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Fetal phthalates and bisphenols and childhood lipid and glucose metabolism. A population-based prospective cohort study.

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Abstract

Background and aims—Fetal exposure to endocrine disruptors such as phthalates and bisphenols may lead to developmental metabolic adaptations. We examined associations of

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DECLARATION OF INTEREST

The authors declare no conflicts of interest.

maternal phthalate and bisphenol urine concentrations during pregnancy with lipids, insulin, and glucose concentrations at school age.

Methods—In a population-based, prospective cohort study among 757 mother-child pairs, we measured maternal phthalate and bisphenol urine concentrations in first, second and third trimester of pregnancy. We measured non-fasting lipids, glucose and insulin blood concentrations of their children at a mean age of 9.7 (standard deviation 0.2) years. Analyses were performed for boys and girls separately.

Results—An interquartile range (IQR) higher natural log transformed third trimester maternal urine phthalic acid concentration was associated with a 0.20 (95% confidence interval (CI) 0.07–0.34) standard deviation score (SDS) higher triglycerides concentration among boys. Maternal bisphenol urine concentrations were not associated with non-fasting lipid concentrations during childhood. An IQR higher natural log transformed second trimester maternal high molecular weight phthalates (HMWP) and di-2-ethylhexylphthalate (DEHP) urine concentration were associated with a 0.19 (95% CI 0.31–0.07) respectively 0.18 (95% CI 0.31–0.06) SDS lower glucose concentration among boys. An IQR higher natural log transformed third trimester maternal bisphenol F urine concentration was associated with a 0.22 (95% CI 0.35–0.09) SDS lower non-fasting insulin concentration among boys.

Conclusions—Our results suggest potential persisting sex specific effects of fetal exposure to phthalates and bisphenols on childhood lipid concentrations and glucose metabolism. Future studies are needed for replication and exploring underlying mechanisms.

Keywords

endocrine disruptors; phthalates; bisphenols; lipids; glucose

INTRODUCTION

Endocrine-disrupting chemicals (EDCs), such as phthalates and bisphenols, are widely used in food packaging, household products and medical devices [1–3]. Fetal life may be a specific critical period for the possible effects of phthalates and bisphenols because they pass the placenta [4, 5]. The mechanisms by which phthalates and bisphenols may affect fetal development are by stimulating estrogen and inhibiting androgen receptors, activating peroxisome proliferator-activated receptors (PPARs) or retinoid X receptors (RXRs), and changing the fetal transcriptome [6]. Thus far, cross-sectional studies in adult populations showed inconsistent results for the associations of phthalates and bisphenols with several metabolic diseases in humans, such as obesity, hypertension and diabetes [7–9].

Currently, only limited prospective studies on the associations of fetal exposure to phthalates or bisphenols with metabolic diseases are available and they showed no clear association of fetal exposure to phthalates or bisphenols with childhood lipid and glucose metabolism [10–13]. In a Greek cohort study, first trimester bisphenol A (BPA) urine concentrations were not associated with non-fasting lipid concentrations at 4 years, while third trimester phthalates urine concentrations were negatively associated with non-fasting high density lipoprotein (HDL)-cholesterol concentrations at 4 years, but not with cholesterol concentrations or metabolic outcomes at 6 years [10, 11]. In another study among 227 mother-child pairs from

Mexico, no consistent associations were found for pregnancy-averaged maternal urine BPA or phthalate concentrations with lipid profiles among 8–14-year-old children [12]. Sex- and pubertal status-dependent associations were observed of third trimester phthalate and BPA exposures with C-peptide and fasting glucose at 8–14 years [13]. Although the previous studies explored sex-specific associations, the study populations were smaller than 300 subjects and thus might have been underpowered.

We hypothesized that fetal exposure to phthalates and bisphenols leads to fetal metabolic adaptations, which persistently affect glucose and lipid metabolism. We assessed the sex-specific associations of maternal phthalate and bisphenol urine concentrations in first, second and third trimester of pregnancy with non-fasting lipids, glucose and insulin concentrations in their children at the age of 10 years.

MATERIALS AND METHODS

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards in Rotterdam, the Netherlands [14]. Phthalate and bisphenol concentrations were measured among a subgroup of 1,405 mothers, whose singleton children also participated in postnatal studies. We excluded mothers without information on phthalate and bisphenol urine concentrations for at least one time point in pregnancy and whose children had no measurement of metabolic risk factors at 10 years. The population for analysis comprises 757 mother-child pairs (the specific sample per outcome is shown in Supplemental Figure 1). The study protocol confirms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Centre in Rotterdam. Written informed consent was obtained from all participants.

Maternal phthalate and bisphenol urine concentrations

Phthalate and bisphenol concentrations were measured in spot urine samples obtained from each woman at three time points during pregnancy (median 12.9 weeks of gestation (25^{th}-75^{th} percentiles 12.1 – 14.6); median 20.4 weeks of gestation (25^{th}-75^{th} percentiles 19.9 – 20.9); median 30.2 weeks of gestation (25^{th}-75^{th} percentiles 29.9 – 30.8)). These periods were considered as first, second and third trimester. Urine samples were collected between February 2004 and July 2005. The analyses of phthalate, bisphenol and creatinine concentrations were performed at the Wadsworth Center, New York State Department of Health, Albany, New York, USA, using previously described methods [15]. Urine biomarkers for exposure to phthalate metabolites were grouped according to their molecular weight and parent phthalates into low molecular weight phthalates (LMWP) and high molecular weight phthalates (HMWP), which includes subgroups of di-2-ethylhexylphthalate (DEHP) and di-noctylphthalate (DNOP) metabolites. Phthalic acid (PA) was analyzed separately as a proxy for total phthalate exposure. Bisphenols A (BPA), S (BPS) and F (BPF) were grouped and used as proxy for total bisphenol exposure. Weighted molar sums were calculated for the different groups of phthalates and bisphenols. Individual phthalates and bisphenols were included in the groups if <80% of their concentrations at that

time point was below the limit of detection (LOD). All concentrations below the LOD were substituted by LOD divided by the square root of 2 (LOD/√2) [16]. The descriptive statistics of the individual and grouped phthalates and bisphenols investigated are shown for boys and girls in Table 1 and for the total group in Supplemental Table S1. The intraclass correlation coefficients between the grouped natural log-transformed phthalates and bisphenols across pregnancy were assessed using a single measurement, absolute agreement and two-way mixed effects model and varied between 0.06 and 0.35 (Supplemental Table S1). We also assessed the Pearson's correlation coefficients between all natural log-transformed creatinine-corrected phthalates and bisphenols which showed that the overall correlations were low-moderate, especially between different trimesters and different groups (Supplemental Table S2). To account for urinary dilution, urine concentrations of phthalates and bisphenols were converted to μmol/g creatinine for the metabolite groups. To reduce the potential for exposure misclassification due to temporal variability, we calculated the overall mean exposure during pregnancy by summing the first, second and third trimester phthalate and bisphenol urine concentrations and dividing that by the three time points.

