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Phthalate exposure during pregnancy and long-term weight gain in women

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ABSTRACT

Background: Phthalates are known endocrine disruptors and peroxisome proliferator-activated receptor (PPAR) activators, potentially capable of promoting an obesogenic effect. Pregnant women are especially vulnerable to phthalate exposure due to physiological and metabolic changes during pregnancy, including those related to the metabolism of xenobiotics. Phthalate exposure during pregnancy has been associated with early gestational weight gain, however, its effect on long-term weight gain remains unclear. The aim of the present study was to evaluate the association between phthalate exposure during pregnancy and long-term changes in weight among women.

Methods: Urinary phthalate concentrations, socioeconomic, anthropometry and information on diet and socioeconomic status were collected during pregnancy from 178 women from the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) birth cohort. Maternal body weight and diet information was also collected up to 5 times in the first year postpartum and twice during follow-up visits 5.2–10.7 years later. A path analysis was performed to assess associations between urinary phthalate metabolite levels during pregnancy and change in weight (kg) per year after delivery, including age, education, living with/without partner, parity, daily energy intake and breastfeeding duration.

Results: The mean age at pregnancy was 27.3 ± 5.9 years and mean body mass index during the first postpartum year was 27.07 ± 4.22 kg/m^2. On average, women gained 3.48 kg (0.52 ± 0.84 kg/year). A unit increase in log-transformed mono-3-carboxypropyl phthalate (MCPP) was associated with 0.33 kg (95% CI: 0.09, 0.56) higher weight gain per year, and mono-benzyl phthalate (MBzP) with 0.21 kg (95% CI: −0.38, −0.03) lower weight gain per year.

Conclusion: Exposure to certain phthalates during pregnancy may be associated with long-term weight change in women. More studies on the effects of phthalate exposure during pregnancy on women's long-term health are required.

Abbreviations: ELEMENT, Early Life Exposure in Mexico to Environmental Toxicants; MEHP, mono-2-ethylhexyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MnBP, mono-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, monoethyl phthalate; ΣDBP, sum of di-n-butyl phthalate metabolites; ΣDEHP, sum of di(2-ethylhexyl) phthalate metabolites; DEP, diethyl phthalate; DiNP, di-isononyl phthalate; DiBP, di-isobutyl-phthalate; DOP, di-*n*-octyl phthalate; SG, specific gravity; MW, molecular weight; LOD, limit of detection; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; PBPK, physiologically-based pharmacokinetic; TSH, thyroid-stimulating hormone; T3, free triiodothyronine; BMI, body mass index; GWG, gestational weight gain; WC, waist circumference; FFQ, food frequency questionnaires; SES, socioeconomic status; AMAI, Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública; NHS, Nurses' Health Study; NHANES, National Health and Nutrition Examination Survey; NIEHS/NIH, National Institute of Environmental Health Sciences/National Institutes of Health

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1. Introduction

Pregnancy is a critical period for the development of obesity and overweight status among women due to dramatic metabolic changes that occur during this time. Long-term health effects related to high gestational weight gain (GWG) and postpartum weight retention include diabetes, cardiovascular disease, and other chronic illnesses (Gunderson and Abrams, 2000; Lain and Catalano, 2007). Among some of the factors involved in postpartum weight retention are pre-gestational overweight or obesity status and excessive GWG, while longer breastfeeding duration and moderate exercise have been associated with decreased weight retention (Endres et al., 2015). However, the effects of prenatal exposure to phthalates and other potential obesogens on long-term maternal weight status have not been explored. In addition, pregnancy may be a period of increased susceptibility to the effects of phthalate exposure, as animal studies suggest that pregnancy-related changes in metabolism may result in longer biological residence times for some phthalates, potentially increasing the effect of a given exposure (Clewell et al., 2008). In accordance with this, phthalates exposure during pregnancy has been associated with early GWG, however, the mechanism behind the effect of phthalates on weight gain is unclear (Bellavia et al., 2017).

