Original Article
PEDIATRIC OBESITY

Obesity

Phthalate and Bisphenol Urinary Concentrations, Body Fat Measures, and Cardiovascular Risk Factors in Dutch School-Age Children

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Objective: The purpose of this study was to investigate the associations of urinary phthalates and bisphenols at age 6 years old with body fat and cardiovascular risk factors at 6 and 10 years and with the change from 6 to 10 years.

Methods: Among 471 Dutch children, the phthalates and bisphenols urinary concentrations at 6 years and BMI, fat mass index, android fat mass, blood pressure, glucose, insulin, and lipids blood concentrations at 6 and 10 years were measured.

Results: An interquartile range increase in di-*n*-octyl phthalate (DNOP) metabolites concentrations at 6 years was associated with an increased risk of overweight at 6 and 10 years (odds ratio: 1.44; 95% CI: 1.11-1.87, and 1.43; 95% CI: 1.09-1.86, respectively). Also, higher DNOP metabolites concentrations were associated with higher fat mass index at 6 years, higher systolic blood pressure at 10 years, a decrease in high-density lipoprotein cholesterol, and an increase in triglycerides concentrations from 6 to 10 years ($P < 0.05$). Higher total bisphenols and bisphenol A concentrations were associated with a decrease in BMI from 6 to 10 years ($P < 0.01$).

Conclusions: DNOP metabolites are associated with overweight and an adverse cardiovascular profile in childhood. Total bisphenols and bisphenol A are associated with a decrease in BMI from 6 to 10 years.

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Study Importance

What is already known?

- Phthalates and bisphenols interfere with metabolic processes and lead to cardiovascular disease in adults.
- Though many previous studies have examined fetal exposure to these chemicals, fewer have examined longitudinal effects of childhood exposure to phthalates and bisphenols on body fat and cardiovascular risk.

What does this study add?

- Adiposity in school-aged children may be influenced by phthalates and bisphenols exposure, specifically by di-*n*-octyl phthalate (DNOP) metabolites and bisphenol A.
- DNOP metabolites seem also to be associated with an adverse cardiovascular profile in childhood.

How might these results change the direction of research?

- Future research should further explore childhood as a vulnerable period of exposure to bisphenols and pthphthalates in relation to later adiposity and cardiovascular health and should explore the potential underlying mechanisms and causality.

Introduction

Endocrine disrupting chemicals (EDCs), such as phthalates and bisphenols, are adverse environmental factors that may affect childhood health (1,2). Phthalate metabolites are synthetic chemical esters of phthalic acid that are widely used in a variety of consumer products to impart flexibility and elasticity to plastics. Bisphenol A (BPA) is used to produce polycarbonate plastics and epoxy resins used in various products, including

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toys, water pipes, and the lining of metal cans, and it has been substituted by synthetic bisphenol analogues like bisphenol S (BPS) (3). Phthalates and bisphenols via epigenetic and endocrine mechanisms may permanently disrupt metabolic pathways contributing to an adverse cardiovascular profile (4,5).

High exposure to phthalate metabolites and bisphenols is increasingly reported to be associated with obesity, hypertension, insulin resistance, dyslipidemia, and cardiovascular disease among adults (6,7). In general, fetuses and children are likely to be more vulnerable to exposure to these chemicals than adults (8). Most previous studies have examined pregnancy as a vulnerable period rather than childhood. Results in children are mostly based on cross-sectional studies and they have not revealed expected effects consistently (9-22). Some cross-sectional studies have suggested associations of higher exposure to phthalate metabolites and BPA with higher BMI as well as hip and waist circumference (9-11,13). In contrast, another cross-sectional study among 845 Danish children aged 4 to 9 years reported that higher phthalate metabolites were negatively associated with height, weight, and BMI (19). Previous cross-sectional studies have found that higher phthalate metabolites and BPA concentrations were associated with adverse childhood cardiovascular profile, such as higher blood pressure, low-grade albuminuria, and insulin resistance (14-18). However, other studies have found negative or no associations between BPA exposure and childhood metabolic outcomes (20-22). This controversy of results from previous studies might be explained by differences in sample size, timing of collection of samples, and in the individual phthalates and bisphenols available. Also, a major literature gap is the lack of longitudinal data evaluating the association of childhood exposure to phthalate metabolites and bisphenols with body fat measures and cardiovascular risk factors (12,22). Assessing these associations using a longitudinal design in childhood and controlling for child's diet and maternal exposure to phthalate metabolites and bisphenols during pregnancy will allow a better understanding of the influence of these chemicals on child's health.

We hypothesized that increased childhood exposure to phthalate metabolites and bisphenols affects accretion of body fat and the development of elevated blood pressure and other adverse cardiovascular outcomes. We examined whether phthalate metabolites and bisphenols urinary concentrations at 6 years were associated with body fat measures and cardiovascular risk factors, including BMI, fat mass index, android fat mass, blood pressure, and glucose, insulin, cholesterol, and triglycerides concentrations at 6 and 10 years, as well as with the change in these outcomes from 6 to 10 years. Additionally, we also explored the associations of phthalate metabolites and bisphenols urinary concentrations with risks of overweight and clustering of cardiovascular risk factors in childhood.

