HHS Public Access

Author manuscript

Hypertension. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Hypertension. 2015 August ; 66(2): 301–308. doi:10.1161/HYPERTENSIONAHA.115.05603.

ASSOCIATION OF EXPOSURE TO DI-2-ETHYLHEXYLPHTHALATE (DEHP) REPLACEMENTS WITH INCREASED BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS

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Abstract

Phthalates are environmental chemicals widely used in consumer and personal care products. In this study we examined associations of urinary phthalates with blood pressure, triglycerides and lipoproteins in children and adolescents, performing a cross-sectional analysis of a subsample of US children 6–19 years of age who participated in the National Health and Nutrition Examination Survey between the years 2009–2012. We quantified exposure to common environmental phthalates, with a focus on the dietary contaminant di-2-ethylhexylphthalate and two increasingly used replacements, di-isononyl phthalate and di-isodecyl phthalate, based on micromolar concentration of urinary metabolites. We assessed descriptive, univariate and multivariable associations with blood pressure and lipids. Controlling for an array of sociodemographic and behavioral factors, as well as diet and body mass, metabolites of di-2-ethylhexylphthalate , di-isononyl phthalate and di-isodecyl phthalate were associated with higher age-, gender- and height-standardized blood pressure. For each log unit increase in di-isodecyl phthalate metabolites, a 0.105 standard deviation unit increase in systolic blood pressure z score was identified (p=0.004); for di-isononyl phthalate metabolites, a 0.113 standard deviation unit increment was identified (p=0.008). For di-2-ethylhexylphthalate metabolites, a 0.103 standard deviation unit increment (p=0.013) was detected. Metabolites of low molecular weight phthalates commonly found in cosmetics and personal care products showed an association with blood pressure (≥90th percentile) in univariate analysis, but this was no longer significant in our full multivariable model,

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Disclosure: None

suggesting specificity. Phthalate metabolites were not associated with triglycerides or high-density lipoproteins. Further, longitudinal studies are needed to confirm these associations, and to assess opportunities for intervention.

Keywords

phthalates; blood pressure; children; hypertyension; high density lipoproteins; tryglicerides; cross-sectional studies

Introduction

Phthalates are environmental chemicals widely used in consumer and personal care products and can be classified into two main groups. Low-molecular weight (LMW) phthalates are frequently added to personal care products to preserve scent, [1] while high-molecular weight (HMW) phthalates are used as plasticizers of polyvinyl chloride (PVC) to increase flexibility, and can be found in a variety of settings ranging from flooring, clear food wrap and intravenous tubing (Online Supplement; Table S1).[2] Since phthalates are not covalenty bound to the PVC polymer, they can easily leach into food, making ingestion one of the major routes for human exposure.[3] Within the HMW phthalate category, di-2-ethylhexylphthalate (DEHP) is of particular interest because industrial processes to produce food frequently use plastic products containing DEHP.[4] As recognition of potential health risks related to DEHP exposure has increased,[5] DEHP is being replaced by di-isononyl phthalate (DINP) and di-isodecyl phthalate (DIDP), two HMW phthalates with similar chemical properties.[6] Specifically, DINP is used in plastic products for food packaging, and DIDP is used in furnishings, cookware, medications, and several other consumer products.[7] These alternatives have not been substantially studied for toxicity in laboratory studies, as these studies are not required for regulatory approval under the 1976 Toxic Substance Control Act.[8]

Dietary exposure to phthalates is a major concern for children because increasing laboratory evidence suggests that exposures to environmental chemicals early in life may disrupt developmental endocrine processes, permanently disturbing metabolic pathways and contributing to adverse cardiovascular profiles.[9, 10] Laboratory studies have found that phthalate metabolites increase release of interleukin-6, a pro-inflammatory cytokine,[11] and expression of integrin in neutrophils, [12] and exhibit cytotoxic effects in endothelial cells. [13] Biomarkers of phthalate exposure have been associated with increases in C-reactive protein and gamma glutamyltransferase,[14] as well as oxidative stress markers malondialdehyde and 8-hydroxydeoxyguanosine.[15, 16] Recent findings suggest that environmental oxidant stressors such as phthalates and bisphenol A may produce increases in low-grade albuminuria,[17, 18] which, in turn, may be associated with increased cardiovascular risk.[19] Phthalates can also activate nuclear receptors PPAR-alpha and PPAR-gamma,[20] and both types of PPARs receptors are present in the arterial tree.[21] Taken together, these finding suggest that there are multiple biologically plausible mechanisms by which phthalates may affect vascular function and increase cardiovascular risk, independent of body mass effects.