Phthalates are a group of chemicals widely used in the manufacture of industrial and consumer products, such as PVC plastics and personal care products (Hauser and Calafat, 2005). Due to their non-covalent bonds to these products, they are easily released into the environment during their manufacture, use, and disposal (Wittassek et al., 2011). Phthalates are considered endocrine and metabolic disruptors with obesogenic functions (De Coster and van Larebeke, 2012; Grun and Blumberg, 2007), as they are weakly estrogenic (Chen et al., 2014), anti-androgenic, and act as thyroid-axis antagonists, and PPAR activators (De Coster and van Larebeke, 2012). PPARs form heterodimers with the retinoid X receptor (RXR) (Chandra et al., 2008) which play a role in glucose and triglyceride homeostasis, preadipocyte differentiation, and the expression of diverse adipogenic genes (Grun and Blumberg, 2007).

Adult women have higher concentrations of phthalate metabolites in their urine than men (CDC, 2017), possibly due to their greater use of personal care products (CDC, 2016). In pregnant women the use of personal care products has been reported as an important source of phthalate exposure (Buckley et al., 2012). However, other sources of phthalate exposure among pregnant women have been found, including bottled water, food contact materials, hair dye or permanents, and the consumption of certain food items and medications (Cantonwine et al., 2014; Yang et al., 2015; Hernandez-Diaz et al., 2013).

In women, exposure to phthalates has been positively associated with body mass index (BMI) and waist circumference (WC) (Hatch et al., 2008; Yaghjyan et al., 2015) in cross-sectional studies, and long-term weight gain in a longitudinal analysis of US women in the Nurses' Health Study (Song et al., 2014). Other related health outcomes associated with phthalate exposure in humans include metabolic syndrome (James-Todd et al., 2016) and diabetes (Svensson et al., 2011). Specifically in Mexican women, a case-control study showed that women with diabetes presented higher levels of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and lower levels of MBzP when compared to non-diabetic women (Svensson et al., 2011).

There is a scarcity of studies regarding phthalate exposure during pregnancy and long-term health in women. To our knowledge, the only previous study evaluating phthalate exposure during pregnancy on maternal weight gain had a short follow-up period of 7 weeks (Bellavia et al., 2017). As a result, the current study aimed to evaluate the association between the phthalate exposure during pregnancy, a vulnerable life stage, and long term weight change over 5.2–10.7 years in women from the ELEMENT cohort study.

2. Methods

2.1. Study population

The present study comprises information from a subsample of 250 women belonging to two of three sequentially-enrolled birth cohorts from the ELEMENT project that recruited women during the first trimester of pregnancy between 1997 and 2004. The ELEMENT project has been described in detail elsewhere (Ettinger et al., 2009; Hu et al., 2006). The research protocol was approved by the Ethics and Research Committees of the National Institute of Public Health in Mexico and the University of Michigan School of Public Health.

Women in the current analysis were selected for a follow-up study of their children in 2010 based on the availability of maternal urine samples collected during pregnancy. Sociodemographic information was collected upon study enrollment, while biological samples, anthropometric, and dietary data were collected three times during pregnancy (1st, 2nd and 3rd trimester). Anthropometric measures and dietary data were collected again at up to five study visits during the first 12 months postpartum (1998–2005) and at two follow-up visits 5.2–10.7 years after the first postpartum year (2008–2011). Information about breastfeeding duration was collected during the child's infancy visits (birth to 36 months) and parity information was collected 13.42 ± 1.65 years after the first month postpartum (Supplementary Table 1).

2.2. Change in Weight and BMI

Weight was measured up to five times during the first year postpartum (1st, 3rd, 4th, 7th and 12th month, depending of the specific cohort design) and twice during follow-up visits (7.1 ± 1.13 and 9.6 ± 1.50 years after the last visit during the first year postpartum) using a hospital scale (accurate to 0.1 kg). Change in weight (kg) and BMI (kg/m^2) per year were calculated for each woman with the following formula: $WB_y = \frac{WB_f - WB_p}{Y_f - Y_p}$, where WB_y = mean change in weight or BMI per year, WB_f = mean weight or BMI in the follow-up visits (2008–2011), WB_p = mean weight or BMI in the first year postpartum (1997–2005), Y_f = earliest follow-up visit date, and Y_p = last postpartum visit. WB_f and WB_p were calculated as arithmetic means using all available measurements for each woman and $Y_f - Y_p$ was expressed in years.