Methods

Study design

This study was embedded in the Generation R Study, a prospective population-based cohort study from early fetal life onward in Rotterdam, the Netherlands (23). Phthalate metabolites and bisphenols urinary concentrations were measured among a subgroup of 775 singleton children aged 6 years. Children in this subgroup were similar to the broader Generation R cohort in terms of sociodemographic and lifestyle characteristics (Supporting Information Table S1). We excluded children with non-Dutch ethnicity because of potential ethnicity-specific differences in the associations (13). The population for analysis comprises 471 Dutch children with information on phthalate metabolites and bisphenols urinary concentrations and at least one measurement of body fat and cardiovascular risk factors at 6 or 10 years (Supporting Information Figure S1). The study was approved by the local Medical Ethics Committee of Erasmus MC (MEC 198.782/2001/31), and written informed consent was obtained from parents.

Phthalate metabolites and bisphenols urinary concentrations

Phthalate metabolites and bisphenols concentrations were measured in a spot urine sample obtained during the study visit at 6 years. As previously described, urine samples were collected between 8 AM and 8 PM, stored at 4°C and transported within 24 hours of receipt to the Star Medisch Diagnostisch Centrum (STAR-MDC) laboratory to be frozen at −20°C. The urine specimens were shipped on dry ice in 4-mL polypropylene vials to the Wadsworth Center, New York State Department of Health, Albany, New York, for analysis (24). We grouped phthalate metabolites according to their molecular weight categories and parent compounds. BPA and BPS were grouped and used as proxy for total bisphenol exposure. Individual bisphenol and phthalate metabolites were only included in groups and assessed individually if less than 80% of the sample concentrations were below the limit of detection (LOD). We calculated the weighted molar sums for groups representing total bisphenols, low-molecular-weight (LMW) phthalates, high-molecular-weight (HMW) phthalates, and for two subgroups within HMW phthalates: di-2-ethylhexyl phthalate (DEHP) and di-n-octyl phthalate (DNOP) metabolites. Phthalic acid was analyzed separately as a proxy for total phthalate exposure. Phthalate metabolites and bisphenols concentrations below LOD were substituted by LOD/$\sqrt{2}$ (25). Supporting Information Table S2 shows the metabolites included in all groups, their urinary concentrations, and detection rates at the age of 6 years. To account for urinary dilution, concentrations of phthalate metabolites and bisphenols were converted to microgram per gram of creatinine (for the separate metabolites) or micromole per gram of creatinine (for the metabolite groups).

Body fat measures and cardiovascular risk factors

Children were invited to visit our research center at 6 and 10 years. We calculated BMI (kilogram per meters squared) from height and weight, both measured without shoes and heavy clothing, and sex- and age-adjusted *z* scores of childhood BMI based on Dutch reference growth charts (Growth Analyzer 4.0, Dutch Growth Research Foundation) (26). BMI categories (normal weight and overweight/obesity) were obtained using the International Obesity Task Force cutoffs (27). We measured total body fat mass by dual-energy x-ray absorptiometry (Lunar iDXA GE 140; GE Healthcare, Chicago, Illinois; enCORE software v.12.6) (28). We divided total fat mass by height^3 at 6 years and by height^4 at 10 years in order to obtain a fat mass index uncorrelated with height after estimating the optimal adjustment by log-log regression analyses (29,30). We also calculated android fat mass as a percentage of total fat mass.

Blood pressure was measured at the right brachial artery four times using the validated automatic sphygmanometer Datascope Accutor Plus (Paramus, New Jersey). The mean value was calculated using

the last three measurements of each participant. Nonfasting blood samples were collected to determine serum concentrations of glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. Insulin concentrations were measured with electrochemiluminescence immunoassay on the E411 module (Roche, Almere, the Netherlands). Glucose (only available at 10 years), total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured using the c702 module on the Cobas 8000 analyzer (Roche).

Based on previous literature, clustering of cardiovascular risk factors was defined as having three or more of the following components: systolic or diastolic blood pressure in the 75th percentile or above; android fat mass percentage in the 75th percentile or above; insulin concentration in the 75th percentile or above; and HDL-cholesterol in the 25th percentile or below or triglycerides in the 75th percentile or above (31).

Covariates

Maternal age and educational level were obtained by questionnaire at enrollment. Maternal phthalate metabolites and bisphenols urinary concentrations were measured at three time points during pregnancy (median 12.9 weeks of gestation [25th-75th percentiles 12.1-14.5]; median 20.4 weeks of gestation [25th-75th percentiles 19.9-20-9]; median 30.2 weeks of gestation [25th-75th percentiles 29.9-30.8]) and the pregnancy-averaged concentrations were calculated (32). Child sex and age were available from medical records. Child ethnicity was based on parental countries of birth obtained through questionnaire. Height was measured without shoes at both 6 and 10 years. The average television-watching time was obtained by questionnaires at both ages. Diet quality was determined by a parent-reported food frequency questionnaire assessed at the child's mean age of 8.1 years. The algorithm to score adherence to Dutch dietary guidelines has been previously described and ranged from 0 to 10 on a continuous scale with higher scores reflecting better adherence to dietary guidelines (33).

