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Urinary Phthalates Are Associated with Higher Blood Pressure in Childhood

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Abstract

Objective—To examine associations of urinary phthalate levels with blood pressure (BP) and serum triglyceride and lipoprotein levels in children.

Study design—We performed a cross-sectional analysis of a subsample of US children aged 6–19 years who participated in the National Health and Nutrition Examination Survey between 2003 and 2008. We quantified exposure to 3 families of phthalates—low molecular weight, high molecular weight and di-2-ethylhexylphthalate (DEHP)—based on molar concentration of urinary metabolites. We assessed descriptive, bivariate, and multivariate associations with BP and lipid levels.

Results—Controlling for an array of sociodemographic and behavioral factors, as well as diet and body mass index, levels of metabolites of DEHP, a phthalate commonly found in processed foods, were associated with higher age-, sex-, and height-standardized BP. For each log unit (roughly 3-fold) increase in DEHP metabolites, a 0.041 SD unit increase in systolic BP z-score was identified ($P = .047$). Metabolites of low molecular weight phthalates commonly found in

cosmetics and personal care products were not associated with BP. Phthalate metabolites were not associated with triglyceride levels, high-density lipoprotein level, or prehypertension.

Conclusions—Dietary phthalate exposure is associated with higher systolic BP in children and adolescents. Further work is needed to confirm these associations, as well as to evaluate opportunities for intervention.

Phthalates, environmental chemicals widely used in consumer products, can be classified into 2 groups/families. Low molecular weight (LMW) phthalates (eg, diethylphthalate, di-n-butylphthalate, di-n-octylphthalate, di-nisobutylphthalate) are frequently added to shampoos, cosmetics, lotions, and other personal care products to preserve scent,¹ whereas high molecular weight (HMW) phthalates (eg, di-2-ethylhexylphthalate [DEHP], di-n-octylphthalate, butyl-benzylphthalate) are used to produce vinyl plastics for diverse applications including flooring, clear food wrap, and intravenous tubing.² In the HMW phthalate category, DEHP is of particular interest, considering that many industrial food production processes use plastic products containing DEHP.³

Dietary exposure to DEHP is of concern in children, given the increasing laboratory evidence suggesting that exposure to environmental chemicals early in life may disrupt developmental endocrine processes, permanently disturbing metabolic pathways and contributing to adverse cardiovascular profiles.⁴ Mono-(2-ethylhexyl) phthalate (MEHP), a DEHP metabolite, may contribute to insulin resistance by increasing the expression of peroxisome proliferator-activated receptors.⁵

Emerging animal evidence also suggests that DEHP may change metabolic profiles and produce dysfunction in cardiac myocytes.⁶ Laboratory studies have found that phthalate metabolites increase the release of interleukin-6, a proinflammatory cytokine,⁷ as well as the expression of integrin in neutrophils.⁸ Biomarkers of phthalate exposure also have been associated with increased levels of C-reactive protein and gamma glutamyltransferase,⁹ as well as levels of the oxidative stress markers malondialdehyde and 8-hydroxydeoxyguanosine.^{10,11} Recent findings suggest an association between environmental oxidant stressors, including phthalates and bisphenol A, and low-grade albuminuria.¹² Given the known link between low-grade albuminuria and cardiovascular risk,¹³ bisphenol A and phthalates may increase cardiovascular risk through direct effects on the kidney. There are multiple biologically plausible mechanisms by which phthalates may increase cardiovascular risk, independent of the effects of body mass.

Associations of phthalates with blood pressure (BP) and dyslipidemia have not been studied to date, even though increases in both have been documented recently.^{14–17} Although these trends have been driven largely by increasing rates of childhood adiposity, environmental contributors also may be a factor independent of obesity and insulin resistance. Environmental exposures are amenable to regulatory and other interventions, unlike dietary and other behavioral changes aimed at reducing BP, which can be difficult to sustain.

We performed a cross-sectional analysis of the 2003–2008 National Health and Nutrition Examination Survey (NHANES) to examine associations between urinary phthalate

concentrations and BP and dyslipidemia in for each of the 3 families of phthalates, examined separately, in children.