2.3. Urinary phthalate measurement

Nine phthalate metabolites were measured in maternal urine samples collected during each trimester of pregnancy: monoethyl phthalate (MEP), MnBP, mono-isobutyl phthalate (MiBP), MBzP, MCPP, mono-2-ethylhexyl phthalate [MEHP], MEHHP, MEOHP and MECPP. All assays were performed at NSF International (Ann Arbor, MI) using high performance liquid chromatography and tandem mass-spectrometry as previously described (Silva et al., 2007; Calafat et al., 2008). The sum of di-2-ethylhexyl phthalate metabolites (ΣDEHP) was calculated by adding the molar fractions of MEHP, MEHHP, MEOHP and MECPP; and the sum of dibutyl phthalate (ΣDBP) was calculated by adding the molar fractions of MiBP and MnBP. This grouping was corroborated by a principal component analysis and factor analysis. To achieve unit comparability, ΣDEHP (nmol/ml) was multiplied by the molecular weight (MW) of MEHP (278.348 g/mol) and ΣDBP (nmol/ml) by the MW of MnBP (222.24 g/mol). The resulting units were ng/ml.

Phthalates measurements below the limit of detection (LOD) were substituted with LOD/√2 (Silva et al., 2007; Hornung and Reed, 1990). A correction for urinary specific gravity was also made (Mahalingaiah et al., 2008; Nahar et al., 2012):

$Pc = P\frac{1.015 - 1}{SG - 1}$; where Pc = corrected phthalate concentration, P = measured phthalate concentration, SG = specific gravity of the sample,

and 1.015 = median specific gravity of all samples collected.

2.4. Covariate information

Dietary information was collected using a validated semi-quantitative questionnaire (Hernandez-Avila et al., 1998) administered during pregnancy at the 1st, 2nd and 3rd trimester visit; up to five times during the first year postpartum and at two follow-up visits 5.2–10.7 years after the first postpartum year. With the use of food composition tables and food frequency and quantity information collected via food frequency questionnaires (FFQ), daily energy intake (EI) (Hernandez-Avila et al., 1998) was calculated for pregnancy, postpartum, and follow-up periods for each woman. Breastfeeding duration was categorized as 1) never to < 1 month, 2) 1 to < 6 months, 3) 6 to < 12 months and 4) 12 months or more. Education information was collected through questionnaires administered during pregnancy as the total number of years the participant attended school, and was categorized in four corresponding education level categories: 1) elementary school (1–6 years), 2) middle school (7–9 years), 3) high school (10–12 years) and 4) undergraduate/graduate school (> 12 years). The parity rate variable was created by dividing the number of children the woman had after the study child (range = 0–4), by the amount of time between the study birth and the date when parity information was collected (10.7–17.6 years after the first month postpartum, mean 13.42 ± 1.65). Calculating parity rate allowed us to account for the time between last weight measurements and parity report (4.95 ± 0.92 years).

Marital status was classified in two categories: 1) living with a partner (married or in free-union); and 2) not living with a partner (single, separated, or divorced). Socioeconomic status (SES) during pregnancy was estimated using a validated scale consisting of thirteen questions on housing quality, services, material goods and head of household education (Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública, AMAI version 13 × 6). This scale classifies households into six SES categories (A/B, C+, C, D +, D, E; with A/B being the highest category) using hierarchical trees (AMAI, 2000; López, 2008). Although information about postpartum physical activity was collected for some ELEMENT participants, this variable was not included in the present analysis due to the small number of participants with this data (n = 5) in the final sample.