Statistical analysis

Phthalate metabolites and bisphenols concentrations were natural log-transformed to reduce variability and account for right skewedness of the distribution and standardized by the interquartile range to ease the interpretation of effect sizes. The distributions of fat mass index, insulin, and triglycerides concentrations were skewed and natural log-transformed. To enable comparison of effect sizes of different outcome measures, we constructed z scores ([observed value – mean]/SD). We performed linear regression models to assess the associations of phthalate metabolites and bisphenols urinary concentrations at 6 years with body fat measures and cardiovascular risk factors at 6 and 10 years and with the change in these outcomes from 6 to 10 years. Nonlinearity was visually assessed using a scatterplot and ruled out. Additionally, we explored, using multinominal logistic regression models, the associations of phthalate metabolites and bisphenols with risks of overweight and clustering of cardiovascular risk factors at 6 and 10 years. Because of the small sample size, we were not able to assess these associations with the change from 6 to 10 years. Basic models included child's sex, age, and height (only for blood pressure models) at outcome measurements. For the models with the change in the outcomes from 6 to 10 years, the corresponding change in age and height was included. Potential confounders were represented in a directed acyclic graph (Supporting Information Figure S2), and those that fulfilled the graphical criteria for confounding and changed the effect estimates >10% for at least one of the outcomes were included. Confounder models additionally included maternal educational level and child's diet quality score and average television-watching time at 6 years. For the models with the change in the outcomes from 6 to 10 years, television-watching time at both ages was included because no multicollinearity issues were observed. Also, we performed a model in which we additionally adjusted for the corresponding phthalate metabolites or bisphenol pregnancy-averaged urinary concentrations. As sensitivity analyses, we additionally adjusted the models for the outcomes at 10 years and for the change in the outcomes from 6 to 10 years by the corresponding outcomes at 6 years. Based on previous literature, we tested for statistical interactions by child sex in these analyses, but none of these was consistently significant (10,11). 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 20%. Ten imputed data sets were created but no substantial differences were found between the original and imputed data sets. We presented results based on pooled imputed data sets. 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 between the exposures (P value threshold of 0.01) (34). All statistical analyses were performed using SPSS Statistics v.25.0 for Windows (IBM Corp., Armonk, New York).

Results

Subject characteristics

Table 1 shows the characteristics of the study population. The mean age of the children who attended the study visits at the research center was between 5.9 and 9.7 years, and more than half (52.4%) were boys. Overall, 11.4% and 15.0% of children had overweight, and 13.9% and 10.2% had clustering of cardiovascular risk factors at 6 and 10 years, respectively.

Phthalate metabolites and bisphenols urinary concentrations and body fat measures

In the confounder models, an interquartile range increase in HMW phthalates urinary concentrations was associated with higher childhood BMI at 10 years ($P < 0.05$) (Table 2). Also, an interquartile range increase in DNOP metabolites urinary concentrations was associated with both higher childhood BMI at 6 and 10 years and an increase in childhood BMI from 6 to 10 years ($P < 0.05$). The association of DNOP metabolites urinary concentrations with childhood BMI at 10 years remained significant after multiple testing corrections (z score: 0.16 [95% CI: 0.06 to 0.25]). In contrast, and after multiple testing correction, an interquartile range increase in total bisphenols and BPA urinary concentrations was associated with a decrease in childhood BMI from 6 to 10 years (z score: −0.13 [95% CI −0.22 to −0.05], z score: −0.14 [95% CI: −0.23 to −0.05], respectively). An interquartile range increase in HMW phthalates and DNOP metabolites urinary concentrations was also associated with higher childhood fat mass index at 6 years ($P < 0.05$). However, these results did not remain significant after multiple testing correction. No associations were observed for phthalate metabolites or bisphenols urinary

TABLE 1 Characteristics of mothers and their children

	Total group (*N* = 471)
Maternal characteristics	
Age, mean (SD), y	31.4 (4.2)
Education, *n* (%)	
Lower	6 (1.3)
Middle	161 (34.5)
Higher	300 (64.2)
Child characteristics at age 6	
Sex, *n* (%)	
Boys	247 (52.4)
Girls	224 (47.6)
Age at visit, mean (SD), y	5.9 (0.2)
Television-watching time, *n* (%)	
<2 hours	394 (89.5)
≥2 hours	46 (10.5)
Height, mean (SD), m	1.2 (0.0)
BMI, mean (SD), kg/m^2	15.9 (1.5)
BMI categories, *n* (%)	
Normal weight	397 (88.6)
Overweight/obesity	51 (11.4)
Fat mass index, median (25th,75th percentile), kg/m^3	3.1 (2.6,3.6)
Android fat mass, mean (SD), %	3.8 (0.9)
Systolic blood pressure, mean (SD), mm Hg	101.7 (8.2)
Diastolic blood pressure, mean (SD), mm Hg	60.0 (6.8)
Insulin, median (25th,75th percentile), pmol/L	127.4 (66.4,191.6)
Total cholesterol, mean (SD), mmol/L	4.2 (0.6)
HDL-cholesterol, mean (SD), mmol/L	1.3 (0.3)
Triglycerides, median (25th,75th percentile), mmol/L	1.0 (0.8,1.4)
Clustering of cardiovascular risk factors, *n* (%)	
Yes	43 (13.9)
Diet quality, mean (SD), score	4.5 (1.2)
Child characteristics at age 10	
Age at visit, mean (SD), y	9.7 (0.2)
Television-watching time, *n* (%)	
<2 hours	299 (79.5)
≥2 hours	77 (20.5)
Height, mean (SD), m	1.4 (0.1)
BMI, mean (SD), kg/m^2	17.0 (2.3)
BMI categories, *n* (%)	
Normal weight	318 (85.0)
Overweight/obesity	56 (15.0)
Fat mass index, median (25th,75th percentile), kg/m^3	2.0 (1.6,2.6)
Android fat mass, mean (SD), %	4.0 (1.2)
Systolic blood pressure, mean (SD), mm Hg	102.9 (7.6)
Diastolic blood pressure, mean (SD), mm Hg	58.9 (6.3)
Glucose, mean (SD), mmol/L	5.5 (0.9)
Insulin, median (25th,75th percentile), pmol/L	193.8 (114.2, 299.3)
Total cholesterol, mean (SD), mmol/L	4.3 (0.6)
HDL-cholesterol, mean (SD), mmol/L	1.5 (0.3)
Triglycerides, median (25th,75th percentile), mmol/L	1.0 (0.7,1.3)
Clustering of cardiovascular risk factors, *n* (%)	
Yes	25 (10.2)