Childhood metabolic risk factors

As described previously, children were invited to visit our research center around the age of 10 years [17]. We obtained non-fasting venous blood samples and measured total cholesterol, HDL-cholesterol, triglycerides, glucose and insulin concentrations. Total cholesterol, HDL-cholesterol, triglycerides and glucose concentrations were measured on the Cobas 8000 analyzer using the c702 module. Insulin was measured with electrochemiluminescence immunoassay (ECLIA) on the E411 module (Roche, Almere, the Netherlands) [18]. Low-density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald formula [19]. For the assessment of the risk of adverse cardio-metabolic risk factors, children were divided into groups based on their concentrations of triglycerides, HDL-cholesterol, LDL-cholesterol and insulin. The 75th percentile was used as the cut-off for triglycerids (≥1.3000mmol/l), LDL-cholesterol (≥2.6927mmol/l) and insulin (≥310.0500pmol/l) and the 25th percentile was used as the cut-off for HDL-cholesterol (≤1.2300mmol/l).

Covariates

Information on maternal characteristics, including age, ethnicity, pre-pregnancy body mass index, use of folic acid supplementation, educational level, parity, and maternal smoking habits and alcohol consumption (specifically in first, second and third trimester of pregnancy or during pregnancy) and maternal diet were obtained from questionnaires during pregnancy. To assess maternal diet, a previously developed food-based diet quality score was used, reflecting adherence to national dietary guidelines [20]. Child's sex was obtained from midwife and hospital records at birth. Weight and height were measured during the visit at our research center to calculate the child's BMI, which was then standardized for age and sex. A simplified Directed Acyclic Graph (DAG) showing the hypothesized relationship between fetal exposure to phthalates and bisphenols, childhood metabolic risk factors and the covariates is presented in Supplemental Figure 2.

Statistical analysis

For all analyses, maternal phthalate and bisphenol urine concentrations were natural log-transformed to reduce variability and account for right skewness of the distribution and further standardized by the interquartile range (IQR) to ease the interpretation of effect sizes. We also natural log-transformed the non-normally distributed childhood metabolic risk factors (triglycerides and insulin) and constructed standard-deviation scores (SDS) [(observed value - mean)/SD] of the sample distribution of all outcomes to enable comparisons of effect sizes. Participants were compared with non-participants on all exposures and covariates by using Chi-square tests, student's t-tests and Mann-Whitney U tests, when applicable.

We assessed linearity of the associations of maternal phthalate and bisphenol urine concentrations (per time point and overall mean during pregnancy) with childhood metabolic risk factors by assessing the residuals of the regression in a P-P plot, assessing homoscedascity and multicollinearity and used linear regression models if the residuals were normally distributed, the residuals were homoscedastic and if the variance inflation factors were below 5.00. To examine the independent associations of maternal first, second and third trimester phthalate and bisphenol urine concentrations with childhood metabolic risk factors, we created a mutually adjusted model by simultaneously including in the model the exposures at all three time points during pregnancy, after testing whether there were no issues with multicollinearity (correlations <0.70) (Supplemental Table S1). We used logistic regression to assess the associations of maternal urine phthalate or bisphenol concentrations with being in the highest risk-category.

First, models were adjusted for child's age and sex only (basic model). Potential confounders were identified based on the graphical criteria for confounding by visualizing a DAG and then we included those in the models that changed the effect estimates >10% for at least one of the outcomes [21]. The inclusion of childhood BMI in the model marginally decreased the effect estimates and we only present the fully adjusted models including childhood BMI. As a sensitivity analysis, we performed the analyses of insulin with glucose included in the model because non-fasting samples were used and the time since the last meal was unknown. Based on our hypothesis of sex-specific effects and based on the influence of folic acid on the metabolism of phthalates and bisphenols, we tested for statistical interaction of child's sex. We also tested for statistical interaction of folic acid supplement use, since folic acid can influence methylation and one of the proposed mechanisms by which phthalates and bisphenols exert their influence could by through changes in DNA methylation [22–24]. We found statistically significant interactions (*p-value*<0.10) for child's sex only and presented all results for boys and girls separately.

To correct for multiple hypothesis testing, each *p-value* was compared with a threshold defined as 0.05 divided by the effective number of independent tests estimated based on the correlation structure between the exposures (*p-value* threshold of 0.0098) [25]. To maintain statistical power and reduce bias related to missing data on covariates, we performed multiple imputation according to the Markov Chain Monte Carlo method. The percentage of missing values for covariates ranged from 0 to 22.7%. Covariates were used as predictor variables and imputed when necessary, while metabolic risk factors were used as predictor

variables only. In addition, birth weight, gestational age at birth, blood pressure at 10 years old and heart frequency at 10 years old were used as predictor variables. Ten imputed datasets were created and no substantial differences were found between the original and imputed datasets. We present results based on pooled imputed datasets. All statistical analyses were performed using the Statistical Package of Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant characteristics

Table 2 shows participant characteristics for the total group and for boys and girls separately. Non-response analyses showed that non-participants tended to have higher urine concentrations of some phthalates, were younger, lower educated and less likely to consume alcohol during pregnancy (Supplemental Tables S3 and S4).

Maternal phthalate urine concentrations and childhood lipid profiles

Table 3 shows that among boys an IQR increase in natural log-transformed third trimester maternal urine phthalic acid concentrations was associated with 0.20 (95% Confidence Interval (CI) 0.07; 0.34) SDS higher natural log transformed triglyceride concentrations (basic models are presented in Supplemental Table S5). This association was also present in the mutually adjusted model (Supplemental Table S6). The associations of higher overall mean maternal DEHP and overall mean maternal DNOP urine concentrations with higher triglycerides concentrations among boys did not remain significant after multiple testing adjustment (Table 3 and Supplemental Table S7). Similarly, the associations among girls of higher second trimester maternal phthalic acid urine concentrations with lower triglyceride concentrations in both the adjusted and mutually adjusted model and the association of higher third trimester maternal DNOP urine concentrations with higher natural log transformed triglyceride concentrations did not remain significant after multiple testing adjustment (Table 3 and Supplemental Table S6). Maternal phthalate urine concentrations were not associated with cholesterol concentrations among boys or girls.

Maternal bisphenol urine concentrations and childhood lipid profiles

Among boys, maternal bisphenol urine concentrations were not associated with childhood total or LDL cholesterol concentrations (Supplemental Table S8). The associations of higher first and third trimester maternal BPF urine concentrations with higher HDL-cholesterol and triglycerides concentrations, respectively, among boys did not remain significant after correction for multiple testing (Table 4). Higher natural log-transformed overall mean maternal bisphenol and BPA urine concentrations were associated with lower natural log transformed triglyceride concentrations among girls, although these associations did not remain significant after correction for multiple testing (Supplemental Table S7). Maternal bisphenol urine concentrations were not associated with total or HDL-, or LDL-cholesterol concentrations among girls (Table 4). No associations were found in the mutually adjusted model (Supplemental Table S9).

Maternal phthalate urine concentrations and childhood glucose metabolism

Among boys, after adjustment for confounders, an IQR higher second trimester and overall mean maternal HMWP and DEHP urine concentrations was associated with a 0.19 (95% CI 0.31–0.07), 0.18 (95% CI 0.30–0.06), 0.18 (95% CI 0.31–0.06), 0.19 (95% CI 0.31–0.07) SDS lower glucose concentrations (Table 5 and Supplemental Table S10, basic models are presented in Supplemental Table S11). In the mutually adjusted model, these associations were attenuated towards non-significance (Supplemental Table S12). Maternal phthalate urine concentrations were not associated with insulin concentrations during childhood (Table 5). When including glucose concentrations in the model, maternal phthalate urine concentrations were again not associated with insulin concentrations during childhood (Supplemental Table S13).