2.5. Statistical analysis

Preliminary analysis of the data included frequency measures of categorical variables such as education level, SES, breastfeeding duration, and marital status. For continuous variables, the presence of outliers was evaluated and distributional statistics such as standard deviation and variance, skewness and kurtosis, and additionally for phthalates, geometric means were calculated. Logarithmic transformations, zero-skewness Box–Cox and zero-skewness log-transformations were evaluated for phthalate concentrations to achieve normality. Due to the similarity of the distributions achieved, logarithmic transformations were performed in order to achieve better interpretability.

Mixed-effects models were used to assess changes in log-transformed urinary phthalate concentrations across pregnancy. Path analysis with maximum likelihood estimation was used to analyze association patterns between phthalate exposure (ΣDEHP, ΣDPB, MBzP, MCPP and MEP) and weight change per year. A path analysis is a type of structural equation model used to evaluate associations. This model is specified by the simultaneous inclusion of multiple observed independent and dependent variables, allowing the estimation of total, direct, and indirect effects through the use of several multiple linear regressions (Schumacker and Lomax, 2010). In this model, a direct effect is the unmediated influence of a variable on other variable, an indirect effect is the effect that is mediated by other variables, and the total effect is the sum of both direct and indirect effects (Schumacker and Lomax, 2010). This approach allowed us to include log-transformed geometric mean and specific gravity corrected phthalate metabolite concentrations for each individual across pregnancy, while also accounting for correlations among phthalate groupings and metabolites.

The choice of covariates and paths in the conceptual model was based on previous literature regarding the predictors of weight change in women [breastfeeding, education and SES (Endres et al., 2015)] and phthalate exposure [dietary sources (Cantonwine et al., 2014), education (Yang et al., 2015), age, marital and socioeconomic status (Wenzel et al., 2018)]. Age, education level, breastfeeding duration, SES, marital status, parity rate and energy intake were included as part of the association pattern to evaluate the direct and indirect effects between phthalate exposures and weight change per year. Age, education level and energy intake were considered confounding variables. Variables and paths were included a priori based on the conceptual model. Paths not statistically significant to the model were eliminated. All analyses were performed using STATA SE version 14.

3. Results

Among the initial subset of 250 ELEMENT women, 229 had phthalate measurements from at least one trimester of pregnancy. Of these 229, 205 had complete information on postpartum weight and weight at follow-up, of which 178 had complete information on age, breastfeeding duration, education level, marital status, energy intake and parity rate. This final analytic sample was not statistically different from the 229 women with phthalate measurements, or from the original cohorts, in terms of baseline sociodemographic characteristics, daily energy intake, breastfeeding duration, and body weight in the first year postpartum (data not shown).

Baseline sociodemographic characteristics are summarized in Table 1. The mean age at pregnancy was 27.3 ± 5.9 years. As of 13.42 ± 1.65 years after the index birth, 56.2% had not had additional children, 32.0% had one additional child, and 11.8% had between 2 and 4 more children. The mean education was 11.0 ± 2.9 years, and 84% of participants were low to middle SES. Mean BMI was 27.1 kg/m^2 during the first year postpartum and 28.6 kg/m^2 at the follow-up visits, and mothers gained an average of 0.52 kg, or a 0.22 unit increase in BMI, per year of follow-up (Table 2).

Geometric mean concentrations of phthalate metabolites corrected for specific gravity are presented in Supplementary Table 2. Comparing phthalate concentrations across pregnancy we found that MEOHP concentrations in the second and third trimester, and MEHP, MECPP, MEHHP, MEOHP MiBP, MBzP, and ΣDEHP concentrations in the third trimester were significantly higher in comparison to the first trimester. There were no statistically significant differences across pregnancy for the rest of the phthalates evaluated (Supplementary Table 3).

The resulting path model for evaluating associations among geometric means of phthalate metabolites across pregnancy, weight change per year, and covariates is illustrated in Fig. 1. The main direct and indirect effect coefficients for weight change per year from the path model are presented in Table 3. Overall, the path analysis model explained 61.96% of the total variance of the weight change per year. Based on total effects, a one unit increase in log-transformed MCPP concentration during pregnancy was significantly associated with a 0.33 kg increase in weight gain per year (95% CI:0.09,0.56) during an average period of 7.1 ± 1.2 years (5.2–10.7 years). In contrast, a one unit increase in log-transformed of MBzP was associated with a 0.21 kg decrease in weight gain per year (95% CI: −0.38, −0.03) during the same time period. Similarly, a one unit increase in log-transformed of MEP was associated with 0.07 kg (95% CI: −0.20, 0.05) lower weight gain per year, although this difference did not reach statistical significance. The total effects did not deviate from the direct effects (Table 3).