Values are means (SD), medians (25th,75th percentile), or numbers of subjects (valid %).

concentrations with android fat mass. Similar results were observed after additional adjustment for maternal phthalate metabolites and bisphenols pregnancy-averaged urinary concentrations (Supporting Information Table S3). Sensitivity analyses showed that, after adjustment for the corresponding outcome at 6 years, results were largely similar, although the effect estimates were slightly attenuated, especially for the associations of HMW phthalates and DNOP metabolites urinary concentrations with childhood BMI at 10 years (Supporting Information Table S4). Results from the basic models are given in Supporting Information Table S5. Figure 1 shows that, after adjustment for confounding, an interquartile range increase in HMW phthalates and DNOP metabolites urinary concentrations was associated with higher risk of childhood overweight at both ages ($P < 0.05$). The associations of DNOP metabolites urinary concentrations with risk of childhood overweight at 6 and 10 years remained significant after multiple testing correction (odds ratio: 1.44 [95% CI: 1.11 to 1.87], 1.43 (95% CI: 1.09 to 1.86], respectively). Results from the basic models are given in Supporting Information Figure S3.

Phthalate metabolites and bisphenols urinary concentrations and cardiovascular risk factors

An interquartile range increase in phthalic acid urinary concentrations was associated with an increase in childhood systolic blood pressure from 6 to 10 years ($P < 0.05$) (Table 3). Also, an interquartile range increase in HMW phthalates and in DNOP metabolites urinary concentrations was associated with higher childhood systolic blood pressure at 10 years ($P < 0.05$). Interquartile range increases in HMW phthalates urinary concentrations were associated with higher diastolic blood pressure at 6 years, whereas interquartile range increases in total bisphenols and BPA urinary concentrations were associated with lower diastolic blood pressure at 6 years ($P < 0.05$). Also, interquartile range increases in total bisphenols and BPA urinary concentrations were associated with an increase in childhood diastolic blood pressure from 6 to 10 years ($P < 0.05$). However, all these associations did not remain significant after multiple testing correction. An interquartile range increase in LMW phthalates and DEHP metabolites urinary concentrations was associated with lower HDL-cholesterol and higher triglycerides concentrations at 10 years, respectively ($P < 0.05$) (Table 4). Also, an interquartile range increase in DNOP metabolites urinary concentrations was associated with a decrease in HDL-cholesterol and an increase in triglycerides from 6 to 10 years ($P < 0.05$). In contrast, an interquartile range increase in total bisphenols and BPA urinary concentrations was associated with lower insulin concentrations at 10 years and with higher HDL-cholesterol at 6 years ($P < 0.05$). However, only the association of DNOP metabolites urinary concentrations with a decrease in HDL-cholesterol from 6 to 10 years remained significant after multiple testing correction (z score: −0.17 [95% CI: −0.28 to −0.06]). Phthalate metabolites and bisphenols urinary concentrations were not associated with glucose concentrations at 10 years (Supporting Information Table S6). Similar results were observed after additional adjustment for maternal phthalate metabolites and bisphenols pregnancy-averaged urinary concentrations (Supporting Information Tables S6-S8). Sensitivity analyses showed that, after adjustment for the corresponding outcome at 6 years, results were similar but the effect estimates were attenuated. In contrast, the association of DNOP metabolites urinary concentrations with lower HDL-cholesterol at 10 years reached statistical significance even after multiple testing correction (z score: −0.14 [95% CI: −0.24 to −0.04]) (Supporting Information Tables S9-S10). Results from the basic models are given in Supporting Information Tables S6 and S11-S12. Figure 2 shows that after adjustment for confounding,

TABLE 2 Associations of phthalate metabolites and bisphenols urinary concentrations with body fat measures in childhood