Maternal bisphenol urine concentrations and childhood glucose metabolism

Among boys, an IQR higher natural log-transformed third trimester maternal BPF urine concentrations was associated with 0.22 (95% CI 0.35; 0.09) and 0.19 (95% CI 0.32; 0.05) SDS lower natural log transformed insulin and glucose concentrations (Table 6, basic models are presented in Supplemental Table S14). The association of third trimester maternal BPF urine concentrations with glucose concentrations and with insulin concentrations when corrected for glucose concentrations did not remain after multiple testing adjustment (Supplemental Table S15). The associations of higher first trimester maternal BPS urine concentrations with lower natural log transformed insulin and glucose concentrations among boys did not remain after adjustment for multiple testing (Table 6). In the fully adjusted and mutually adjusted model, among boys higher third trimester total bisphenol maternal urine concentrations was associated with lower natural log transformed insulin concentrations, although these associations did not remain after correction for multiple testing (Table 6 and Supplemental Table S16). Among girls, maternal bisphenol urine concentrations were not associated with insulin or glucose concentrations (Table 6).

Maternal phthalate and bisphenol urine concentrations and risk of adverse cardio-metabolic risk factors

An IQR increase in the natural log transformed third trimester maternal phthalic acid concentrations was associated with an increased triglycerides concentration among boys (Odds Ratio (OR) 1.67 (95% CI 1.20; 2.31)) (Supplemental Table S17). An IQR increase in the natural log transformed third trimester maternal DNOP concentrations was associated with high triglycerides concentrations among girls (OR 1.62 (95% CI 1.21; 2.18)). Among boys, an IQR increase in the natural log transformed third trimester maternal total bisphenol urine concentrations was associated with lower insulin concentrations (OR 0.64 (95% CI 0.46; 0.90)) (Supplemental Table S18).

DISCUSSION

Main findings

In this population-based prospective cohort study, we observed that higher third trimester fetal exposure to phthalic acid is associated with higher non-fasting triglycerides

concentrations among boys, while we observed no association of fetal exposure to phthalates with other lipid concentrations during childhood. Maternal bisphenol urine concentrations were not associated with non-fasting lipid concentrations during childhood. Fetal exposure to phthalates was not associated with non-fasting insulin concentrations at 10 years old. Higher second trimester and overall mean HMWP and DEHP urine concentrations were associated with lower non-fasting glucose concentrations among boys. Higher third trimester maternal urine BPF concentrations were also associated with lower non-fasting insulin concentrations among boys.

Interpretation of main findings

Exposure to phthalates and bisphenols is ubiquitous. Previous animal and cross-sectional human studies have suggested associations of higher exposure to phthalates and bisphenols with adverse lipid and glucose metabolism [26, 27]. However, results from the few prospective studies in humans are inconsistent [10–13]. Fetal exposure to endocrine disruptors such as phthalates and bisphenols may lead to developmental metabolic adaptations, which could have long term consequences. In the current study, we examined the associations of maternal urine phthalate and bisphenol concentrations during pregnancy with non-fasting lipids, glucose, and insulin concentrations at school age.

The associations of fetal phthalate or bisphenol exposure with lipid concentrations during childhood have been studied in three prospective human studies [10–12]. In a study among 260 mother-child pairs, maternal third trimester urine mEP concentrations were inversely associated with non-fasting HDL-cholesterol concentrations at 4 years, but not at 6 years [11]. No associations were found between maternal phthalate concentrations and total cholesterol concentrations in childhood [11]. Among 235 mothers from the same cohort, no associations were observed for maternal urine BPA concentrations with non-fasting blood concentrations of total cholesterol and HDL-cholesterol among 4-year-old children [10]. In another study among 227 mother-child pairs, no consistent associations were observed for the pregnancy-averaged maternal urine phthalate and BPA concentrations with fasting triglycerides, total cholesterol, HDL-cholesterol and calculated LDL-cholesterol among 8–14-year-old children [12]. In the present study, higher third trimester maternal urine phthalic acid concentrations were associated with higher non-fasting triglycerides concentrations among boys. Since phthalic acid is a common metabolite of all phthalates, the higher effect estimates for phthalic acid than for HMWP or DEHP metabolites could be explained by effects of metabolites of newer phthalates which were not measured separately but are included in the phthalic acid measurement. The only other study that investigated non-fasting triglycerides concentrations after fetal exposure to phthalates in humans did not find any associations among all children and among boys and girls separately, which could be due to a power issue [11]. The association of higher maternal urine BPA concentrations with lower triglycerides concentrations among girls in the present study was not in line with our hypothesis, which was mainly based on the earlier reported association of higher BPA concentrations with increased risk of cardiovascular disease [28]. However, our observation was in line with results from a recent meta-analysis of cross-sectional human studies suggesting that higher BPA concentrations were associated with lower triglycerides [29]. The associations of overall mean BPA concentrations with triglycerides in our study have to

be interpreted with caution, due to the fact that they did not remain significant after correction for multiple testing and could thus be a chance finding. In the current study, no other associations of bisphenols with lipid concentrations were found. No previous longitudinal human studies looked into the association of these newer bisphenols such as BPS or BPF with lipid concentrations during childhood. Animal studies that investigated these associations found varying effects for specific bisphenols [30]. These differences in associations could suggest distinct underlying mechanisms for different bisphenols and this urges further investigation of the newer bisphenols or trimester specific effects.

The associations of fetal exposure to bisphenols with childhood glucose metabolism markers have also been studied in multiple animal studies, which in general showed tendencies for associations of higher fetal exposure to BPA with diabetogenic effects [31, 32]. In humans, cross-sectional studies have also shown an association between higher exposure to several phthalates and diabetes [9]. To our knowledge, among humans this association has only been studied in one prospective study [13]. In that study, a few sex- and pubertal status-dependent associations were observed of third trimester phthalate and BPA exposures with C-peptide, a marker of insulin secretion, and fasting glucose among 219 children at 8–14 years old [13]. More specifically, higher maternal total DBP and mCPP urine concentrations were associated with lower fasting glucose concentrations among pubertal boys, while higher maternal mEP urine concentrations were associated with lower C-peptide index among prepubertal girls [13]. No associations of fetal BPA with childhood metabolic outcomes were reported [13]. In the current study, we observed that fetal exposure to HMWP and DEHP was associated with non-fasting glucose concentrations. This is partially in line with the previous study, that found that higher phthalate exposure was associated with lower glucose and insulin concentrations. The absence of an association of BPA with glucose and insulin concentrations in the current study is in line with the previous study [13]. Among boys, we observed an association between third trimester maternal BPF concentrations with lower insulin and glucose concentrations and between third trimester maternal BPA concentrations with lower insulin concentrations after correction for glucose. It is important to note that the association of higher third trimester maternal BPF concentrations with lower glucose concentrations among boys and the association of higher third trimester maternal BPA concentrations with lower insulin concentrations after correction for glucose among boys did not remain significant after correction for multiple testing and could thus be a chance finding, while it is in line with the lower insulin concentrations that were found. We cannot compare these association with previous studies, as these effects of BPF were not previously assessed in humans. These results suggest that fetal exposure to bisphenols could be associated with lower non-fasting glucose and insulin concentrations later in life, however, these results need to be replicated with fasting glucose and insulin levels to more accurately assess insulin sensitivity.