Based on the total effects, higher education was positively

Table 1
Baseline sociodemographic characteristics.

	n	%	Mean	SD	Range
Age at pregnancy (years)	178		27.32	5.88	14–44
Parity (number of children)[a]	178		0.58	0.76	0–4
Parity rate (number of children/year)[a]	178		0.04	0.06	0–0.37
Energy intake in pregnancy (kcal)	178		1912.80	536.01	859.96–3792.98
Energy intake postpartum (kcal)	178		1797.96	484.67	789.08–3342.58
Education	178		11.03	2.86	2–20
Elementary school	11	6.18			
Middle school	56	31.46			
High school	83	46.63			
Undergraduate and graduate school	28	15.73			
SES[b]	169				
A/B	0	0.00			
C+	5	2.96			
C	22	13.02			
D+	52	30.77			
D	60	35.50			
E	30	17.75			
Marital status	178				
Living with a partner	159	89.33			
Living with no partner	19	10.67			
Breastfeeding duration	178				
0 months	11	6.18			
1–6 months	67	37.64			
7–12 months	48	26.97			
> 12 months	52	29.21			

SD: standard deviation, SES: socioeconomic status.
Note: .
[a] The variable parity and parity rate only includes the number of children the woman had 13.42 ± 1.65 years after the index child.
[b] A/B is the highest SES category.

Table 2
Anthropometric measurements by follow-up period (n = 178).

	Mean	SD	Range
Height (m)	1.54	0.06	1.37–1.72
Mean weight during first year postpartum (kg)	63.79	10.55	43.05–96.13
Mean BMI during first year postpartum (kg/m^2)	27.07	4.22	17.69–41.61
Mean weight during follow-up visits (kg)	67.27	11.44	44.6–108.5
Mean BMI during follow-up visits (kg/m^2)	28.56	4.63	18.34–43.06
Weight change (kg)[a]	3.48	5.70	−17.08–26.43
Weight change (kg) per year	0.52	0.84	−2.82–3.57
BMI change (kg/m^2)[a]	1.49	2.40	−6.78–9.95
BMI change (kg/m^2) per year	0.22	0.35	−1.13–1.43

SD: standard deviation, BMI: body mass index.
Note: .
[a] The period considered for the weight and BMI change was 7.1 ± 1.2 years (5.2–10.7 years).

associated with annual weight change, with increases of 0.15, 0.19, and 0.22 kg/year for middle school, high school, and college, respectively, compared to the elementary school category ($p < 0.05$). Similarly, each increase of 100 kcal in daily energy intake during the postpartum period was marginally associated with a 0.02 kg increase in weight per year ($p = 0.053$). Also, a year increase in age at pregnancy was associated with a decrease of 0.02 kg per year in weight during follow-up. Parity rate, marital status and daily energy intake during pregnancy were not significantly associated with weight change rate ($p > 0.05$) (Table 3). Although SES and EI during the follow-up were initially considered as part of the path model, they were not included in the final model due minor contributions when level of education, and pregnancy and postpartum EI were included, respectively. Path coefficients for remaining endogenous variables are presented in Supplementary Table 4.

Finally, in a complementary analysis including the nine individual phthalates, we observed that the lack of statistical significance of the association between ΣDEHP, ΣDBP and weight change/year could be explained by the contradicting and non-statistically significant effects of the metabolites that compose these groups, with the exception of MiBP (Supplementary Table 5). The goodness of fit of both path analyses was evaluated.

4. Discussion

In the present study, we aimed to explore the association of phthalate exposure during pregnancy with long-term weight gain among Mexican women from the ELEMENT birth cohort. We observed that urinary MCPP concentrations during pregnancy were associated with greater weight gain, while MBzP was associated with lower weight gain, over an average of 7 years after the first year postpartum.