Endocrine disrupting chemicals urinary concentrations	Difference (95% CI) in *z* scores									
	BMI			Fat mass index			Android fat mass			
	6 years	10 years	Change from 6-10 years	6 years	10 years	Change from 6-10 years	6 years	10 years	Change from 6-10 years
Phthalic acid	0.02 (−0.07,0.10)	0.03 (−0.08,0.15)	0.00 (−0.08,0.08)	0.00 (−0.09,0.09)	0.02 (−0.08,0.12)	−0.00 (−0.07,0.06)	−0.02 (−0.13,0.09)	0.01 (−0.10,0.13)	−0.00 (−0.09,0.08)
LMW phthalate	0.04 (−0.04,0.12)	0.06 (−0.04,0.17)	0.01 (−0.05,0.08)	0.05 (−0.02,0.12)	0.08 (−0.01,0.17)	0.02 (−0.03,0.08)	0.04 (−0.05,0.13)	0.08 (−0.02,0.18)	0.01 (−0.06,0.08)
HMW phthalate	0.08 (−0.02,0.17)	0.14 (0.02,0.26)*	0.06 (−0.02,0.14)	0.10 (0.01,0.19)*	0.09 (−0.02,0.20)	−0.01 (−0.08,0.06)	0.05 (−0.07,0.16)	0.06 (−0.06,0.19)	0.02 (−0.08,0.10)
DEHP metabolites	0.06 (−0.05,0.16)	0.10 (−0.04,0.23)	0.04 (−0.05,0.12)	0.10 (−0.00,0.20)	0.09 (−0.02,0.21)	0.00 (−0.07,0.08)	0.05 (−0.08,0.17)	0.06 (−0.07,0.20)	0.01 (−0.09,0.11)
DNOP metabolites	0.08 (0.00,0.16)*	0.16 (0.06,0.25)[a]	0.07 (0.00,0.13)*	0.08 (0.00,0.15)*	0.08 (−0.01,0.17)	−0.02 (−0.07,0.03)	0.06 (−0.03,0.15)	0.07 (−0.03,0.16)	0.00 (−0.07,0.07)
Total bisphenols	−0.01 (−0.11,0.10)	−0.13 (−0.26,0.01)	−0.13 (−0.22, −0.05)*,[a]	−0.05 (−0.15,0.06)	−0.06 (−0.18,0.05)	−0.04 (−0.11,0.03)	−0.09 (−0.21,0.04)	−0.12 (−0.25,0.01)	−0.04 (−0.14,0.06)
BPA	0.01 (−0.10,0.12)	−0.12 (−0.26,0.02)	−0.14 (−0.23, −0.05)*,[a]	−0.03 (−0.14,0.07)	−0.06 (−0.19,0.06)	−0.05 (−0.13,0.02)	−0.07 (−0.20,0.06)	−0.12 (−0.25,0.02)	−0.06 (−0.16,0.04)
BPS	−0.02 (−0.13,0.09)	−0.12 (−0.25,0.02)	−0.08 (−0.16,0.01)	−0.03 (−0.13,0.08)	−0.06 (−0.18,0.06)	−0.02 (−0.09,0.05)	−0.08 (−0.20,0.05)	−0.11 (−0.24,0.03)	−0.02 (−0.12,0.08)

Values are linear regression coefficients (95% CI) and reflect the differences in *z* scores for childhood BMI, fat mass index, and android fat mass at 6 and 10 years and the change in the outcomes in *z* scores from 6 to 10 years for an interquartile range increase in each natural log-transformed phthalate metabolites and bisphenols urinary concentrations in micromoles per gram of creatinine. Change from 6 to 10 years corresponds to the difference in the outcome between 6 and 10 years. Models are adjusted for maternal educational level and child sex, age (except for sex- and age-adjusted BMI *z* scores), diet quality score, and television-watching time.
[a]Result remained significant after multiple testing correction.
*$P < 0.05$.

an interquartile range increase in LMW phthalates was associated with a higher risk of clustering of cardiovascular risk factors at 10 years, whereas an interquartile range increase in HMW phthalates was associated with a lower risk of clustering of cardiovascular risk factors at 6 years ($P < 0.05$). These associations did not remain significant after multiple testing correction. Bisphenols urinary concentrations were not associated with clustering of cardiovascular risk factors. Results from the basic models are given in Supporting Information Figure S4.

Discussion

In a population-based study, we observed that higher DNOP metabolites urinary concentrations were associated with an increased risk of overweight and obesity and with lower HDL-cholesterol and tended to be associated with higher systolic blood pressure and higher triglycerides in school-age children. Higher total bisphenols and BPA urinary concentrations were associated with lower BMI and tended to be associated with higher diastolic blood pressure and lower insulin in school-age children.

Interpretation of main findings

As a result of the widespread use of phthalate metabolites and bisphenols-related products, children can be exposed to these potential harmful chemicals through different pathways, such as ingestion, inhalation, and dermal contact (11). Phthalates and bisphenols may interfere with endocrine processes, resulting in a deviation from the normal homeostatic control that may lead to an adverse cardiovascular profile (1). We hypothesized that increased exposure to phthalate metabolites and bisphenols affect body fat and cardiovascular development already in childhood.

A previous narrative review reported positive associations of exposure to phthalate metabolites with childhood BMI, subscapular skinfold thickness, and hip and waist circumferences in five studies, the associations of which were mostly observed among boys (3). However, a recent meta-analysis of 29 studies in children and adults has reported inconsistencies in results from published literature on the association between the exposure to phthalates and adiposity (35). In the current study, we observed that higher HMW phthalate concentrations, specifically DNOP metabolites, at 6 years were associated with higher BMI and an increased risk of overweight and obesity in school-age children. Contrarily to previous studies and surprisingly due to estrogenicity of bisphenols and antiandrogenicity of some phthalates, we did not observe a statistical interaction by child's sex. However, we cannot exclude the possibility that our results might have been underpowered to detect differences by sex because of the small sample size. Most studies of bisphenols were only focused on BPA and reported that, in childhood, higher BPA concentrations were associated with increased BMI, hip and waist circumferences, and body fat (9,21). However, we observed that higher total bisphenols and BPA urinary concentrations were associated with a decrease in BMI from 6 to 10 years but not with fat mass index or android fat mass. Based on previous studies, we did not hypothesize this association beforehand. Although we cannot disregard the possibility of a true association, it might be due to residual confounding.