A previous study from our group identified a relationship between dietary phthalates exposure (DEHP metabolites) and increased systolic BP in children using data from 2003–2008 National Health and Nutrition Examination Survey.[22] Since DEHP is being replaced by DINP and DIDP, as reflected in biomonitoring data showing a decrease in the levels of DEHP metabolites by 17–37% between 2001 and 2010,[23] it is appropriate to examine the relationship of urinary phthalates and blood pressure, especially in the context of increasing DINP and DIDP use. We also examined the relationship between urinary phthalates and dyslipidemia, performing cross-sectional analyses in a fasting subsample of US children and adolescents in the 2009–2012 NHANES.

Methods

Data source and sample

NHANES is a biannual, multicomponent, nationally representative survey of the noninstitutionalized US population administered by the National Centers for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). Data from the 2009–2012 questionnaire, laboratory, diet and physical examination components were used in the present analysis. Of the 8,515 children ages 6–19 who participated, our analytic sample comprised 1,619 participants with urinary phthalate measurements. Of these, fasting triglycerides were available for 367 (measured in 12–19 year olds), as were 1,329 for blood pressure (BP, measured in 8–19 year olds), and 1,405 for HDL levels (measured in 6–19 year olds). The New York University School of Medicine Institutional Review Board exempted this project from review on the basis of its analysis of an already collected and deidentified dataset.

Measurement of urinary phthalates

Phthalates were measured in one spot urine sample from each participant, and analyzed using high-performance liquid chromatography and tandem mass spectroscopy (HPLC-MS/MS). More extensive methodological description is provided elsewhere.[24]

We grouped urinary biomarkers for exposure according to their use in product categories (Online Supplement-Table S1). We calculated molar sums for LMW and HMW metabolites and, within the HMW category, molar sums for DEHP, DIDP and DINP metabolites dividing by the creatinine (Cr) concentration of the sample to account for dilution (see Online Supplement – Expanded Material and Methods). Our primary exposure variables were log-transformed molar concentrations of LMW, HMW, DEHP, DIDP and DINP metabolites, though secondary analyses analyzed individual metabolites to determine which metabolites are driving associations.

Measures of Cardiovascular Risks

In NHANES, using an aneroid sphygmomanometer certified examiners assess systolic (first Korotkoff phase) and diastolic (fifth Korotkoff phase) BP three consecutive times in all children 8–19 years of age after they sit quietly for 5 minutes. A fourth attempt may be made if one or more of the initial measurements is incomplete or interrupted.[25] We followed the common practice of averaging BP measurements for purposes of generating continuous

and categorical BP variables. Because BP varies widely by age, gender and height, we calculated systolic/diastolic BP Z-scores from mixed-effects linear regression models derived using data from 1999–2000 Centers for Disease Control and Prevention (CDC) NHANES (see Online Supplement – Expanded Material and Methods). We categorized BP outcomes into present/absent prehypertension (BP≥90th percentile for age/height Z-score/ gender).

We used cutpoints of HDL <40 mg/dL and triglycerides ≥100 mg/dL, the same applied to assess components of the metabolic syndrome in analyses of adolescents in 2001–2006 NHANES.[26] Triglycerides were log-transformed to account for skewed distribution.

Potential Confounders

Information on height and weight was based on measures taken by trained health technicians, who used data recorders and used standardized measurement procedures. We derived body mass index (BMI) Z-scores from 2000 CDC norms, incorporating height, weight and gender; overweight and obese were categorized as BMI Z-score ≥1.036 and ≥1.64.[27]

To measure caloric intake, trained interviewers fluent in Spanish and English elicited total 24-hour calorie intake in person, using standard measuring guides to assist reporting of volumes and dimensions of food items (available on the CDC NHANES Web site). To differentiate normal from excessive caloric intake, we used age- and gender-specific US Department of Agriculture cutpoints for calories/day in high physical activity children.[28] Self-reported data on leisure-time physical activity (PA) obtained during household interviews was also included in our analysis (see Online Supplement – Expanded Material and Methods). Because exposure to tobacco smoke is a risk factor for metabolic syndrome in adolescence,[29] we included serum cotinine in multivariable models, as measured using HPLC-MS/MS. We categorized serum cotinine levels into low (<0.015 ng/mL), medium (<2 and ≥0.015 ng/mL) and high (≥2 ng/mL) categories.