In conclusion, our results add to the growing body of evidence that fetal exposure of specific phthalates and bisphenols could influence later metabolic health in humans. We cannot draw conclusions about causality due to the observational nature of this study. The effect estimates observed in this study are small, but they are of interest from a public health perspective because of the widespread use of bisphenols and phthalates.

Possible underlying mechanisms

From animal studies it has been suggested that phthalates, via the PPARalpha-receptor, can increase HDL-cholesterol concentrations and decrease production of triglycerides by influencing lipid oxidation and fatty acid synthesis and can increase the uptake of triglycerides [33–35]. It is not clear whether these mechanisms are as important in humans as they are in animals. The discrepancy between the findings in human studies and animal studies might thus be based on an interspecies difference of unknown origin. This could also explain the absence of effect of most studied phthalates on lipid concentrations observed in this study. On the other hand, laboratory studies have found that phthalate metabolites increase cytokine production and thus can lead to an adverse inflammatory environment [36]. This could be the reason that higher exposure to phthalic acid was found to be associated with higher triglycerides concentrations among boys in this study. Specific phthalates have also been shown to affect insulin signaling [37].

It has been found that BPA could affect fatty acid and glucose metabolism and it is thought that exposure to BPA alters the glucose-stimulated insulin response [38–40]. However, in this study fetal exposure to BPA was not associated with lipid concentrations or glucose metabolism at 10 years old. In contrast to a previous study that suggested that BPF exposure could lead to hyperglycemia in zebrafish, we found that higher BPF concentrations during pregnancy were associated with lower insulin concentrations and not with higher glucose concentrations in children at 10 years old [41].

Both phthalates and bisphenol A influence epigenetic regulatory mechanisms, which may need considerable time to lead to measurable changes in circulating biomarkers and this timing issue could possibly explain the discrepancies [42–44]. It has even been suggested that exposure to bisphenols influences health in subsequent generations [45, 46]. The relationship between exposure to endocrine disruptors and metabolic disturbances is potentially sex-specific [47]. This could be due to sex-specific differences in PPAR-activity of phthalates and the estrogenic effect of BPA [48, 49]. In animals, epigenetic reprogramming is also considered a potential molecular mechanism that might underlie the sex-specific associations of the prenatal exposure to endocrine disruptors with metabolic outcomes later in life [50, 51]. Further studies are needed to elucidate the underlying mechanisms of endocrine disruptors on lipid and glucose metabolism in humans specifically.

Methodological considerations

An important strength of this study is the population-based cohort design from fetal life onward, with repeated measurements of maternal phthalate and bisphenol concentrations. We also measured childhood lipid and glucose concentrations in a large number of mother-child pairs. Selection bias due to selective loss to follow-up would be of concern in any study if the associations of prenatal phthalate and bisphenol concentrations with childhood lipid and glucose metabolism are different between participants and non-participants. This seems unlikely, but cannot be excluded with certainty, because the reported differences in ethnicity could influence diet and lifestyle choices which could influence the associations. Furthermore, we measured maternal phthalate and bisphenol urine concentrations once per trimester. It is possible that one urine sample per trimester does not accurately represent the

concentration during the whole trimester because of the reported short biological half-lives of phthalates and bisphenols [6, 52]. However, it has been found that a single urine sample reflects phthalate exposure up to three months [53]. Variability has also been reported to be biomarker specific, with strong correlations for LMWP metabolites and reasonable correlations for BPA and DEHP metabolites [54, 55]. In this study, we found moderate variability for phthalates and high variability for bisphenols during pregnancy. We also used the overall mean to partly correct for the remaining variability. These associations were comparable to the trimester-specific associations. The main limitation of using a linear regression approach is that it does not take into account the association of the investigated exposure with other exposures. This could provide unreliable results if the exposures are highly correlated, which the exposures are not (Supplemental Table S2). We used non-fasting blood samples collected at different times during the day depending on the time of visit. This could have led to non-differential misclassification of children and consequently an underestimation of the associations. However, previous studies in adults have shown that non-fasting blood lipid concentrations can accurately predict increased risks of cardiovascular events later in life and that semi-fasting insulin resistance is moderately correlated with fasting values [56, 57]. We also assessed the association of phthalates and bisphenols with insulin, independent of glucose, to partially correct for the varying times since last meal and found comparable results. However, these results need to be replicated with non-fasting lipid, insulin and glucose concentrations in children. Future studies could also assess the effects of childhood exposure to phthalates and bisphenols on metabolic outcomes. Finally, we collected information on many potential confounders, although, as in any observational study, residual confounding due to unmeasured variables might remain an issue.

CONCLUSION

Results from our population-based prospective cohort study suggest persisting effects of fetal exposure to phthalates and bisphenols on childhood lipid concentrations which could be sex specific. Future studies are needed for replication and exploring underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Maternal phthalic acid is associated with higher triglycerides during childhood.
- Maternal bisphenols are not associated with lipid concentrations during childhood.
- Maternal phthalates are associated with lower glucose levels during childhood.
- Maternal bisphenol F is associated with lower insulin levels during childhood.

Table 1.

Urinary concentrations of phthalates and bisphenols during pregnancy, stratified in boys and girls.