An accumulating body of evidence suggests that phthalate metabolites and bisphenols exposure may contribute to acute and chronic cardiovascular risks, altered blood pressure, and atherosclerosis, as well as

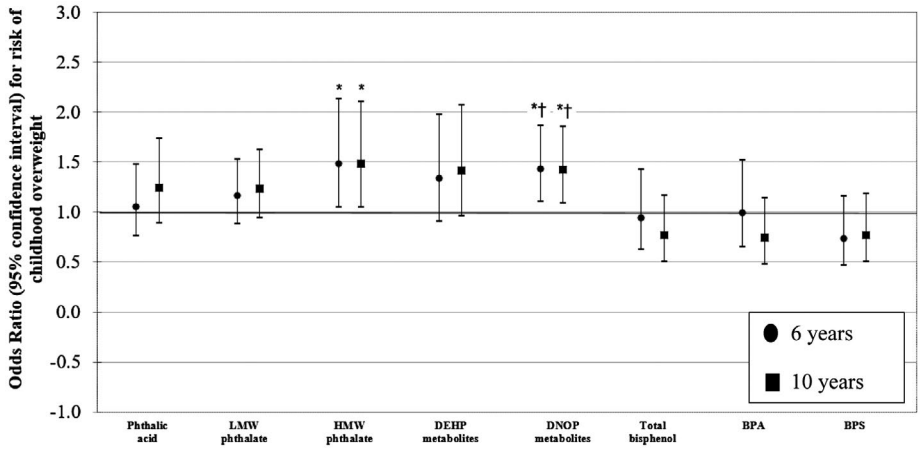

Figure 1 Associations of phthalate metabolites and bisphenols urinary concentrations with risk of overweight in childhood. Values are odds ratios (95% CI) on a logarithmic scale and represent the risk of childhood overweight and obesity at 6 and 10 years for an interquartile range increase in each natural log-transformed phthalate metabolites and bisphenols urinary concentrations in micromoles per gram of creatinine. Models are adjusted for maternal educational level and child diet quality score and television-watching time. *$P < 0.05$. †Result remained significant after multiple testing correction.

low-grade inflammation, diabetes, insulin resistance, and hyperlipidemia later in life (6,7). The associations of phthalate metabolites and bisphenols exposure with cardiovascular outcomes during childhood have also been explored (14-18,20,22). Previous studies reported that childhood exposure to phthalate metabolites and bisphenols is associated with an adverse metabolic profile, such as increased blood pressure and low-grade albuminuria (14-16,20). However, a study among 2,555 US children aged 6 to 19 years did not report an association of phthalate metabolites with triglycerides and HDL-cholesterol concentrations (14). Also, other studies did not report associations of BPA exposure with childhood metabolic outcomes, including glucose, insulin resistance, and blood lipids from midchildhood until adolescence (21,22). In the present study and similarly to previous studies, we observed that higher phthalic acid and HMW phthalates, specifically DNOP metabolites, tended to be associated with higher childhood systolic blood pressure. We also observed that higher LMW phthalates, DEHP metabolites, and DNOP metabolites tended to be associated with lower HDL-cholesterol and higher triglycerides concentrations in school-age children. On the other hand, we observed that higher total bisphenols and BPA urinary concentrations tended to be associated with an increase in diastolic blood pressure from 6 to 10 years and with lower insulin at 10 years. The positive association of total bisphenols and BPA with diastolic blood pressure from 6 to 10 years should be interpreted with caution because the effect estimates attenuated after additional adjustment for the outcome at 6 years and a negative association was observed at 6 years.

The potential mechanisms underlying the associations of phthalate metabolites with overweight and an adverse cardiovascular profile might include the activation of peroxisome proliferator-activated receptors (PPARs) and imbalance of steroid and thyroid hormones (36-38). Activation of PPARs can increase lipid accumulation and release adipocyte-related hormones, leading to higher susceptibility for the development of obesity (36). Likewise, the perturbation of the steroid and thyroid hormones system, which are critical for the maintenance of basal metabolism, may also have obesogenic effects (37,38). Similar mechanisms have been found for bisphenols (36,37). However, this is not in line with our results, which showed an association of bisphenols with lower BMI in children.

Altogether, our results suggest that DNOP metabolites and bisphenols exposure may affect childhood BMI. The associations of phthalate metabolites and bisphenols with cardiovascular risk factors, except for DNOP metabolites and HDL-cholesterol from 6 to 10 years, were no longer significant after multiple testing correction and thus we cannot exclude the possibility of results being chance findings. The observed effect estimates might be small on an individual level but can be important on a population-based level, as children are widely exposed to these EDCs and overweight and obesity and adverse cardiovascular risk factors tend to track into poorer cardiovascular health later in life. Because of the observational design of this study, we cannot draw conclusions about causality. Further studies are needed to replicate these findings and investigate potential mechanisms.

Strengths and limitations

The major strengths of this study were the availability of urinary measurements of diverse phthalate metabolites and BPS in addition to the detailed data available on childhood body fat measures and cardiovascular risk factors. Also, contrary to most previous studies that were embedded in a cross-sectional design and thus can be affected by reverse causality, we were able to address the associations of exposure to phthalate metabolites and bisphenols at 6 years with body fat and cardiovascular risk factors at 10 years. This study also has limitations. This study was conducted in a low-risk small sample, which might have resulted in insufficient power to detect associations, especially after conducting multiple testing correction. No substantial differences in terms of sociodemographic and lifestyle characteristics were observed between children in this subgroup and in the broader cohort, and thus, although it cannot be excluded, selection bias seems unlikely. In our study, we relied on a single-spot urinary measurement of phthalate metabolites and bisphenols as an estimate of exposure. Both phthalate metabolites and bisphenols have short biological half-lives (39,40),

TABLE 3 Associations of phthalate metabolites and bisphenols urinary concentrations with blood pressure in childhood