Race/ethnicity was categorized into Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black and Other. Poverty-income ratio was categorized into quartiles, within the sample for which urinary phthalates were measured. Age was categorized into two groups: 6–11 and 12–19 years, in the same way as obesity prevalence estimates are produced from NHANES.[27]

To maximize sample size in multivariable analysis, “missing” categories[30] were created for all potential confounders, except BMI category. Physical activity data was missing in 81.1%, serum cotinine was missing in 10.5%, and poverty income ratio in 9.1%. Recognizing concerns raised about addition of missing categories in multiple linear regression,[31] as a robustness check, we repeated our main multivariable analysis as a complete case analysis, omitting observations that had missing values for cotinine and poverty-income ratio.

Statistical analysis

We conducted univariable, bivariable and multivariable analyses using statistical techniques that reflect the complex survey sampling design, using Stata 12.0 (College Station, TX), and following NCHS guidelines.[30] Blood pressure analyses were performed using environmental sample weights. For analyses of fasting triglycerides, we performed unweighted analyses, following the practice of Stahlhut et al.[32] This approach was chosen because fasting samples and urinary phthalate measurements are collected from partially overlapping subsamples for triglycerides. While there are subsample weights for each, NCHS advises against use of either subsample weight, because each accounts for different patterns of nonresponse.

Urinary metabolite concentrations were log-transformed to account for skew in the distribution of urinary phthalates. We performed univariate regressions of logs of the micromolar concentrations of metabolite groups against blood pressure, triglycerides and lipoproteins and each of the demographic, dietary, anthropometric and the other covariates. We used multivariable linear regression analysis to model continuous dependent variables, and logistic regression to model dichotomous variables in separate models. We adjusted all multivariable models for urinary creatinine; for BMI category, demographic and exposure characteristics (race/ethnicity, age category, poverty-income ratio, gender, serum cotinine) and lifestyle characteristics (measures of caloric intake, physical activity).

In secondary analyses, we also analyzed individual phthalate metabolites from any of the significant models to determine which metabolites were driving the association. We performed a complete case analysis to ensure that our results were not driven by artifactual associations with missing categories for caloric intake and cotinine. In addition, given the high number of missing values for physical activity data, we utilized multiple imputation techniques [33] to generate randomly a replacement value for each missing data point (see Online Supplement – Expanded Material and Methods). Finally, to ensure that our results for nonfasting outcomes were not an artifact of statistical weighting, we also repeated our analysis in unweighted modeling.

Results

Table 1 shows the characteristics of the study population and Table 2 reports the results of univariate regression analyses of phthalate metabolites against potential confounders while controlling for urinary creatinine. These analyses revealed increases in LMW metabolites among girls and lower concentrations of all metabolites among adolescents, except for LMW. Socioeconomic status was inversely related to LMW metabolites, with the fourth quartile (the highest) having the lowest level of urinary LMW metabolites. Socioeconomic status was not associated with any of the other urinary phthalates. LMW metabolite concentrations were higher among those categorized as overweight/obese and with higher BP (at least 90th percentile), an association that was no longer present once BMI was included in the model (Model B).

Significant differences were not identified for prehypertension, HDL and triglycerides. However, increases in systolic BP (SBP) Z-score emerged in multivariable modeling in association with urinary HMW, DEHP, DINP and DIDP metabolites. For each log unit

increase of HMW metabolites, we identified a 0.12 SD unit increment in systolic BP Z-score (p=0.009); for DEHP metabolites, a 0.10 SD unit increment (p=0.013); for DIDP metabolites, a 0.105 SD unit increment (p=0.004); for DINP metabolites, a 0.113 SD unit increment (p=0.008). A significant 0.09 SD unit increment (p=0.041) in diastolic BP Z-score, was also identified for DEHP metabolites (Table 3).