Methods

The NHANES is a biannual multicomponent, nationally representative survey of the noninstitutionalized US population administered by the National Centers for Health Statistics of the Centers for Disease Control and Prevention (CDC). We used data from the NHANES questionnaire, laboratory, diet, and physical examination components in the present analysis. Out of the 9270 participating children aged 6–19 years, our analytic sample comprised 2838 subjects with urinary phthalate data. Fasting triglyceride levels were available for 906 of these subjects (measured in those age 12–19 years); BP measurements, for 2447 (measured in those aged 8–19 years); and nonfasting lipid levels, for 2555 (measured in those aged 6–19 years). The New York University School of Medicine's Institutional Review Board exempted this study from review on the basis of its analysis of an already collected and deidentified dataset.

Phthalates were measured in a spot urine sample obtained from each subject and analyzed by high-performance liquid chromatography–tandem mass spectroscopy. Details on this methodology are provided elsewhere.¹⁷ For phthalate concentrations below the level of detection (5.1% for MEHP; <1% for all other metabolites studied), we substituted the limit of detection divided by the square root of 2, as routinely assigned by NHANES. To adjust for urinary dilution, we included urinary creatinine as a covariate.¹⁸

We grouped urinary biomarkers for exposure according to their use in product categories. We calculated molar sums for LMW phthalate, HMW phthalate, and DEHP metabolites as described previously.¹⁹ LMW phthalate concentration was calculated as the sum of molar concentrations of monoethyl phthalate (MEP), mono-n-butyl-phthalate (MBP), and mono-isobutyl phthalate; HMW phthalate concentration, as the sum of mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(3-carboxypropyl) phthalate, mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), MEHP, and monobenzylphthalate expressed as a function of MEHP. DEHP concentration was calculated by adding the molarities of MEHP, MECPP, MEHHP, and MEOHP.

In NHANES, using an aneroid sphygmomanometer, certified examiners measure systolic BP (SBP) (first Korotkoff phase) and diastolic BP (DBP) (fifth Korotkoff phase) 3 consecutive times in all children aged 8–19 years who had been sitting quietly for 5 minutes. A fourth attempt may be made if 1 or more of the initial measurements is incomplete or interrupted. We followed the common practice of averaging BP measurements for the purpose of generating continuous and categorical BP variables. Because BP varies widely by age, sex, and height, we calculated SBP and DBP *z*-scores from mixed-effects linear regression models derived using data from 1999–2000 CDC NHANES. We input height *z*-scores derived from CDC norms,¹⁶ sex, and age to compute expected SBP and DBP, and calculated BP *z*-scores from the measured BP using the formula $z = (x - \mu)/\sigma$, where *x* is the measured BP, μ is the expected BP, and σ is derived from the same NHANES data.¹⁴ We

categorized BP outcomes as present or absent prehypertension (BP $\geq$ 90th percentile for age/height z-score/sex).

We used cutpoints of high-density lipoprotein (HDL) level <40 mg/dL and triglyceride levels ≥ 100 mg/dL, which were recently applied to assess components of the metabolic syndrome in analyses of adolescents in the 2001–2006 NHANES.¹⁵ Triglyceride levels were log-transformed to account for a skewed distribution.

Height and weight data were based on measurements obtained by trained health technicians who used data recorders and followed standardized measurement procedures. We derived body mass index (BMI) z-scores from 2000 CDC norms, incorporating height, weight, and sex. Overweight and obese were categorized as BMI z-score ≥ 1.036 and ≥ 1.64 ,¹⁶ respectively.

Other measures came from surveys and laboratory assessments. To measure caloric intake, trained interviewers fluent in Spanish and English elicited total 24-hour calorie intake in person, using standard measuring guides (available on the CDC NHANES Web site; www.cdc.gov/nchs/nhanes/measuring_guides_dri/measuringguides.htm) to aid reporting of volumes and dimensions of food items. To differentiate normal and excessive caloric intake, we used age- and sex-specific US Department of Agriculture cutpoints for daily caloric intake in children with high levels of physical activity.²⁰ Daily hours of television watched came from caregiver reports in children aged <12 years and by self-report in older children. We assigned a cutpoint for dichotomization of this covariate of ≥ 2 hours/day, based on a previously reported association with obesity in NHANES.²¹ Because exposure to tobacco smoke is a risk factor for metabolic syndrome in adolescence,²² we included serum cotinine level, measured by high-performance liquid chromatography–tandem mass spectroscopy, in our multivariate models. We categorized serum cotinine level as low (<0.015 ng/mL), medium (≥ 0.015 and <2 ng/mL), or high (≥ 2 ng/mL).