	First trimester Median (25th-75th percentile)		Second trimester Median (25th-75th percentile)		Third trimester Median (25th-75th percentile)	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Phthalic Acid (PA) (nmol/L)	343.1 (179.4 – 645.5)	365.1 (185.0 – 779.4)	903.8 (372.0 – 1658.6)	832.3 (337.8 – 1687.7)	368.7 (188.9 – 778.0)	419.5 (219.9 – 889.9)
Low-molecular-weight phthalates (LMWP) (nmol/L)	1094.8 (477.8 – 2653.5)	1102.0 (400.8 – 3118.0)	520.5 (228.1 – 1281.0)	573.8 (221.4 – 1659.0)	921.1 (372.6 – 2244.8)	1008.3 (410.7 – 2773.1)
Monomethylphthalate (mMP) (nmol/L)	28.7 (15.1 – 54.5)	30.2 (15.3 – 55.7)	17.9 (9.9 – 33.6)	19.1 (9.3 – 35.4)	19.4 (10.2 – 37.8)	24.8 (11.6 – 52.7)
Monoethylphthalate (mEP) (nmol/L)	677.8 (210.3 – 2329.3)	710.8 (208.1 – 2574.9)	315.4 (112.6 – 970.4)	376.9 (124.0 – 1409.1)	581.0 (205.4 – 1818.1)	658.1 (219.9 – 2378.1)
Mono-isobutylphthalate (mIBP) (nmol/L)	101.5 (45.9 – 217.6)	98.1 (43.0 – 191.3)	36.5 (19.3 – 78.6)	39.9 (18.8 – 78.8)	69.3 (39.7 – 138.3)	84.2 (43.8 – 174.4)
Mono-n-butylphthalate (mBP) (nmol/L)	78.5 (32.5 – 150.0)	72.6 (32.7 – 140.2)	43.0 (23.5 – 82.7)	41.3 (22.3 – 85.6)	52.9 (27.2 – 97.2)	56.9 (28.0 – 117.1)
High molecular-weight phthalates (HMWP) (nmol/L)	217.3 (111.0 – 414.9)	218.4 (115.8 – 385.5)	131.8 (73.7 – 242.3)	121.9 (67.8 – 221.4)	156.7 (92.5 – 268.9)	178.2 (97.4 – 318.1)
Monobenzylphthalate (mBzBP) (nmol/L)	22.0 (8.7 – 47.9)	22.4 (9.4 – 47.8)	19.6 (7.7 – 37.5)	19.2 (8.2 – 42.5)	10.8 (3.9 – 23.7)	12.8 (4.1 – 25.2)
Mono-hexylphthalate (mHxP) (nmol/L)	1.0 (0.4 – 2.2)	0.9 (0.3 – 1.9)	NA	NA	NA	NA
Mono-2-heptylphthalate (mHpP) (nmol/L)	2.1 (0.8 – 5.3)	2.1 (0.8 – 5.5)	NA	NA	NA	NA
Monocyclohexyl-phthalate (mCHP) (nmol/L)	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	NA	NA	NA	NA
***Di-2-ehtylhexylphthalate (DEHP)* (nmol/L)**	171.9 (89.8 – 315.1)	174.2 (89.9 – 300.7)	96.8 (49.9 – 184.2)	89.4 (48.2 – 164.9)	132.3 (75.3 – 225.9)	146.8 (80.3 – 274.1)
Mono-(2-ethyl-5-carboxy-pentyl)phthalate (mECPP) (nmol/L)	51.6 (25.9 – 100.0)	51.2 (27.1 – 99.4)	33.8 (17.4 – 64.9)	30.6 (17.8 – 58.6)	54.1 (28.9 – 103.7)	59.8 (30.4 – 110.3)
Mono-(2-ethyl-5-hydroxy-hexyl)phthalate (mEHHP) (nmol/L)	41.4 (20.8 – 79.9)	43.5 (20.5 – 75.0)	19.2 (10.0 – 37.1)	17.8 (9.2 – 34.2)	31.0 (17.1 – 59.4)	39.4 (18.2 – 75.2)
Mono-(2-ethyl-5oxohexyl)phthalate (mEOHP) (nmol/L)	27.0 (12.1 – 55.6)	26.5 (12.5 – 49.5)	25.2 (12.4 – 57.5)	22.5 (10.6 – 52.5)	22.0 (13.3 – 42.3)	26.9 (14.0 – 50.0)
Mono-[(2-carboxymethyl)-hexyl] phthalate (mCMHP) (nmol/L)	44.2 (24.3 – 67.8)	46.9 (24.5 – 83.2)	12.51 (6.8 – 24.2)	12.3 (6.9 – 22.9)	9.7 (6.0 – 19.7)	12.4 (5.7 – 22.5)
Di-n-octylphthalate (DNOP)	5.7 (3.2 – 11.2)	6.4 (2.9 – 10.7)	3.5 (2.0 – 6.8)	3.3 (1.9 – 6.1)	6.6 (3.7 – 12.1)	6.9 (3.8 – 13.2)
Mono(3-carboxypropyl)- phthalate (mCPP) (nmol/L)	5.7 (3.2 – 11.2)	6.4 (2.9 – 10.7)	3.5 (2.0 – 6.8)	3.3 (1.9 – 6.1)	6.6 (3.7 – 12.1)	6.9 (3.8 – 13.2)
Bisphenols (nmol/L)	9.7 (3.6 – 21.7)	8.7 (3.4 – 21.6)	6.0 (2.8 – 12.5)	5.8 (2.9 – 13.5)	8.4 (3.8 – 17.0)	10.0 (4.5 – 19.3)
Bisphenol A (BPA) (nmol/L)	5.0 (1.0 – 12.4)	4.6 (1.0 – 15.0)	5.7 (2.6 – 11.6)	5.1 (2.5 – 11.8)	5.9 (2.5 – 11.0)	7.0 (2.8 – 13.2)
Bisphenol S (BPS) (nmol/L)	0.8 (0.1 – 3.0)	0.6 (0.1 – 2.3)	0.1 (0.1 – 0.5)	0.1 (0.1 – 0.4)	NA	NA

	First trimester Median (25th-75th percentile)		Second trimester Median (25th-75th percentile)		Third trimester Median (25th-75th percentile)	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Bisphenol F (BPF) (nmol/L)	0.6 (0.6 – 1.7)	0.6 (0.6 – 2.4)	NA	NA	0.6 (0.6 – 2.6)	0.6 (0.6 – 1.3)

Values represent medians (25th-75th percentiles). Absolute urinary concentration of the limit of detection (in nmol/L urine), grouped exposures (in nmol/L urine), and individual exposures (in nmol/L urine) with concentrations below the limit of detection imputed as limit of detection/square root of 2. Only values that are included in the calculation of the grouped exposures are included in this table.

NA: not applicable due to >80% of concentrations below limit of detection.

Table 2.

Characteristics of mothers and their children.

	Total group n = 757	Boys n = 382 (50.5%)	Girls n = 375 (49.5%)
Maternal characteristics			
Age at enrolment, mean (SD) (years)	31.0 (4.6)	31.1 (4.5)	30.9 (4.7)
Parity, n (%)			
Nullipara	464 (61.6%)	232 (60.9%)	232 (62.4%)
Multipara	289 (38.4%)	149 (39.1%)	140 (37.6%)
Ethnicity, n (%)			
European	478 (63.6%)	245 (64.5%)	233 (62.6%)
Non-European	274 (36.4%)	135 (35.5%)	139 (37.4%)
Education, n (%)			
Low	52 (7.1%)	26 (7.0%)	26 (7.2%)
Middle	286 (39.0%)	141 (37.8%)	145 (40.2%)
High	396 (54.0%)	206 (55.2%)	190 (52.6%)
Pre-pregnancy BMI, median (95% range) (kg/m2)	22.7 (18.6 – 34.7)	22.6 (18.5 – 34.4)	22.8 (18.6 – 35.1)
Maternal diet quality score, mean (SD)[a]	7.9 (1.5)	7.9 (1.6)	7.9 (1.4)
Folic acid supplementation, n (%), yes	503 (82.2%)	259 (83.8%)	244 (80.5%)
Smoking during pregnancy, n (%), yes	165 (23.9%)	81 (23.6%)	84 (24.1%)
First trimester, n (%), yes	104 (20.7%)	67 (20.1%)	73 (21.4%)
Second trimester, n (%), yes	75 (11.3%)	35 (10.4%)	40 (12.3%)
Third trimester, n (%), yes	68 (10.5%)	36 (10.7%)	32 (10.2%)
Alcohol consumption during pregnancy (any), n (%), yes	419 (61.2%)	221 (64.8%)	198 (57.6%)
First trimester, n (%), yes	361 (53.6%)	194 (57.7%)	167 (49.4%)
Second trimester, n (%), yes	251 (38.1%)	133 (40.2%)	118 (36.1%)
Third trimester, n (%), yes	256 (39.7%)	147 (44.3%)	109 (34.8%)
Child characteristics			
Age, mean (SD) (years)	9.7 (0.2)	9.7 (0.3)	9.7 (0.2)
BMI, median (95% range) (kg/m^2)	16.8 (14.0 – 25.0)	16.6 (13.9 – 24.1)	17.1 (14.0 – 25.5)
Triglycerides, median (95% range) (mmol/L)	1.0 (0.4 – 2.5)	0.9 (0.4 – 2.6)	1.0 (0.5 – 2.3)
Total cholesterol, mean (SD) (mmol/L)	4.3 (0.6)	4.2 (0.6)	4.4 (0.6)
HDL cholesterol, mean (SD) (mmol/L)	1.5 (0.3)	1.5 (0.3)	1.4 (0.3)
LDL cholesterol, mean (SD) (mmol/L)	2.3 (0.6)	2.2 (0.6)	2.4 (0.6)
Insulin, median (95% range) (pmol/L)	198.9 (37.5 – 671.0)	193.3 (31.5 – 571.0)	207.4 (38.5 – 804.6)
Glucose, mean (SD) (mmol/L)	5.5 (0.9)	5.5 (0.9)	5.4 (0.9)