Regression analyses of individual metabolites (Table 4) suggest that associations of SBP Z-score with HMW metabolites are driven mainly by non-DEHP metabolites (DIDP and DINP). Significant association of MCOP (0.11 SD/log unit increase, p=0.006), MNP (0.09 SD/log unit increase, p=0.006), MCNP (0.10 SD/log unit increase, p=0.008), were identified with systolic BP Z-score. Among DEHP metabolites, significant associations of MEHHP (0.09 SD/log unit increase, p=0.012), MEOHP (0.08 SD/log unit increase, p=0.025), MECPP (0.11 SD/log unit increase, p=0.014) were identified with systolic BP Z-score. Association with diastolic BP Z-score were also identified for MEHHP (0.09 SD/log unit increase, p=0.023), and for MEOHP (0.09 SD/log unit increase, p=0.045).

Unweighted analyses confirmed SBP Z-score associations in unweighted modeling for DIDP and DINP (0.09 SD unit increment per log unit DIDP increase and 0.05 SD unit increment per log unit DINP increase in full multivariable model, p= 0.001 and p=0.010, respectively; Online Supplement; Table S2) but the association with DEHP metabolites was no longer significant in unweighted modeling. Results were unchanged in complete case analyses (data not shown). Multiple imputation of physical activity data also did not change the results (data not shown).

With respect to triglyceride and HDL outcomes, no significant association was detected with metabolites of urinary phthalates in our study population.

Discussion

In this study we identify a significant association of DINP and DIDP metabolites, currently used as DEHP replacements, with higher systolic blood pressure. To provide better clinical context, a 0.11 SD increment in systolic blood pressure Z-score, which reflects closely the increments detected for DEHP, DIDP and DINP, corresponds to an increase of 1.1 mmHg in males. Although small, the systolic blood pressures increments observed in this study are significant when considered at the population level, in which even small increments can result in large increases in prehypertension and hypertension prevalence, shifting the distribution of blood pressure and increasing the number of individuals who are above the cutpoints for prehypertension and hypertension. A 0.115 SD increment in SBP Z-score, assuming a normal distribution, equates to a 2.2% increase in prehypertension, substantial when compared to the 5.3% prevalence in the study population. While our study did not identify association of DINP metabolites with prehypertension, it was not powered to do so, with 5.3% weighted prevalence in our study population of 1,329. Assuming a normal distribution of SBP, our study has 16.4% power to detect 1.35-log difference in prehypertension between the 10th and 90th percentiles of DINP in our sample (i.e., a 0.152 SD unit increase in SBP Z-score in our linear models). With respect to hypertension, only 13 participants in our sample were hypertensive (0.7% weighted prevalence).

In our analysis, no association of urinary phthalates was identified with triglyceride or HDL. It should be noted that, while HDL data were available for the full sample, triglycerides data were available only in a small number of participants (n=367), and this represents a limitation of the current study.

Phthalate exposure has been associated with oxidative stress, possibly through activation of peroxisome proliferator–activated receptors[34] or through changes in mitochondrial membranes potential and permeability,[35] and this could be a plausible mechanism to explain our findings. However, since oxidative stress biomarkers such as F2-isoprostane and 8-hydroxydeoxyguanosine are not available for 2009–2012 NHANES, this hypothesis could not be further substantiated in the present study.

A cross-sectional study has significant limitations, and our findings could be explained by unmeasured confounding factors or reverse causation, i.e. that children and adolescents with higher increments in systolic BP z-score have increased urinary excretion of phthalates because of increased consumption of packaged foods. However, the association between DINP/DIDP metabolites and increased blood pressure remained significant after the inclusion of a rich set of information about demographics, exposures, and lifestyle variables, thus providing more convincing evidence for non-spuriousness. In particular, addition of a lifestyle variable likely to be associated with processed food consumption (excessive caloric intake) did not change our estimate of the DIDP/DINP metabolite associations with SBP Z-score.