We categorized race/ethnicity into Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other. Caregiver education was categorized as less than 9th grade, 9th–12th grade, high school/graduate equivalency diploma, some college, and college degree or greater. The poverty–income ratio was categorized into quartiles within the sample in which urinary phthalates were measured. Age was categorized into 2 groups, 6–11 years and 12–19 years, in the same way as obesity prevalence estimates are produced from NHANES data.²³

To maximize sample size in multivariate analysis, we created “missing” categories for all potential confounders, except BMI category. Television watching was missing in 24.4% of subjects, and serum cotinine level was missing in 9.6%. Otherwise, $<5\%$ of values were missing for any other confounding variable. Recognizing concerns raised about adding missing categories in multiple linear regression,²⁴ as a robustness check, we repeated our main multivariate analysis as a complete-case analysis, omitting observations with missing values for any of the covariates.

Our univariate, bivariate, and multivariate analyses were conducted using statistical techniques reflecting the complex survey sampling design, with Stata 12.0 (StataCorp,

College Station, Texas), and following National Centers for Health Statistics guidelines.²⁵ We performed unweighted analyses of fasting triglyceride levels, following the approach of Stahlhut et al.²⁶ We took this approach because fasting samples and urinary phthalate measurements are collected from partially overlapping subsamples. Although there are subsample weights for each, the National Centers for Health Statistics advises against the use of either subsample weight, because each accounts for different patterns of nonresponse.

We log-transformed urinary metabolite concentrations to account for skewness in the distribution of urinary phthalates. We performed univariate regressions of logs of the molar concentrations of metabolite groups against BP, triglycerides, HDL, low-density lipoprotein, and each of the demographic, dietary, anthropometric, and other covariates. We used multivariate linear regression analysis to model continuous dependent variables and logistic regression to model dichotomous variables in separate models. We adjusted all multivariate models for urinary creatinine, BMI category, demographic and exposure characteristics (ie, race/ethnicity, age category, caregiver education, poverty–income ratio, sex, and serum cotinine level), and lifestyle characteristics (ie, caloric intake and television watching).

Because previous studies show differences in urinary biomarkers in different racial/ethnic groups,¹⁷ we also developed stratified univariate and multivariate regression models of significant associations of phthalates with BP outcomes within categories for each of the potential confounding variables. Our race/ethnicity-stratified models examined effects within the non-Hispanic black, Hispanic, and non-Hispanic white groups to maintain large stratum-specific samples. As a further test of heterogeneity, we added stratum–phthalate interaction terms to regression models controlling for all covariates to test those interactions for statistical significance. Interaction terms with a *P* value <.05 were considered to confirm a stratum-specific effect.

In secondary analyses, we also analyzed individual phthalate metabolites from any of the significant models to determine which metabolites were driving the association. We also performed a complete-case analysis to ensure that our results were not driven by artifactual associations with missing categories. Finally, to ensure that our results for nonfasting outcomes were not an artifact of statistical weighting, we also repeated our analyses in unweighted models.

Results

Characteristics of the study population are presented in Table I. Our χ^2 testing revealed no significant demographic differences between children and adolescents with phthalate measurements and those without measurements. Regression analyses of phthalate metabolites against potential confounders while controlling for urinary creatinine level revealed increased levels of all metabolites in girls and in children with lower cotinine concentrations, and lower concentrations of HMW and DEHP metabolites in adolescents (Table II). College education and socioeconomic status were inversely related to levels of LMW metabolites, but not HMW and DEHP metabolites. HMW and DEHP metabolite concentrations were higher in subjects with excessive caloric intake. Given the known

demographic differences in BP, the results of our univariate analyses support our selection of potential confounders for inclusion in the multivariate analyses.

Although our multivariate modeling revealed no significant differences for prehypertension or DBP z -score, or for HDL, increases in SBP z -score emerged in association with urinary DEHP metabolite levels. For each log unit (roughly 3-fold) increase in DEHP metabolite levels ($P = .047$), we identified a 0.041 SD unit increment in SBP z -score (Table III).