To our knowledge, one previous study evaluated phthalate exposure and long-term weight gain in adult women (Song et al., 2014). Contrary to our results, in a sample of U.S. women 32–79 years old from the Nurses' Health Study (NHS) and NHS II, higher urinary concentrations of MBzP, as well as phthalic acid, bisphenol A and ΣDBP metabolites, were significantly associated with increased annual weight gain during a ten year period. A mean weight gain of 2.09 kg over this period was reported, which is lower than the mean weight gain of 3.5 kg over a smaller period of time (7.1 years) found in the present study (Song et al., 2014). One potential explanation for the discrepancies between this study and our findings is the timing of exposure measurement, as our study measured phthalate exposure during pregnancy whereas the NHS study included non-pregnant women. In addition, women participating in NSH and NSH II were older than women in our study.

A previous study in the LIFECODES pregnancy cohort evaluated associations between urinary phthalate metabolites in the first trimester and early GWG in the first to second trimester (Bellavia et al., 2017). It was found that the highest two quartiles of MBzP and MEP concentrations were associated with lower GWG, compared to the lowest two MBzP and MEP quartiles. In contrast, MCPP concentrations were non-linearly associated with higher GWG, but this association was not statistically significant (Bellavia et al., 2017). Although this study only described associations of phthalates with early GWG, they observed similar relationships of MBzP, MCPP and MEP with maternal weight gain to those observed in the present study (Bellavia et al., 2017). Additionally, GWG has been associated with long-term weight gain. For example, a birth cohort study of English women found that women who had GWG above the recommendation had 3 times the risk of high central adiposity and being overweight 16 years after delivery (Fraser et al., 2011).

Cross-sectional associations between phthalate exposure and adiposity have been evaluated in various populations with inconsistent results. In contrast to our findings, in the NHANES 1999–2002, MEP quartiles were positively associated with BMI and WC in adolescent girls ($p < 0.05$) and in 20–59 year old women ($p = 0.1$) (Hatch et al., 2008). Similar to the NHANES study, a cross-sectional study of Chinese adults reported that MBzP concentrations were associated with increased odds of obesity in women aged over 45 years; however, MBzP was also associated with decreased odds of central obesity measured by WC (Dong et al., 2017). Moreover, in a cross-sectional study of adults aged over 20 years in the NHANES 1999–2006, MBzP was inversely associated with lean mass (Corbasson et al., 2016), a contributor to the overall weight. Similarly, inverse associations between MBzP and weight gain in infants and school-aged children have been previously described (Kasper-Sonnenberg et al., 2012; Valvi et al., 2015). However, as these findings have been in children and non-pregnant adults and only consider cross-sectional exposure, the generalizability to exposure during pregnancy and long-term weight in women is unclear.