Phthalate exposure is measured at one time point in this analysis, and monoesters of phthalates are typically known to have half-lives of 12–48 hours,[36] which may not relate well with the sustained changes that lead to the development of hypertension. However, repeated bouts of oxidative stress associated with ubiquitous phthalate exposure may result in short-term changes in arterial tone, which can predispose to development of vasomotor dysfunction.[37, 38] Furthermore, phthalate accumulation has been detected in human adipose tissues[39] and in phthalate-treated rats,[40] thereby lengthening half-life beyond that identified in the few adult pharmacokinetic studies.[41] There are no data available on DIDP/DINP and temporal variability over time but, even if current urinary phthalates are weak indices of exposure, our estimates of association should be biased towards the null for dichotomous outcomes.[42]

In this study, we did not identify an association between DIDP/DINP metabolites and overweight status, which was detected for LMW phthalates. LMW phthalates was also the only category for which we found a significant, inverse relationship, with socioeconomic status. This is consistent with a previous study from our group in which a similar association was detected in 2003–2008 NHANES data[22] and, as other authors have previously noted, may reflect different lifestyle (reduced/different use of scented products for personal care) and food choices (different diets with less consumption of processed and prepackaged food), which, in turn, vary by socioeconomic factors. [43, 44]Available evidence does not suggest a consistent association of phthalates with obesity but, among phthalates, the LMW group in particular has been more consistently associated with obesity in children and adolescents.[45] The lack of association of DINP/DIDP metabolites with BMI, and the fact that the inclusion

of BMI in our multivariable model did not influence the significance of the association with BP, points towards an effect that is independent of increased body mass, and lends support to the notion of oxidative damage as a potential mechanisms by which phthalates can contribute to increasing cardiovascular risk. Along the same line, the inclusion in our model of caloric intake and physical activity, two lifestyle variables likely to be associated with processed food consumption, did not change the association between DIDP/DIDP metabolites and increase in systolic BP z-score. Additional, longitudinal studies are required to substantiate our findings and to identify the underlying mechanisms, through a comprehensive examination of several cardiovascular parameters and using more direct measures of cardiovascular risk, such as carotid intima-media thickness, brachial artery distensibility and pulse wave velocity measurement.[46, 47]

Perspectives

Rates of childhood hypertension have reached almost epidemic proportions[48, 49] and the evidence suggesting links between phthalates and adverse health effects is rapidly increasing. Phthalates simultaneously affects multiple cellular targets,[50] and produce changes in the metabolic profile of cardiac cells[51] as well as oxidative stress.[14] Phthalates can also have additional, indirect effects on cardiovascular risk, as women exposed to phthalates during pregnancy have been shown to have significantly increased odds of delivering preterm[52] and the link between preterm birth (gestational age) and hypertension risk is clear and well established.[53] In light of this and the potential associated health costs, as evidenced in a recently published analysis on the burden and disease costs of exposure to endocrine disrupting chemicals in the EU,[54] there is a need for increased regulatory consideration and policy initiatives to limit exposure to ubiquitous environmental chemicals with the potential to increase cardiovascular risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by grant R01ES022972. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

Abbreviations

BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
DEHP	di-2-ethylhexylphthalate
DINP	di-isononyl phthalate
DIDP	di-isodecyl phthalate
HDL	High-density lipoprotein

HPLC-MS/MS	high-performance liquid chromatography and tandem mass spectroscopy
LMW	Low-molecular weight
MEP	mono-ethyl phthalate
MBP	mono-n-butyl-phthalate
MiBP	mono-isobutyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate
MCOP	mono-carboxyisooctyl phthalate
MCNP	mono-carboxyisononyl phthalate
MECPP	mono-(2-ethyl-5-carboxypentyl) phthalate
MEHHP	mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
MEHP	mono-(2-ethylhexyl) phthalate
MBzP	mono-benzylphthalate
MMP	mono-n-methylphthalate
MNP	mono-isononylphthalate
NCHS	National Centers for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PPARs	peroxisome proliferator-activated receptors
PIR	poverty-income ratio
SE	standard error
SBP	systolic blood pressure
TG	triglyceride

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Novelty and Significance

What Is New?

- Dietary exposure to phthalates is associated with higher blood pressure in children and adolescents

What Is Relevant?

- High blood pressure is a leading cause of heart disease and stroke, with a variety of factors contributing to its development
- Exposures to environmental chemical represent a group of understudied, but potentially important, factors
- Phthalates are chemicals widely used in consumer and personal care products and exposure is highly prevalent

Summary

Children and adolescents exposed to phthalates have significantly increased systolic blood pressure. Regulatory actions are needed to decrease exposure to ubiquitous environmental chemicals with the potential to increase the risk for developing cardiovascular events.