Regression analyses of individual metabolites suggested that associations between SBP z -score with HMW metabolites are driven by DEHP metabolites (Table IV). Significant associations between MEHP (0.051 SD/log unit increase; $P = .014$), MBP (0.062 SD/log unit increase; $P = .046$), MEHHP (0.042 SD/log unit increase; $P = .022$), and MEOHP (0.043 SD/log unit increase; $P = .021$) with SBP z -score were identified, as was an association of MEP with prehypertension (OR, 1.20; $P = .038$). MEP and MBP are more commonly identified as metabolites of LMW phthalates, whereas MEHP, MEOHP, and MEHHP are primary metabolites of DEHP identified in human studies.^{27,28} MECPP, another primary metabolite of DEHP, was positively, but not significantly, associated with SBP z -score ($P = .098$).

Stratified modeling revealed divergence in association with SBP z -score by sex (effect only in males), age group (younger children only), and BMI category (nonoverweight subpopulation only) (Table V; available at www.jpeds.com). The introduction of interaction terms failed to corroborate a significant difference in association by BMI category ($P = .838$ for HMW; $P = .662$ for DEHP) or adolescence ($P = .238$ for HMW; $P = .863$ for DEHP), however. The significance of associations between HMW/DEHP levels and SBP z -score strengthened when interaction terms were added ($P = .23-.37$ for HMW; $P = .12-.25$ for DEHP). For sex, the interaction terms were nearly significant ($P = .064$ for HMW; $P = .067$ for DEHP), with attenuation of the association between HMW/DEHP and SBP z -score to nonsignificance ($P = .183$ for HMW; $P = .238$ for DEHP).

Unweighted analyses confirmed statistically stronger, but essentially unchanged in size, SBP z -score associations in unweighted modeling (0.044 SD unit increment per log unit DEHP increase in the full multivariate model; $P = .005$) (Table VI; available at www.jpeds.com). Results were unchanged in complete-case analyses (data not shown).

Discussion

In a nationally representative sample, we identified associations between urinary DEHP phthalate levels and elevated SBP. Although the effects that we report are subclinical, even small increments across a population can produce large increases in prehypertension and hypertension, shifting at-risk populations to a condition that may persist in later life. A 0.041 SD increment in SBP z -score, assuming a normal distribution, equates to a 0.7% increase in prehypertension, which is substantial given the 7.3% prevalence in the study population. In a 12-year-old male of average height, an increase in DEHP metabolites from the 25th to the 75th percentile would produce a 1.0-mm Hg increase in SBP. Although this increment is apparently modest, it compares favorably with results in a randomized trial of early nutrition

in preterm infants, in which a 10% change in human milk as a proportion of enteral intake produced a 0.3-mm Hg decrement in mean arterial BP at age 13–16.²⁹

This association could reflect multiple comparisons, or perhaps more importantly, reverse causality. For example, children with elevated BP may have unhealthy eating behaviors that include consumption of more packaged foods that contain phthalates, resulting in higher urinary levels. Yet controlling for BMI category (which presumably would be more strongly related to consumption of foods) strengthened rather than diminished the association. Moreover, the addition of 2 lifestyle variables considered likely associated with processed food consumption (ie, excessive caloric intake and increased television watching) did not change our estimated associations between DEHP metabolite levels and SBP z-score. Even though liver function may alter phthalate metabolism,³⁰ it is not a confounder, as we have demonstrated (data not shown), owing to the absent association of phthalates with continuous or categorized alanine amino-transferase concentrations. Our analyses drew on a rich set of data on demographics, exposures, and lifestyle variables, providing more convincing evidence of the nonspuriousness of the association.

Phthalates are typically known to have half-lives of 12–48 hours,³¹ whereas prehypertension is more likely to be a chronic process that emerges from arterial wall stiffening. Nonetheless, oxidant stress, such as that produced by phthalates, may produce short-term changes in arterial tone.^{32–34} Although urinary phthalates are more likely to represent current exposure as opposed to chronic exposure, fat deposition of phthalates is also important.³⁵ A previous study suggested moderate sensitivity (56%) and high specificity (73%) for MEHP (a DEHP metabolite) from a single urine sample over a 3-month period.³⁶ We note that MBP, which was also associated with SBP z-score in the present study, had stronger sensitivity and specificity (67% and 87%, respectively) in that 3-month study. Even if current urinary phthalates are weak indices of early life exposure, our estimates of association should be biased toward the null.³⁷