Pregnancy may be a life stage during which women are particularly

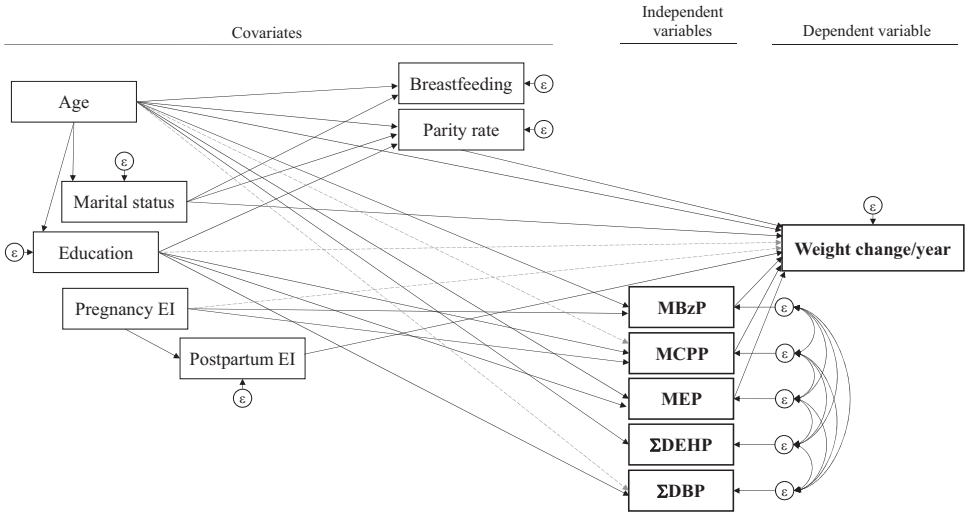

Fig. 1. Final path model of the relation between phthalate exposures and weight change per year. EI: energy intake. Notes: continuous lines indicate direct effects, while the dotted gray lines represent indirect effects. Age, marital status and education information were collected during pregnancy. The breastfeeding lasted up to 36 months after delivery; weight change was calculated for the period between the first year postpartum and the follow-up visits (5–10 years, mean 7.1 ± 1.2) and parity rate was measured 4.95 ± 0.92 years after the last weight measurements.

vulnerable to the effects of phthalate exposure. First, pregnancy is a dynamic process related to several physiological changes that affect the pharmacodynamics of xenobiotics, such as phthalates, in the maternal body. In a physiologically-based pharmacokinetic (PBPK) model, pregnant rats presented a reduced capacity for glucuronide conjugation due to a decrease in glucuronyltransferase compared to male rats. This reduction may subsequently cause an increase in free mono-butyl phthalate (MnBP) residence time, in both maternal and fetal plasma, suggesting longer exposure (Clewell et al., 2008). Second, dramatic changes in metabolism occur during pregnancy, including increases in maternal fat stores and changes in insulin sensitivity that prepare the body for the increased energy demands of gestation and lactation (Lain and Catalano, 2007). During the postpartum period, metabolism, hormone concentrations, and body weight typically return to pre-pregnancy levels, but approximately 20% of women retain excessive weight from pregnancy to one year post-delivery (Collings et al., 2018; Gunderson et al., 2008). Factors such as breastfeeding duration, diet, social support, sleep deprivation, and depression are thought to play a role in postpartum weight retention, but the effects of environmental exposures have not been explored.

Phthalate exposure during pregnancy could potentially have an impact on long-term maternal weight through endocrine disruption or interference with PPAR activation. Evidence of relationships between phthalate exposures and alterations in hormone levels during pregnancy has been previously described. For example, a birth cohort study in Puerto Rico reported an inverse association between MCPP and free triiodothyronine (T3), and a positive association between MBzP and thyroid-stimulating hormone (TSH) during pregnancy (Johns et al., 2015). Although the potential impact of subclinical alterations during pregnancy remains understudied, it is known that thyroid hormones are involved in the regulation of basal metabolism and thermogenesis, lipid and glucose metabolism, and food intake (Longhi and Radetti, 2013). TSH, T3 and free T3 concentrations have been positively associated with weight, body fat, BMI, WC and waist/hip ratio in both euthyroid men and non-pregnant women (Fontenelle et al., 2016).

Phthalates are also known activators of PPARα, PPARβ, and PPARγ, which are involved in glucose and fatty acid homeostasis (Bility et al., 2004). PPARs form heterodimers with RXR (Chandra et al., 2008), the signaling of which affects glucose and triglyceride disposition, promotes preadipocyte differentiation, and promotes the expression of diverse adipogenic genes (Grun and Blumberg, 2007). During pregnancy, PPARs also play a role in regulating inflammation, angiogenesis,

Table 3
Main direct and indirect effects for the Path model (n = 178).

