5	19	1.0–3.6–17
Mono(3-carboxypropyl) phthalate (µg/L)	MCPP	0.2	100	0.7	1.3	1.9	3.4	9.1	0.6 – 2.2 – 11
Monocarboxy-isononyl phthalate (µg/L)	MCNP	0.2	97.5	0.51	0.81	1.2	2.2	9.5	0.5–1.4–12
Sum of HMW[c] metabolite concentrations (µM)	*ΣHMW*	–	–	*0.16*	*0.30*	*0.47*	*0.73*	*1.75*	*0.12–0.53–2.24*

[a] Values under the limit of detection (LOD) were replaced by the instrumental reading values.

[b] Concentrations were standardized for collection conditions (hour of sampling, gestational age at collection, duration of storage at room temperature before freezing, day of sampling), creatinine concentrations and analysis period (Mortamais et al., 2012).

[c] Including DEHP metabolites concentration.

Table 2

Associations between one interquartile range increase in ln-transformed phthalate metabolite concentrations and femoral length (prenatal measures), length at birth and model-predicted height at different ages.

	Femoral length (mm)[a]			Body length[b] (cm) At birth		Model-predicted height (cm)[c]					
Phthalate metabolites	**2nd trimester (22.5 GW)**	**3rd trimester (32.6 GW)**	***p*-value[d]**		***p*-value**	**6 mo**	**12 mo**	**24 mo**	**36 mo**	**60 mo**	***p*-value[d]**
Σ*LMW*	−0.01 (−0.24, 0.22)	0.02 (−0.26, 0.29)	0.75	0.01 (−0.22, 0.24)	0.94	0.08 (−0.13, 0.30)	0.04 (−0.19, 0.28)	−0.01 (−0.29, 0.28)	−0.01 (−0.35, 0.33)	0.05 (−0.41, 0.50)	0.88
MEP	−0.05 (−0.28, 0.18)	−0.07 (−0.33, 0.20)	0.96	0.03 (−0.19, 0.25)	0.77	−0.02 (−0.22, 0.19)	−0.06 (−0.29, 0.16)	−0.07 (−0.35, 0.20)	−0.06 (−0.39, 0.26)	−0.06 (−0.50, 0.38)	0.67
MBP	0.12 (−0.05, 0.29)	0.06 (−0.14, 0.26)	0.16	−0.03 (−0.20, 0.14)	0.73	0.1 (−0.06, 0.25)	0.07 (−0.10, 0.24)	0.00 (−0.21, 0.21)	−0.01 (−0.26, 0.24)	0.04 (−0.29, 0.37)	0.49
MiBP	−0.02 (−0.25, 0.21)	−0.04 (−0.31, 0.22)	0.70	−0.10 (−0.32, 0.13)	0.38	0.08 (−0.14, 0.29)	0.11 (−0.11, 0.34)	0.09 (−0.19, 0.37)	0.09 (−0.25, 0.42)	0.16 (−0.28, 0.61)	0.16