Endocrine disrupting chemicals urinary concentrations	Difference (95% CI) in *z* scores					
	Systolic blood pressure			Diastolic blood pressure		
	6 years	10 years	Change from 6-10 years	6 years	10 years	Change from 6-10 years
Phthalic acid	−0.03 (−0.14,0.07)	0.07 (−0.05,0.18)	0.14 (0.03,0.25)*	0.02 (−0.09,0.12)	0.02 (−0.10,0.14)	0.09 (−0.05,0.23)
LMW phthalate	−0.00 (−0.09,0.09)	0.03 (−0.06,0.13)	0.04 (−0.06,0.13)	0.04 (−0.05,0.13)	0.01 (−0.10,0.11)	0.00 (−0.12,0.12)
HMW phthalate	0.08 (−0.03,0.20)	0.13 (0.01,0.25)*	0.07 (−0.05,0.19)	0.12 (0.01,0.23)*	0.09 (−0.04,0.22)	0.04 (−0.11,0.18)
DEHP metabolites	0.05 (−0.07,0.18)	0.10 (−0.03,0.23)	0.08 (−0.05,0.21)	0.10 (−0.03,0.22)	0.05 (−0.09,0.18)	0.03 (−0.14,0.19)
DNOP metabolites	0.06 (−0.03,0.15)	0.10 (0.00,0.19)*	0.06 (−0.03,0.16)	0.08 (−0.01,0.17)	0.09 (−0.01,0.19)	0.04 (−0.08,0.16)
Total bisphenols	−0.01 (−0.13,0.12)	−0.02 (−0.15,0.11)	−0.03 (−0.17,0.10)	−0.13 (−0.25, −0.00)*	0.01 (−0.13,0.15)	0.18 (0.02,0.35)*
BPA	−0.02 (−0.16,0.11)	−0.03 (−0.16,0.11)	−0.02 (−0.16,0.12)	−0.13 (−0.26, −0.00)*	0.00 (−0.14,0.15)	0.18 (0.01,0.35)*
BPS	0.10 (−0.03,0.23)	0.08 (−0.06,0.21)	−0.02 (−0.15,0.12)	−0.03 (−0.16,0.10)	0.08 (−0.06,0.22)	0.14 (−0.02,0.31)

Values are linear regression coefficients (95% CI) and reflect the differences in *z* scores for childhood blood pressure at 6 and 10 years and the change in the outcomes in *z* scores from 6 to 10 years for an interquartile range increase in each natural log-transformed phthalate metabolites and bisphenols urinary concentrations in micromoles per gram of creatinine. Changes from 6 to 10 years correspond to the difference in the outcome between 6 and 10 years. Models are adjusted for maternal educational level and child sex, age, height, diet quality score, and television-watching time.
*$P<0.05$.

TABLE 4 Associations of phthalate metabolites and bisphenols urinary concentrations with insulin and lipids profile in childhood

Endocrine disrupting chemicals urinary concentrations	Difference (95% CI) in z scores											
	Insulin			Total cholesterol			HDL-cholesterol			Triglycerides		
	6 years	10 years	Change from 6-10 years	6 years	10 years	Change from 6-10 years	6 years	10 years	Change from 6-10 years	6 years	10 years	Change from 6-10 years
Phthalic acid	−0.06 (−0.18,0.06)	−0.03 (−0.16,0.11)	0.04 (−0.17,0.24)	0.04 (−0.08,0.16)	0.09 (−0.05,0.22)	−0.03 (−0.14,0.08)	0.06 (−0.05,0.18)	−0.05 (−0.18,0.08)	−0.07 (−0.20,0.05)	0.07 (−0.05,0.19)	0.06 (−0.07,0.19)	−0.02 (−0.21,0.17)
LMW phthalate	−0.04 (−0.14,0.07)	0.04 (−0.08,0.16)	0.05 (−0.13,0.23)	0.06 (−0.05,0.16)	0.09 (−0.03,0.20)	−0.03 (−0.13,0.06)	0.00 (−0.10,0.10)	−0.12 (−0.23,−0.00)*	−0.09 (−0.20,0.01)	0.08 (−0.03,0.18)	0.09 (−0.03,0.20)	−0.01 (−0.18,0.15)
HMW phthalate	−0.07 (−0.20,0.06)	0.01 (−0.14,0.16)	0.11 (−0.11,0.33)	0.02 (−0.11,0.15)	0.03 (−0.11,0.17)	−0.00 (−0.12,0.12)	0.07 (−0.05,0.20)	0.03 (−0.11,0.17)	−0.09 (−0.22,0.04)	−0.02 (−0.15,0.11)	0.14 (−0.01,0.28)	0.16 (−0.04,0.37)
DEHP metabolites	−0.08 (−0.22,0.06)	0.04 (−0.12,0.20)	0.15 (−0.10,0.40)	0.03 (−0.12,0.17)	0.07 (−0.09,0.22)	0.02 (−0.11,0.15)	0.10 (−0.04,0.23)	0.07 (−0.08,0.23)	−0.03 (−0.18,0.11)	0.03 (−0.12,0.17)	0.19 (0.03,0.34)*	0.14 (−0.08,0.37)
DNOP metabolites	−0.04 (−0.14,0.07)	−0.00 (−0.13,0.12)	0.07 (−0.12,0.26)	0.01 (−0.09,0.12)	−0.03 (−0.15,0.10)	0.00 (−0.10,0.10)	0.01 (−0.09,0.11)	−0.08 (−0.20,0.04)	−0.17 (−0.28,−0.06)[a,*]	−0.09 (−0.20,0.01)	0.06 (−0.06,0.18)	0.19 (0.02,0.37)*
Total bisphenols	−0.03 (−0.18,0.13)	−0.17 (−0.33,−0.01)*	−0.17 (−0.43,0.09)	0.10 (−0.05,0.25)	−0.01 (−0.16,0.15)	−0.12 (−0.25,0.02)	0.17 (0.02,0.32)*	0.01 (−0.15,0.16)	−0.07 (−0.22,0.08)	0.01 (−0.14,0.17)	−0.06 (−0.21,0.10)	−0.13 (−0.37,0.10)
BPA	−0.03 (−0.19,0.13)	−0.19 (−0.36,−0.03)*	−0.19 (−0.46,0.07)	0.07 (−0.09,0.23)	−0.04 (−0.20,0.12)	−0.12 (−0.26,0.02)	0.20 (0.04,0.35)*	0.01 (−0.15,0.17)	−0.08 (−0.24,0.07)	0.02 (−0.14,0.18)	−0.02 (−0.18,0.14)	−0.09 (−0.33,0.16)
BPS	−0.02 (−0.17,0.13)	0.06 (−0.10,0.22)	0.07 (−0.17,0.31)	0.14 (−0.01,0.29)	0.04 (−0.12,0.19)	−0.05 (−0.17,0.08)	−0.02 (−0.16,0.13)	−0.04 (−0.19,0.11)	0.04 (−0.10,0.18)	0.10 (−0.06,0.25)	−0.10 (−0.25,0.06)	−0.15 (−0.37,0.08)