Table 1

Study population characteristics.

Characteristics	Value
Male sex, n (%)	688 (51.7)
Mean age (SE)	13.0 (0.1)
Race/ethnicity	
Hispanic-Mexican American, n (%)	316 (13.2)
Hispanic-Other Hispanic, n (%)	152 (6.8)
Non-Hispanic White, n (%)	375 (56.4)
Non-Hispanic Black, n (%)	329 (14.4)
Other, n (%)	157 (9.2)
Poverty-income ratio	
First quartile (< 0.83), n (%)	273 (13.4)
Second quartile (0.83 to 1.59), n (%)	303 (16.2)
Third quartile (1.60 to 3.09), n (%)	314 (23.8)
Fourth quartile (at least 3.1), n (%)	326 (37.5)
Missing	113 (9.1)
Serum cotinine	
< 0.015 ng/mL, n (%)	307 (21.4)
0.015–1.9 ng/mL, n (%)	734 (56.0)
At least 2.0 ng/mL, n (%)	149 (12.1)
Missing	139 (10.5)
Physical activity ≥ 60min/day, n (%)	214 (18.3)
Missing	1109 (81.1)
Excessive caloric intake compared to active child needs for age and gender, n (%)	311 (22.1)
Missing	51 (2.3)
Blood pressure at least 90th percentile, n (%)	89 (5.3)
Overweight, n (%)	522 (37.5)
Obese, n (%)	283 (18.4)
Low molecular weight phthalate metabolite, median concentration (IQR)	0.443 μmolar (0.214, 0.997)
High molecular weight phthalate metabolite, median concentration (IQR)	0.352 μmolar (0.173, 0.677)
DEHP metabolite, median concentration (IQR)	0.157 μmolar (0.077, 0.313)
DIDP metabolite, median concentration (IQR)	0.009 μmolar (0.005, 0.016)
DINP metabolite, median concentration (IQR)	0.071 μmolar (0.034, 0.174)

All percentages are weighted using population weights for the sample in which phthalate metabolites were measured.

Table 2

Comparison of urinary phthalate metabolites in study population with blood pressure data in pooled 2009–2012 NHANES (n=1329)

Characteristics	Mean urinary LMW metabolite (μmolar)	p value*	Mean urinary HMW metabolite (μmolar)	p value	Mean urinary DEHP metabolite (μmolar)	p value*	Mean urinary DIDP metabolite (μmolar)	p value	Mean urinary DINP metabolite (μmolar)	p value
Sex										
Male	0.379	Ref.	0.387	Ref.	0.195	Ref.	0.009	Ref.	0.071	Ref.
Female	0.479	**0.003**	0.397	0.85	0.194	0.96	0.010	0.68	0.077	0.58
Age group, y										
6–11	0.593	Ref.	0.514	Ref.	0.241	Ref.	0.013	Ref.	0.103	Ref.
12–19	0.511	0.16	0.357	**0.002**	0.174	**0.011**	0.009	<**0.001**	0.072	**0.01**
Race/ethnicity										
Hispanic-Mexican American	0.631	Ref.	0.404	Ref.	0.208	Ref.	0.009	Ref.	0.065	Ref.
Hispanic-Other Hispanic	0.332	**0.001**	0.416	0.84	0.196	0.77	0.011	**0.008**	0.081	0.15
Non-Hispanic White	0.442	**0.001**	0.417	0.80	0.194	0.60	0.011	0.06	0.093	**0.046**
Non-Hispanic Black	0.779	0.07	0.336	0.17	0.172	0.18	0.009	0.54	0.057	0.42
Other	0.528	0.43	0.417	0.85	0.205	0.95	0.008	0.73	0.080	0.30
Poverty-income ratio										
First quartile (< 0.83)	0.666	Ref.	0.413	Ref.	0.204	Ref.	0.009	Ref.	0.073	Ref.
Second quartile (0.83 to 1.59)	0.619	0.73	0.446	0.58	0.219	0.64	0.010	0.51	0.076	0.86
Third quartile (1.60 to 3.09)	0.568	0.40	0.387	0.62	0.178	0.17	0.010	0.60	0.079	0.73
Fourth quartile (at least 3.1)	0.451	**0.032**	0.411	0.98	0.199	0.87	0.011	0.21	0.089	0.42
Missing	0.527	0.42	0.326	0.20	0.158	0.25	0.008	0.65	0.071	0.91
Serum cotinine										
Less than 0.015 ng/mL	0.469	Ref.	0.356	Ref.	0.171	Ref.	0.010	Ref.	0.081	Ref.
0.015–1.9 ng/mL	0.560	**0.022**	0.420	0.07	0.208	**0.041**	0.010	0.49	0.078	0.80
At least 2.0 ng/mL	0.659	**0.013**	0.366	0.85	0.166	0.81	0.008	0.14	0.079	0.91
Missing	0.423	0.54	0.450	0.17	0.194	0.50	0.015	**0.028**	0.096	0.35
Physical activity										
Insufficient (<60min/day)	0.147	Ref.	0.167	Ref.	0.092	Ref.	0.005	Ref.	0.019	Ref.
Sufficient (>=60min/day)	0.540	<**0.001**	0.389	<**0.001**	0.197	<**0.001**	0.009	<**0.001**	0.073	<**0.001**