Σ*HMW*[e]	0.02 (−0.19, 0.23)	0.06 (−0.18, 0.31)	0.27	−0.04 (−0.25, 0.17)	0.70	0.09 (−0.10, 0.29)	0.10 (−0.11, 0.31)	0.06 (−0.20, 0.32)	0.01 (−0.30, 0.32)	−0.06 (−0.47, 0.36)	0.34
MBzP	0.04 (−0.18, 0.25)	0.07 (−0.18, 0.32)	0.64	−0.02 (−0.24, 0.19)	0.82	0.18 (−0.02, 0.38)	0.24 (0.02, 0.45)	0.22 (−0.04, 0.49)	0.17 (−0.14, 0.48)	0.08 (−0.34, 0.50)	0.04
MCOP	0.11 (−0.11, 0.32)	0.04 (−0.20, 0.29)	0.74	0.02 (−0.19, 0.23)	0.88	−0.04 (−0.25, 0.16)	−0.03 (−0.25, 0.19)	−0.03 (−0.31, 0.24)	−0.05 (−0.38, 0.27)	−0.08 (−0.51, 0.36)	0.35
MCPP	0.21 (−0.02, 0.43)	0.18 (−0.07, 0.44)	0.07	0.00 (−0.21, 0.22)	0.98	0.03 (−0.16, 0.23)	0.01 (−0.21, 0.22)	−0.01 (−0.27, 0.26)	0.00 (−0.31, 0.31)	0.03 (−0.39, 0.45)	0.63
MCNP	0.20 (0.00, 0.39)	0.24 (0.01, 0.47)	0.04	0.19 (−0.01, 0.38)	0.06	0.01 (−0.17, 0.19)	−0.04 (−0.24, 0.15)	−0.06 (−0.30, 0.18)	−0.06 (−0.35, 0.23)	−0.08 (−0.46, 0.30)	0.24
Σ*DEHP*	−0.03 (−0.25, 0.19)	−0.01 (−0.27, 0.25)	0.64	−0.03 (−0.25, 0.18)	0.77	0.05 (−0.15, 0.26)	0.04 (−0.18, 0.26)	−0.01 (−0.29, 0.26)	−0.06 (−0.38, 0.27)	−0.11 (−0.54, 0.32)	0.71
MECPP	−0.02 (−0.23, 0.19)	0.02 (−0.23, 0.26)	0.50	−0.03 (−0.23, 0.18)	0.80	0.08 (−0.12, 0.27)	0.06 (−0.15, 0.27)	0.00 (−0.25, 0.26)	−0.03 (−0.34, 0.27)	−0.07 (−0.48, 0.34)	0.74
MEHHP	−0.03 (−0.25, 0.18)	−0.03 (−0.28, 0.22)	0.66	−0.08 (−0.29, 0.13)	0.45	0.03 (−0.16, 0.23)	0.04 (−0.17, 0.25)	0.01 (−0.25, 0.27)	−0.03 (−0.34, 0.28)	−0.09 (−0.51, 0.32)	0.75
MEOHP	−0.03 (−0.24, 0.18)	−0.04 (−0.29, 0.20)	0.68	−0.04 (−0.25, 0.16)	0.68	0.04 (−0.17, 0.25)	−0.02 (−0.25, 0.21)	−0.12 (−0.40, 0.16)	−0.17 (−0.51, 0.16)	−0.23 (−0.67, 0.22)	0.50
MEHP	0.00 (−0.23, 0.23)	0.02 (−0.25, 0.28)	0.95	0.08 (−0.14, 0.30)	0.48	0.05 (−0.15, 0.24)	0.05 (−0.16, 0.26)	0.01 (−0.25, 0.27)	−0.03 (−0.33, 0.28)	−0.08 (−0.49, 0.33)	0.70