Values are linear regression coefficients (95% CI) and reflect the differences in the *z* scores of childhood insulin and lipids profile at 6 and 10 years and the change in the outcomes in *z* scores from 6 to 10 years for an interquartile range increase in each natural log-transformed phthalate metabolites and bisphenols urinary concentrations in micromoles per gram of creatinine. Changes from 6 to 10 years correspond to the difference in the outcome between 6 and 10 years. Models are adjusted for maternal educational level and child sex, age, diet quality score, and television-watching time.
[a]Result remained significant after multiple testing correction.
*$P<0.05$.

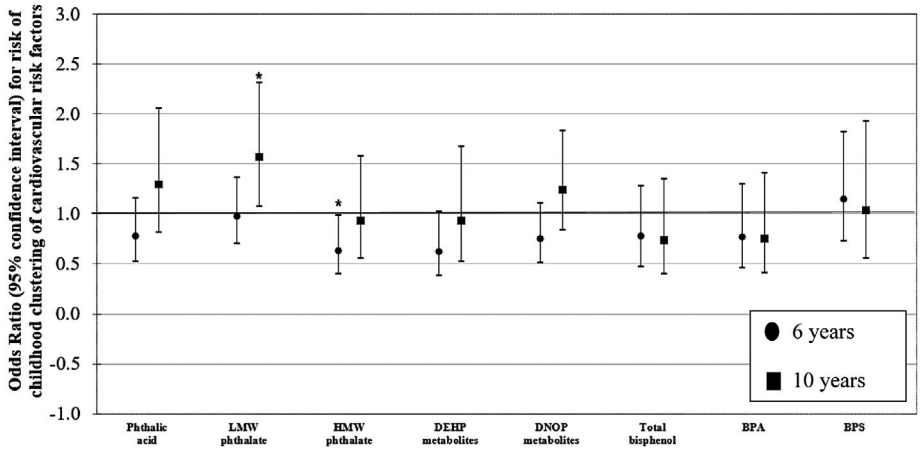

Figure 2 Associations of phthalate metabolites and bisphenols urinary concentrations with risk of clustering of cardiovascular risk factors in childhood. Values are odds ratios (95% CI) on a logarithmic scale and represent the risk of clustering of cardiovascular risk factors at 6 and 10 years for an interquartile range increase in each natural log-transformed phthalate metabolites and bisphenols urinary concentrations in micromoles per gram of creatinine. Models are adjusted for maternal educational level and child sex, age, diet quality score, and television-watching time. *$P < 0.05$.

although it has been suggested that a single urine sample for phthalate concentrations reasonably reflects exposure for up to 3 months (41). Thus, measurement error may have led to underestimation of the effect estimates, especially for bisphenols. Moreover, the use of nonfasting blood samples of childhood glucose, insulin, and lipids profile may also have led to underestimation of the observed associations. However, previous studies have shown that semifasted insulin resistance is moderately correlated with fasting values (42) and that nonfasting blood lipids levels can accurately predict increased risks of cardiovascular events later in life (43). We collected information on many potential confounding variables, but residual confounding due to unmeasured lifestyle variables might still be an issue. Previous evidence supports a link between early puberty and adiposity (44). We do not have information on pubertal development. Future studies should assess these associations while considering pubertal status of the children. The current study was focused on phthalate and bisphenol urinary concentrations. Other EDCs, such as pesticides, might be related with adiposity outcomes in children (45). These associations should be explored in future studies.

Conclusion

Our study suggests that adiposity in school-aged children may be influenced by phthalate metabolites and bisphenols exposure, specifically by DNOP metabolites and BPA. DNOP metabolites seem also to be associated with an adverse cardiovascular profile in childhood. Further studies are needed, both to replicate our findings and to explore the potential mechanisms involved.O

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Author contributions: CCVS, VJ, LT, and SS: designed and conducted the study. MM and KK: performed the analysis of samples at Wadsworth Center for phthalate metabolites and bisphenols. CCVS and SS: analyzed the data. CCVS, VJ, and SS: wrote the manuscript. VJ, LT, and SS: contributed to the interpretation of the data and gave input at all stages of the study. CCVS and SS: had primary responsibility for final content. CMS, HM, MM, KK, and LT: advised and reviewed the manuscript. All authors read and approved the final version of the manuscript.

Supporting information: Additional Supporting Information may be found in the online version of this article.

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