Characteristics	Mean urinary LMW metabolite (μmolar)	p value*	Mean urinary HMW metabolite (μmolar)	p value	Mean urinary DEHP metabolite (μmolar)	p value*	Mean urinary DIDP metabolite (μmolar)	p value	Mean urinary DINP metabolite (μmolar)	p value
Missing	0.530	**<0.001**	0.407	**<0.001**	0.193	**<0.001**	0.010	**<0.001**	0.083	**<0.001**
Caloric intake compared w/needs in active child of age/gender										
Appropriate	0.535	Ref.	0.390	Ref.	0.186	Ref.	0.010	Ref.	0.078	Ref.
Excessive	0.540	0.93	0.427	0.36	0.213	0.28	0.011	0.25	0.086	0.43
Missing	0.522	0.92	0.605	0.22	0.251	0.50	0.011	0.72	0.115	0.26
Overweight status										
Not overweight (<85th percentile)	0.476	Ref.	0.391	Ref.	0.191	Ref.	0.010	Ref.	0.077	Ref.
Overweight (≥85th percentile)	0.653	**0.002**	0.421	0.35	0.197	0.76	0.010	0.46	0.087	0.24
Obese status										
Not obese (<95th percentile)	0.505	Ref.	0.392	Ref.	0.192	Ref.	0.010	Ref.	0.077	Ref.
Obese (≥95th percentile)	0.695	**0.001**	0.451	0.30	0.198	0.83	0.011	0.53	0.099	0.11
Pre-hypertension										
<90th percentile	0.530	Ref.	0.399	Ref.	0.191	Ref.	0.010	Ref.	0.080	Ref.
≥90th percentile	0.651	**0.038**	0.465	0.62	0.234	0.33	0.009	0.73	0.087	0.82

Ref.; Reference

*Derived using univariate regression of log molar concentration of urinary metabolites. Mean urinary phthalate metabolites represents retransformed mean from log base.

Table 3

Linear and Logistic Regression Analysis of Cardiometabolic Outcomes Associated with Urinary Phthalate Metabolites.

Blood Pressure Outcome (n=1329)	**Z-score Increment, Systolic Blood Pressure**	**Z-score Increment, Diastolic Blood Pressure**	**Odds Ratio, Blood Pressure ≥90th Percentile**
LMW Metabolites	+0.02 (−0.05, +0.10)	+0.04 (−0.16, +0.24)	1.12 (0.79, 1.59)
HMW Metabolites	+0.12 (+0.03, +0.21)†	+0.06 (−0.03, +0.16)	1.30 (0.78, 2.17)
DEHP Metabolites	+0.10 (+0.03, +0.18)*	+0.09 (+0.04, +0.17)*	1.31 (0.90, 1.91)
DIDP Metabolites	+0.11 (+0.04, +0.17)†	+0.03 (−0.04, +0.10)	0.99 (0.66, 1.48)
DINP Metabolites	+0.11 (+0.03, +0.19)†	+0.02 (−0.09, +0.13)	1.19 (0.72, 1.98)
Triglyceride Outcome (n=350)	**Odds Ratio, Elevated Triglycerides**	**Increment, Triglycerides**	
LMW Metabolites	0.83 (0.62, 1.12)	−0.04 (−0.10, +0.007)	
HMW Metabolites	1.07 (0.81, 1.42)	−0.008 (−0.06, +0.04)	
DEHP Metabolites	0.91 (0.69, 1.19)	−0.02 (−0.07, +0.03)	
DIDP Metabolites	1.01 (0.76, 1.36)	−0.01 (−0.06, +0.04)	
DINP Metabolites	1.19 (0.97, 1.47)	+0.005 (−0.03, +0.04)	
HDL Outcome (n=1186)	**Odds Ratio, Low HDL**	**Increment, HDL**	
LMW Metabolites	1.17 (0.81, 1.71)	+0.46 (−0.57, +1.50)	
HMW Metabolites	0.93 (0.66, 1.32)	+0.98 (−0.25, +2.20)	
DEHP Metabolites	0.89 (0.58, 1.36)	+1.20 (−0.17, +2.58)	
DIDP Metabolites	0.97 (0.77, 1.23)	−0.11 (−1.56, +1.33)	
DINP Metabolites	0.89 (0.74, 1.05)	+0.47 (−0.46, +1.40)	