	Direct effects			Indirect effects		
Paths	β	95% CI	*p* value	β	95% CI	*p* value
Effects on weight change/year[a]						
MBzP	−0.21	−0.38, −0.03	0.02*			
MCPP	0.33	0.09,0.56	0.007*			
MEP	−0.07	−0.20,0.05	0.24			
Age	−0.02	−0.05,0.0001	0.05	−0.002	−0.01,0.01	0.78
Education[b]						
Middle school				0.15	0.002, 0.30	0.047*
High school				0.19	0.02,0.36	0.03*
Undergraduate/graduate school				0.22	0.03,0.41	0.03*
Parity rate[c]	1.01	−1.34,3.37	0.40			
Pregnancy EI[d]				0.01	−0.003,0.03	0.11
Postpartum EI[d]	0.02	−0.0003,0.05	0.05			
Marital status[e]	−0.22	−0.62,0.18	0.27	0.03	−0.04,0.10	0.43

Notes: .
* $p < 0.05$. CI: confidence interval, EI: energy intake.
[a] The period considered for the weight change was 7.1 ± 1.2 years (5.2–10.7 years).
[b] Elementary school is the reference group in education.
[c] The variable parity rate only includes the number of children the woman had 13.42 ± 1.65 years after the index child.
[d] The energy intake unit is 100 kcal.
[e] Living with a partner is the reference group for marital status.

and oxidative stress (Ganss, 2017). In vitro studies suggest that the molecular weight of phthalate metabolites may play a role in PPAR activation, as large chain monoesters induced a greater adipogenic effect, an indicator of PPARγ activation, in 3T3-L1 fibroblasts (Bility et al., 2004). This might explain the lack of statistical significance in the association of MEP with weight change in the current study, as MBzP and MCPP are high molecular weight metabolites and MEP is a low molecular weight metabolite.

The current study has a number of limitations. Phthalate metabolites were measured three times during pregnancy and summarized as a proxy of overall exposure in this period. Due to the short biological half-lives of phthalates and temporal variability of urinary phthalate levels during pregnancy (Cantonwine et al., 2014; Braun et al., 2012; Watkins et al., 2017), this measure may not fully characterize exposure. Furthermore, the lack of information on diet quality is a limitation, as phthalates have been associated with intake of spices, meat, and organic and dairy products in previous studies of pregnant women (Cantonwine et al., 2014; Serrano et al., 2014). Likewise, in a study of NHANES 2003–2010 participants, energy and fat consumption from fast food were associated with higher exposures to di-isononyl phthalate (DiNP), a parent compound of MCPP, in comparison with non-consumers (Zota et al., 2016). In the present study, we addressed this issue by adjusting for mean energy intake during pregnancy and the first postpartum year, which has been proposed as a valid method to control confounding in epidemiological studies due to the association of energy intake with disease risk, physical activity, body weight, and metabolic efficiency (Willett et al., 1997).

Furthermore, information regarding parity after the index ELEMENT child was collected an average of 4.95 ± 0.92 (range: 3–7) years after the last maternal weight measurement. However, information on births specifically during the study period was unavailable, and it is likely that the majority of births occurred within the first few years post ELEMENT recruitment as these were prime child-bearing years. In addition, we expressed parity as a rate to adjust for varying follow-up times. In addition, our analysis met the linearity and normality assumptions of structural equation models (VanderWeele, 2012), so our results should not be affected by these limitations. Specifically, the normality of the response variable and the linearity of associations between the response variable and the continuous independent variables were verified using statistical tests and graphical methods. Furthermore, interactions (derived from the conceptual model) between some of the covariates were evaluated, but were not statistically significant.

A major strength of the present study is that it is based on mothers from a long-standing birth cohort study, which permits the evaluation of long-term maternal health. To our knowledge, this is the first study to evaluate the association between phthalate exposure during pregnancy and subsequent long-term changes in weight in adult women. Additionally, we used path analysis, which has greater statistical power than traditional regression models due to the consideration of relationships between covariates (VanderWeele, 2012), including correlations between multiple phthalate metabolite levels during pregnancy.

5. Conclusion

We observed significant relationships between select urinary phthalate metabolite concentrations in pregnancy and long-term changes in maternal weight. Exposure to MCPP during pregnancy was associated with higher than average weight gain, while MBzP exposure was associated with lower than average weight gain over several years of follow-up. Further studies are needed to confirm these findings, and to explore the long-term effects of prenatal phthalate exposure on maternal health.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.10.014.

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