Values represent mean (SD), median (95% range) or number of subjects (valid %).

[a] As based on the food frequency questionnaire filled out in early pregnancy.

Table 3.

Associations of maternal urinary phthalate concentration during pregnancy with childhood lipid profile at 10 years stratified for boys and girls.

		Measures of lipid profile at 10 years (in standard deviation scores, 95% confidence interval)											
		Triglycerides			Total Cholesterol			HDL Cholesterol			LDL Cholesterol		
Exposure	**Trimester**	**Boys (n = 381)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 382)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 380)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 379)**	**Girls (n = 375)**	**p-value for interaction**
PA	First trimester	−0.01 (−0.14; 0.11)	0.04 (−0.08; 0.16)	0.57	−0.01 (−0.13; 0.100)	0.04 (−0.09; 0.17)	0.55	0.00 (−0.12; 0.13)	0.05 (−0.07; 0.17)	0.42	−0.02 (−0.14; 0.09)	0.01 (−0.12; 0.14)	0.73
	Second trimester	0.06 (−0.10; 0.21)	−0.14 (−0.27; −0.00) *	0.06 #	−0.01 (−0.15; 0.13)	−0.04 (−0.19; 0.11)	0.72	0.01 (−0.15; 0.16)	0.06 (−0.08; 0.19)	0.42	−0.02 (−0.16; 0.12)	−0.02 (−0.17; 0.12)	0.81
	Third trimester	0.20 (0.07; 0.34) †	0.06 (−0.07; 0.19)	0.12	0.05 (−0.08; 0.17)	0.07 (−0.08; 0.21)	0.87	−0.11 (−0.24; 0.03)	−0.06 (−0.19; 0.07)	0.42	0.04 (−0.09; 0.16)	0.08 (−0.06; 0.22)	0.75
LMWP	First trimester	−0.11 (−0.25; 0.02)	0.05 (−0.08; 0.18)	0.09 #	−0.02 (−0.14; 0.11)	0.09 (−0.05; 0.23)	0.44	0.08 (−0.05; 0.21)	0.04 (−0.09; 0.16)	0.79	−0.05 (−0.17; 0.07)	0.06 (−0.08; 0.20)	0.36
	Second trimester	0.05 (−0.10; 0.20)	−0.11 (−0.25; 0.03)	0.18	−0.05 (−0.19; 0.09)	0.04 (−0.12; 0.19)	0.45	0.08 (−0.07; 0.22)	0.05 (−0.09; 0.18)	0.87	−0.11 (−0.25; 0.03)	0.06 (−0.09; 0.21)	0.14
	Third trimester	0.15 (−0.01; 0.30)	0.06 (−0.09; 0.21)	0.44	0.01 (−0.14; 0.16)	0.07 (−0.10; 0.23)	0.70	−0.09 (−0.24; 0.07)	−0.03 (−0.17; 0.12)	0.43	0.03 (−0.12; 0.17)	0.06 (−0.10; 0.23)	0.87
HMWP	First trimester	0.08 (−0.04; 0.20)	0.01 (−0.12; 0.13)	0.35	0.04 (−0.07; 0.15)	−0.00 (−0.14; 0.13)	0.56	−0.01 (−0.13; 0.11)	0.02 (−0.10; 0.14)	0.46	0.00 (−0.11; 0.11)	−0.01 (−0.14; 0.13)	0.80
	Second trimester	0.07 (−0.06; 0.20)	−0.10 (−0.22; 0.02)	0.05 #	−0.01 (−0.13; 0.11)	−0.08 (−0.21; 0.05)	0.43	−0.01 (−0.14; 0.12)	0.00 (−0.12; 0.12)	0.70	−0.02 (−0.14; 0.10)	−0.06 (−0.19; 0.07)	0.57
	Third trimester	0.12 (−0.01; 0.25)	0.03 (−0.08; 0.13)	0.18	−0.03 (−0.15; 0.09)	−0.02 (−0.14; 0.09)	1.00	−0.01 (−0.14; 0.11)	0.05 (−0.05; 0.15)	0.43	−0.08 (−0.20; 0.04)	−0.07 (−0.18; 0.04)	0.95
DEHP	First trimester	0.09 (−0.03; 0.22)	0.01 (−0.12; 0.13)	0.28	0.07 (−0.05; 0.18)	−0.01 (−0.14; 0.13)	0.39	−0.01 (−0.13; 0.11)	0.02 (−0.11; 0.14)	0.55	0.03 (−0.09; 0.14)	−0.01 (−0.14; 0.13)	0.64
	Second trimester	0.10 (−0.04; 0.23)	−0.11 (−0.24; 0.02)	0.04 *	−0.00 (−0.13; 0.12)	−0.10 (−0.24; 0.04)	0.30	−0.01 (−0.14; 0.12)	0.00 (−0.13; 0.13)	0.81	−0.02 (−0.14; 0.10)	−0.08 (−0.22; 0.06)	0.53
	Third trimester	0.12 (−0.01; 0.25)	0.02 (−0.09; 0.12)	0.17	0.01 (−0.11; 0.13)	−0.03 (−0.15; 0.09)	0.61	−0.01 (−0.13; 0.12)	0.05 (−0.05; 0.16)	0.50	−0.04 (−0.16; 0.08)	−0.08 (−0.19; 0.03)	0.60

		Measures of lipid profile at 10 years (in standard deviation scores, 95% confidence interval)											
		Triglycerides			Total Cholesterol			HDL Cholesterol			LDL Cholesterol		
Exposure	**Trimester**	**Boys (n = 381)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 382)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 380)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 379)**	**Girls (n = 375)**	**p-value for interaction**
DNOP	First trimester	0.11 (−0.00; 0.22)	0.00 (−0.11; 0.11)	0.13	0.03 (−0.08; 0.13)	0.02 (−0.10; 0.14)	0.82	−0.02 (−0.12; 0.09)	0.01 (−0.10; 0.12)	0.63	−0.02 (−0.12; 0.08)	0.02 (−0.10; 0.14)	0.70
	Second trimester	0.10 (−0.04; 0.23)	−0.01 (−0.13; 0.11)	0.24	−0.04 (−0.16; 0.08)	0.00 (−0.13; 0.13)	0.66	−0.06 (−0.19; 0.06)	−0.04 (−0.15; 0.08)	0.77	−0.04 (−0.16; 0.08)	0.02 (−0.11; 0.15)	0.51
	Third trimester	0.04 (−0.08; 0.17)	0.12 (0.01; 0.24) *	0.43	−0.09 (−0.20; 0.03)	0.04 (−0.09; 0.16)	0.13	−0.05 (−0.17; 0.08)	−0.07 (−0.18; 0.05)	0.78	−0.10 (−0.22; 0.02)	0.02 (−0.10; 0.15)	0.13