Increases are per log unit in urinary LMW/HMW/DEHP/DINP/DIDP metabolite concentration. See methods for calculation.

Models control for gender, caloric intake, physical activity, poverty-income ratio, serum cotinine, urinary creatinine, BMI category, race/ethnicity and age categories.

Results using weighted modeling are presented here for blood pressure and HDL outcomes; trygliceride outcome results are presented unweighted (see methods).

* p <0.05

† p <0.01

‡ p<0.001

Table 4

Associations of Individual Urinary Phthalate Metabolites with Blood Pressure Outcomes in Linear and Logistic Regression Analyses

Increments/Odds Ratio	Change, z-score SBP (n=1328)	Change, z-score DBP (n=1328)	Odds Ratio, BP≥ 90th Percentile (n=1328)
Low-molecular weight phthalates			
Log-transformed MEP	+0.05 (−0.02, +0.13)	+0.07 (−0.10, +0.23)	1.16 (0.76, 1.79)
Log-transformed MBP	−0.07 (−0.18, +0.04)	+0.03 (−0.14, +0.20)	0.57 (0.25, 1.31)
Log-transformed MiBP	−0.02 (−0.12, +0.09)	−0.02 (−0.20, +0.15)	1.02 (0.53, 1.94)
Log-transformed MMP	−0.02 (−0.07, +0.04)	−0.03 (−0.13, +0.07)	0.95 (0.72, 1.25)
High-molecular weight metabolites (non-DEHP)			
Log-transformed MBzP	−0.01 (−0.11, +0.09)	−0.002 (−0.14, +0.13)	0.78 (0.47, 1.30)
Log-transformed MCPP	+0.07 (−0.03, +0.18)	+0.05 (−0.07, +0.16)	0.97 (0.52, 1.83)
Log-transformed MCOP	+0.11 (0.03, +0.18)†	+0.02 (−0.08, +0.12)	1.21 (0.75, 1.94)
Log-transformed MNP	+0.09 (0.03, +0.14)†	+0.05 (−0.04, +0.14)	1.28 (0.92, 1.79)
Log-transformed MCNP	+0.10 (0.03, +0.17)†	+0.04 (−0.03, +0.11)	1.06 (0.72, 1.54)
High-molecular weight metabolites of DEHP			
Log-transformed MEHP	+0.06 (−0.03, +0.12)	+0.04 (−0.02, +0.10)	1.09 (0.79, 1.50)
Log-transformed MEHHP	+0.09 (+0.02, +0.16)*	+0.09 (+0.01, +0.16)*	1.27 (0.89, 1.81)
Log-transformed MEOHP	+0.08 (+0.01, +0.16)*	+0.09 (0.002, +0.16)*	1.18 (0.83, 1.66)
Log-transformed MECPP	+0.11 (+0.03, +0.19)*	+0.07 (−0.01, 0.16)	1.47 (0.95, 2.27)

Increases are per log unit in urinary LMW/HMW/DEHP/DIDP/DINP metabolite concentration. See methods for calculation.

All models control for continuous urinary creatinine, age and caloric intake as well as gender, poverty-income ratio, serum cotinine, BMI, race/ethnicity categories, and physical activity.

* p <0.05

† p<0.01

‡ p<0.001