[a]Mixed models adjusted for maternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age, weight gain during pregnancy and parity. Random effect on intercept and gestational age.

[b] Multiple linear regression models adjusted for maternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age, weight gain during pregnancy and parity.

[c] GEE models adjusted for maternal and paternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age at birth, weight gain during pregnancy and parity.

[d] *P*-value for the global difference (null hypothesis: no effect of the phthalate metabolite over all the whole age range).

[e] Including DEHP metabolites.

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Table 3

Associations between one interquartile range increase in ln-transformed phthalate metabolite concentrations and estimated fetal weight (EFW), birthweight and model-predicted weight at different ages.

	EFW[a] (g)			Birthweight[b] (g) At birth		Model-predicted weight[c] (g)					
Phthalate metabolite	**2nd trimester (22.5 GW)**	**3rd trimester (32.6 GW)**	***p*-value[d]**		***p*-value**	**6 mo**	**12 mo**	**24 mo**	**36 mo**	**60 mo**	***p*-value[d]**
Σ*LMW*	0.3 (−4.7, 5.2)	8.9 (−14.5, 32.2)	0.25	4.9 (−29.3, 39.2)	0.78	17 (−53, 87)	22 (−66, 110)	60 (−56, 177)	104 (−40, 249)	189 (−29, 408)	0.41
MEP	−1 (−5.8, 3.8)	−1.9 (−24.6, 20.8)	0.49	−0.01 (−33.0, 33.0)	1.0	27 (−41, 95)	36 (−49, 122)	81 (−32, 194)	132 (−9, 273)	234 (21, 446)	0.33
MBP	−0.2 (−3.8, 3.4)	11.5 (−5.6, 28.5)	0.14	3.1 (−22.3, 28.4)	0.81	5 (−46, 57)	6 (−58, 71)	20 (−65, 105)	33 (−73, 140)	57 (−103, 217)	0.83
MiBP	−0.4 (−5.3, 4.4)	−2.6 (−25.5, 20.2)	0.77	−4.7 (−38.3, 28.8)	0.78	13 (−56, 81)	48 (−38, 135)	73 (−41, 187)	70 (−72, 212)	44 (−171, 259)	0.15
Σ*HMW*[e]	−3.3 (−7.7, 1.2)	−13.6 (−34.9, 7.8)	0.03	−14.1 (−44.8, 16.6)	0.37	18 (−45, 82)	36 (−44, 117)	52 (−54, 158)	56 (−77, 188)	56 (−145, 256)	0.91
MBzP	−5.5 (−10.1, −0.9)	−9.9 (−31.6, 11.8)	0.13	−6.6 (−38.1, 25.0)	0.68	71 (6, 135)	103 (22, 185)	126 (19, 234)	129 (−6, 263)	122 (−82, 325)	0.15
MCOP	−1.4 (−5.9, 3.1)	−4.9 (−26.5, 16.7)	0.49	−18.6 (−49.9, 12.7)	0.24	−14 (−81, 53)	−23 (−107, 62)	−20 (−131, 91)	−10 (−149, 129)	15 (−195, 225)	0.85
MCPP	−1.8 (−6.5, 2.9)	11.7 (−10.7, 34)	0.27	8.4 (−24.0, 40.9)	0.61	38 (−26, 103)	43 (−38, 125)	48 (−60, 156)	59 (−75, 194)	89 (−114, 293)	0.78
MCNP	−4.6 (−8.8, −0.5)	−8.2 (−28, 11.5)	0.13	−19.7 (−48.3, 8.9)	0.18	−4 (−63, 55)	−14 (−89, 61)	−20 (−118, 78)	−20 (−143, 103)	−18 (−204, 168)	0.93
Σ*DEHP*	−2 (−6.6, 2.7)	−10.1 (−32.5, 12.2)	0.05	−7.7 (−39.8, 24.3)	0.63	4 (−63, 70)	12 (−72, 96)	17 (−94, 128)	14 (−124, 153)	6 (−204, 216)	0.97
MECPP	−2.3 (−6.7, 2.1)	−15.1 (−36.3, 6.1)	0.04	−7.8 (−38.2, 22.7)	0.62	−4 (−68, 59)	0 (−79, 80)	7 (−99, 112)	8 (−124, 139)	7 (−192, 206)	0.97
MEHHP	−1.7 (−6.1, 2.8)	−7.1 (−28.7, 14.5)	0.04	−4.2 (−35.2, 26.8)	0.79	10 (−54, 74)	24 (−57, 106)	33 (−75, 140)	29 (−105, 164)	17 (−186, 220)	0.94
MEOHP	−1.7 (−6, 2.7)	−7.6 (−28.9, 13.6)	0.07	−6.8 (−37.2, 23.7)	0.66	12 (−57, 81)	1 (−86, 88)	−16 (−132, 99)	−29 (−173, 115)	−51 (−269, 167)	0.95
MEHP	−0.5 (−5.3, 4.3)	−1 (−24.2, 22.1)	0.1	−8.6 (−41.9, 24.7)	0.61	11 (−52, 74)	24 (−56, 104)	32 (−74, 137)	28 (−104, 160)	17 (−183, 217)	0,93

[a]Mixed models adjusted for femoral length, maternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age, weight gain during pregnancy and parity. Random effect on intercept and gestational age.

[b] Multiple linear regression models adjusted for birth length, maternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age, weight gain during pregnancy and parity.