Values are regression coefficients (95% confidence interval) from linear regression models that reflect the difference in cardiometabolic risk factors in SDS for an interquartile range increase in each natural log-transformed phthalate (in µmol/g creatinine). Triglycerides are natural log transformed. Model includes child's age and sex- and age-standardized BMI and maternal age, education, parity, ethnicity, pre-pregnancy body mass index, folic acid supplement use, maternal diet quality score, alcohol consumption and smoking habits (specifically in early, mid and late pregnancy). P-values for interaction of sex are presented.

p-value<0.10;

* *p-value*<0.05;

† Significant after correction for multiple testing (*p-value* threshold of 0.0098).

DEHP, di-2-ethylhexylphthalate; DNOP, di-n-octylphthalate; HMWP, high molecular weight phthalate; LMWP, low molecular weight phthalate; PA, phthalic acid; SDS, standard deviation scores.

Table 4.

Associations of maternal urinary bisphenol concentration during pregnancy with childhood lipid profile at 10 years stratified for boys and girls.

		Measures of lipid profile at 10 years (in standard deviation scores, 95% confidence interval)											
		Triglycerides			Total Cholesterol			HDL Cholesterol			LDL Cholesterol		
Exposure	**Trimester**	**Boys (n = 381)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 382)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 380)**	**Girls (n = 375)**	**p-value for interaction**	**Boys (n = 379)**	**Girls (n = 375)**	**p-value for interaction**
BP	First trimester	−0.04 (−0.19; 0.11)	−0.09 (−0.21; 0.03)	0.60	0.00 (−0.14; 0.14)	−0.03 (−0.16; 0.10)	0.68	0.08 (−0.07; 0.22)	0.05 (−0.07; 0.16)	0.72	−0.02 (−0.15; 0.12)	−0.02 (−0.15; 0.11)	0.95
	Second trimester	0.06 (−0.07; 0.19)	−0.09 (−0.22; 0.04)	0.11	−0.00 (−0.12; 0.12)	−0.02 (−0.16; 0.12)	0.89	0.00 (−0.13; 0.13)	0.05 (−0.08; 0.17)	0.56	−0.03 (−0.15; 0.09)	−0.02 (−0.15; 0.12)	0.89
	Third trimester	0.03 (−0.10; 0.16)	−0.04 (−0.17; 0.09)	0.38	0.01 (−0.11; 0.13)	−0.05 (−0.19; 0.09)	0.56	0.03 (−0.10; 0.15)	0.04 (−0.09; 0.16)	0.89	−0.00 (−0.12; 0.11)	−0.06 (−0.20; 0.08)	0.71
BPA	First trimester	0.01 (−0.14; 0.16)	−0.10 (−0.22; 0.02)	0.23	−0.03 (−0.17; 0.11)	0.03 (−0.10; 0.17)	0.65	0.05 (−0.10; 0.20)	0.07 (−0.05; 0.19)	0.88	−0.06 (−0.20; 0.08)	0.04 (−0.09; 0.17)	0.30
	Second trimester	0.06 (−0.07; 0.19)	−0.09 (−0.22; 0.03)	0.11	−0.01 (−0.12; 0.11)	−0.01 (−0.15; 0.13)	0.99	−0.01 (−0.14; 0.11)	0.06 (−0.07; 0.18)	0.36	−0.02 (−0.14; 0.10)	−0.01 (−0.15; 0.12)	0.94
	Third trimester	0.03 (−0.10; 0.15)	−0.05 (−0.18; 0.07)	0.35	0.04 (−0.08; 0.15)	−0.06 (−0.20; 0.07)	0.25	0.03 (−0.09; 0.15)	0.00 (−0.12; 0.12)	0.59	0.03 (−0.09; 0.14)	−0.05 (−0.18; 0.08)	0.47
BPS	First trimester	0.05 (−0.07; 0.18)	0.02 (−0.09; 0.13)	0.67	0.06 (−0.06; 0.17)	−0.09 (−0.21; 0.03)	0.09 #	−0.10 (−0.22; 0.02)	−0.01 (−0.12; 0.11)	0.21	0.11 (−0.01; 0.22)	−0.10 (−0.22; 0.02)	0.02 *
	Second trimester	0.04 (−0.10; 0.17)	−0.01 (−0.12; 0.11)	0.68	0.04 (−0.09; 0.16)	−0.01 (−0.14; 0.13)	0.78	0.09 (−0.04; 0.22)	−0.03 (−0.15; 0.09)	0.09 #	−0.05 (−0.18; 0.07)	0.03 (−0.10; 0.15)	0.24
	Third trimester	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
BPF	First trimester	−0.08 (−0.23; 0.07)	−0.06 (−0.19; 0.07)	0.78	0.08 (−0.06; 0.21)	0.02 (−0.12; 0.16)	0.81	0.18 (0.04; 0.32) *	0.02 (−0.11; 0.15)	0.14	0.01 (−0.13; 0.14)	0.04 (−0.10; 0.18)	0.56
	Second trimester	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Third trimester	0.15 (0.0; 0.29) *	0.03 (−0.10; 0.17)	0.22	0.04 (−0.09; 0.17)	0.03 (−0.11; 0.18)	0.74	−0.02 (−0.16; 0.12)	−0.01 (−0.14; 0.12)	0.94	−0.01 (−0.14; 0.11)	0.03 (−0.11; 0.17)	0.45

Values are regression coefficients (95% confidence interval) from linear regression models that reflect the difference in cardiometabolic risk factors in SDS for an interquartile range increase in each natural log-transformed bisphenol (in μmol/g creatinine). Triglycerids are natural log transformed. Model includes child's age and standardized BMI and maternal age, education, parity, ethnicity, pre-pregnancy body mass index, folic acid supplement use, maternal diet quality score, alcohol consumption and smoking habits (specifically in early, mid and late pregnancy). P-values for interaction of child's sex are presented.

[#] *p-value*<0.10;

[*] *p-value*<0.05;

[†] Significant after correction for multiple testing (*p-value* threshold of 0.0098).

BP, bisphenols; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; NA: not applicable due to >80% of concentrations below limit of detection; SDS, standard deviation scores.

Table 5.

Associations of maternal urinary phthalate concentration during pregnancy with childhood glucose metabolism at 10 years stratified for boys and girls.

		Measures of glucose metabolism at 10 years (in standard deviation scores, 95% confidence interval)					
		Insulin			Glucose		
Exposure	**Trimester**	**Boys (n = 380)**	**Girls (n = 373)**	**p-value for interaction**	**Boys (n=382)**	**Girls (n = 374)**	**p-value for interaction**
PA	First trimester	−0.02 (−0.14; 0.10)	0.02 (−0.11; 0.15)	0.49	−0.05 (−0.17; 0.07)	0.04 (−0.10; 0.17)	0.55
	Second trimester	−0.06 (−0.21; 0.08)	−0.01 (−0.15; 0.14)	0.48	−0.15 (−0.30; −0.01) *	0.02 (−0.13; 0.16)	0.15
	Third trimester	0.01 (−0.12; 0.14)	0.03 (−0.11; 0.16)	0.86	−0.03 (−0.16; 0.10)	−0.02 (−0.16; 0.12)	0.85
LMWP	First trimester	0.02 (−0.11; 0.14)	0.05 (−0.09; 0.19)	0.53	−0.01 (−0.14; 0.12)	−0.08 (−0.22; 0.05)	0.30
	Second trimester	0.05 (−0.09; 0.19)	−0.04 (−0.18; 0.11)	0.60	0.02 (−0.13; 0.16)	−0.05 (−0.20; 0.10)	0.43
	Third trimester	0.00 (−0.15; 0.15)	0.05 (−0.11; 0.21)	0.61	−0.03 (−0.18; 0.12)	−0.04 (−0.21; 0.12)	0.64
HMWP	First trimester	−0.02 (−0.13; 0.09)	0.06 (−0.07; 0.19)	0.29	−0.11 (−0.22; 0.00)	0.01 (−0.13; 0.14)	0.25
	Second trimester	−0.10 (−0.22; 0.02)	0.02 (−0.11; 0.15)	0.08 *	−0.19 (−0.31; −0.07) †	0.03 (−0.10; 0.16)	0.02 *
	Third trimester	−0.08 (−0.20; 0.04)	0.02 (−0.09; 0.13)	0.25	−0.10 (−0.22; 0.03)	0.03 (−0.09; 0.14)	0.22
DEHP	First trimester	−0.03 (−0.14; 0.09)	0.06 (−0.08; 0.19)	0.33	−0.11 (−0.23; 0.00)	0.01 (−0.13; 0.14)	0.24
	Second trimester	−0.11 (−0.24; 0.02)	0.01 (−0.12; 0.15)	0.12	−0.18 (−0.31; −0.06) †	0.04 (−0.10; 0.18)	0.02 *
	Third trimester	−0.09 (−0.21; 0.03)	0.02 (−0.09; 0.13)	0.24	−0.10 (−0.23; 0.02)	0.03 (−0.08; 0.15)	0.19
DNOP	First trimester	−0.02 (−0.12; 0.09)	0.03 (−0.09; 0.15)	0.52	−0.07 (−0.18; 0.03)	0.05 (−0.07; 0.18)	0.15
	Second trimester	−0.04 (−0.16; 0.08)	0.02 (−0.11; 0.14)	0.42	−0.09 (−0.22; 0.03)	0.05 (−0.08; 0.18)	0.14
	Third trimester	−0.02 (−0.14; 0.10)	0.03 (−0.09; 0.15)	0.55	−0.08 (−0.20; 0.04)	0.06 (−0.06; 0.19)	0.10

Values are regression coefficients (95% confidence interval) from linear regression models that reflect the difference in cardiometabolic risk factors in SDS for an interquartile range increase in each natural log-transformed phthalate (in µmol/g creatinine). Triglycerids are natural log transformed. Model includes child's age and standardized BMI and maternal age, education, parity, ethnicity, pre-pregnancy body mass index, folic acid supplement use, maternal diet quality score, alcohol consumption and smoking habits (specifically in early, mid and late pregnancy). P-values for interaction of sex are presented.

p-value<0.10;

* *p-value*<0.05;

† Significant after correction for multiple testing (*p-value* threshold of 0.0098).

DEHP, di-2-ethylhexylphthalate; DNOP, di-n-octylphthalate; HMWP, high molecular weight phthalate; LMWP, low molecular weight phthalate; PA, phthalic acid; SDS, standard deviation scores.

Table 6.

Associations of maternal urinary bisphenol concentration during pregnancy with childhood glucose metabolism at 10 years stratified for boys and girls.

		Measures of glucose metabolism at 10 years (in standard deviation scores, 95% confidence interval)					
		Insulin			Glucose		
Exposure	**Trimester**	**Boys (n = 380)**	**Girls (n = 373)**	**p-value for interaction**	**Boys (n = 382)**	**Girls (n = 374)**	**p-value for interaction**
BP	First trimester	0.02 (−0.12; 0.16)	−0.03 (−0.16; 0.10)	0.44	0.00 (−0.14; 0.14)	−0.03 (−0.16; 0.10)	0.73
	Second trimester	−0.00 (−0.12; 0.12)	−0.02 (−0.15; 0.12)	0.93	−0.01 (−0.14; 0.11)	0.07 (−0.07; 0.21)	0.49
	Third trimester	−0.16 (−0.28; −0.04) *	−0.07 (−0.20; 0.07)	0.35	−0.03 (−0.15; 0.09)	−0.07 (−0.21; 0.07)	0.61
BPA	First trimester	0.08 (−0.06; 0.22)	−0.05 (−0.18; 0.08)	0.14	0.00 (−0.14; 0.14)	−0.01 (−0.14; 0.12)	0.89
	Second trimester	−0.00 (−0.12; 0.12)	−0.00 (−0.14; 0.13)	0.92	−0.02 (−0.15; 0.10)	0.07 (−0.07; 0.21)	0.41
	Third trimester	−0.10 (−0.21; 0.02)	−0.08 (−0.21; 0.05)	0.83	0.04 (−0.07; 0.16)	−0.12 (−0.25; 0.01)	0.05 *
BPS	First trimester	−0.13 (−0.25; −0.02) *	−0.01 (−0.13; 0.11)	0.19	−0.15 (−0.26; −0.03) *	−0.02 (−0.14; 0.10)	0.12
	Second trimester	−0.05 (−0.18; 0.08)	−0.03 (−0.16; 0.09)	0.98	−0.06 (−0.19; 0.07)	0.02 (−0.11; 0.15)	0.33
	Third trimester	NA	NA	NA	NA	NA	NA
BPF	First trimester	0.06 (−0.08; 0.20)	−0.02 (−0.15; 0.12)	0.38	0.07 (−0.07; 0.21)	−0.05 (−0.19; 0.10)	0.24
	Second trimester	NA	NA	NA	NA	NA	NA
	Third trimester	−0.22 (−0.35; −0.09) †	−0.05 (−0.19; 0.09)	0.15	−0.19 (−0.32; −0.05) *	0.05 (−0.10; 0.19)	0.01 *

Values are regression coefficients (95% confidence interval) from linear regression models that reflect the difference in glucose metabolism in SDS for an interquartile range increase in each natural log-transformed bisphenol (in µmol/g creatinine). Model includes child's age and standardized BMI and maternal age, education, parity, ethnicity, pre-pregnancy body mass index, folic acid supplement use, maternal diet quality score, alcohol consumption and smoking habits (specifically in early, mid and late pregnancy). P-values for interaction of child's sex are presented.

p-value<0.10;

* *p-value*<0.05;

† Significant after correction for multiple testing (*p-value* threshold of 0.0098).

BP, bisphenols; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; NA: not applicable due to >80% of concentrations below limit of detection; SDS, standard deviation scores.