[c] GEE models adjusted for adjusted for predicted length or height at the same age, maternal and paternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age at birth, weight gain during pregnancy and parity.

[d] *P*-value for the global difference (null hypothesis: no effect of the phthalate metabolite over all the whole age range).

[e] Including DEHP metabolites.

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Table 4

Associations between one interquartile range in ln-transformed phthalate metabolite concentrations and model-predicted weight growth velocities (g/month) at 3, 6, 12, 24 and 48 months.

Phthalate metabolite	Age (months) 3	6	12	24	48	Global test (*p*-value)[b]
ΣLMW	−1.2[a] (−11, 8.6)	−0.4 (−8, 7.2	2.6 (−2.5, 7.7)	4.2 (0.6, 7.8)	4.1 (0.3, 8)	0.35
MEP	−0.5 (−10.1, 9.1)	0 (−7.4, 7.4)	2.6 (−2.3, 7.5)	4.1 (0.6, 7.6)	4.2 (0.4, 7.9)	0.35
MBP	0.1 (−7.1, 7.3)	0.2 (−5.3, 5.8)	1.6 (−2.1, 5.4)	2.1 (−0.6, 4.8)	1.9 (−0.9, 4.7)	0.71
MiBP	4.8 (−4.8, 14.5)	6.9 (−0.6, 14.3)	4 (−1, 9)	0 (−3.5, 3.6)	−1.5 (−5.2, 2.3)	0.23
ΣHMW[c]	3.7 (−5.3, 12.7)	4.1 (−2.8, 11.1)	3.1 (−1.5, 7.7)	1.2 (−2, 4.5)	0.7 (−2.8, 4.2)	0.78
MBzP	11.7 (2.6, 20.8)	8.2 (1.2, 15.2)	4.3 (−0.4, 9)	1.2 (−2.2, 4.6)	0.1 (−3.4, 3.7)	0.07
MCOP	−2.7 (−12.1, 6.7)	−1.5 (−8.7, 5.8)	0.7 (−4.2, 5.6)	1.9 (−1.6, 5.3)	2.2 (−1.4, 5.9)	0.68
MCPP	6 (−3.1, 15.1)	2.1 (−5, 9.1)	0.3 (−4.4, 5)	0.8 (−2.5, 4.2)	1.4 (−2.1, 5)	0.67
MCNP	−0.2 (−8.6, 8.1)	−1.5 (−7.9, 5)	−0.3 (−4.6, 4)	0.7 (−2.3, 3.8)	1 (−2.3, 4.2)	0.73
ΣDEHP	0.5 (−8.9, 9.9)	1.8 (−5.4, 9.1)	1.6 (−3.2, 6.4)	0.4 (−3, 3.9)	0.1 (−3.5, 3.8)	0.95
MECPP	−0.5 (−9.5, 8.4)	1 (−5.8, 7.9)	1.6 (−3, 6.2)	0.9 (−2.4, 4.1)	0.7 (−2.8, 4.1)	0.91
MEHHP	2 (−7.1, 11.1)	3.2 (−3.9, 10.2)	2.1 (−2.5, 6.8)	0.3 (−3, 3.6)	−0.2 (−3.7, 3.3)	0.92
MEOHP	−0.3 (−10, 9.5)	−1.7 (−9.2, 5.8)	−1.8 (−6.8, 3.2)	−1.1 (−4.7, 2.4)	−0.8 (−4.6, 3)	0.97
MEHP	1.8 (−7.1, 10.8)	2.9 (−4, 9.8)	2 (−2.6, 6.6)	0.3 (−3, 3.5)	−0.1 (−3.6, 3.3)	0.90

[a] Results are expressed as regression coefficient (95% confidence interval) for increase in each exposure variable. GEE model adjusted for maternal and paternal height and BMI, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, maternal age, gestational age at birth, weight gain during pregnancy and parity.

[b] *P*-value for the global difference (null hypothesis: no effect of the phthalate metabolite over the whole age range).

[c] Including DEHP metabolites.