The absence of an association between DEHP metabolite levels and obesity in the present study is not surprising, given that previous studies have not consistently associated phthalates with obesity.^{19,38} This lack of association may stem from increases in arterial tone caused by DEHP through oxidative stress or endothelial injury. We suggest this idea because oxidative damage to the kidney has been identified as a potential mechanism through which phthalates and other environmental oxidants, such as bisphenol A, may contribute to cardiovascular risk.^{12,13} DEHP metabolites also may contribute to insulin resistance, producing microvascular changes that may result in higher BP.⁵ Corroboration of these ideas and identification of mechanism with require longitudinal studies. Ideally, such studies will use more direct measures, such as carotid intima-media thickness, brachial artery distensibility, and pulse wave velocity measurement.^{40,41}

Although the present study did not identify an association between DEHP and prehypertension, it was not powered to do so, with a 7.1% weighted prevalence in our study population of 2447. Assuming a normal distribution of SBP, the present study has only 14% power to detect a 2.9% difference in prehypertension between the 10th and 90th percentiles of DEHP in our sample (a 3 log unit difference, associated with a 0.15 SD unit higher SBP

z-score in our linear models). The power to detect differences in hypertension (1.4% in our subpopulation) was even more modest.

We identified a near-significant interaction of DEHP metabolites with sex, suggesting a possible role of reduced androgen activity. Sex differences in associations of visceral and body fat with BP in adolescents are well known,⁴² and functional variations in the androgen receptor gene has been identified as a potential mechanism.⁴³ Indeed, phthalates have been associated with reduced transcription of the androgen receptor.⁴⁴ Further research is needed to elaborate and confirm this possible mechanism.

In the context of epidemic increases in childhood hypertension⁴⁵ and the federal government's recognition of metabolic disruption by environmental chemicals,⁴⁶ the evidence presented herein, along with previous epidemiologic studies²⁶ and growing evidence of metabolic changes in cardiac myocytes^{6,46} and oxidative stress^{9–11}, calls for further observational and interventional studies in children and adolescents. These studies should focus on the possible synergy between ongoing dietary and behavioral interventions and policy initiatives to limit disruptive chemical exposures in efforts to reduce cardiovascular morbidity.

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Glossary

BMI	Body mass index
BP	Blood pressure
CDC	Centers for Disease Control and Prevention
DBP	Diastolic BP
DEHP	Di-2-ethylhexylphthalate
HDL	High-density lipoprotein
HMW	High molecular weight
LMW	Low molecular weight
MBP	Mono-n-butyl-phthalate
MECPP	Mono-(2-ethyl-5-carboxypentyl) phthalate
MEHHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
MEOHP	Mono-(2-ethyl-5-oxohexyl) phthalate
MEP	Mono-ethyl phthalate
NHANES	National Health and Nutrition Examination Survey

SBP

Systolic BP

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Table I

Characteristics of the study population

Characteristic	Value
Male sex, n (%)	1276 (51.8)
Age, y, mean (SD)	13.6 (3.4)
Race/ethnicity, n (%)	
Hispanic-Mexican American	729 (12.1)
Hispanic-other Hispanic	152 (5.9)
Non-Hispanic white	688 (62.5)
Non-Hispanic black	780 (14.6)
Other	98 (4.9)
Poverty-income ratio, n (%)	
First quartile (<0.83)	584 (17.6)
Second quartile (0.83–1.59)	599 (17.8)
Third quartile (1.60–3.09)	565 (25.1)
Fourth quartile (≥ 3.1)	589 (36.1)
Parent/caregiver education, n (%)	
Less than 9th grade	298 (6.2)
9th–12th grade	417 (11.9)
High school or GED	607 (24.8)
Some college	684 (32.6)
College or greater	335 (21.0)
Serum cotinine, n (%)	
<0.015 ng/mL	392 (16.4)
0.015–1.9 ng/mL	1470 (58.8)
2.0 ng/mL	355 (15.3)
Television watching ≥ 2 h/d, n (%)	1324 (47.8)
Excessive caloric intake compared to active child needs for age and sex, n (%)	671 (26.7)
BP at least 90th percentile, n (%)	179 (7.3)
Overweight, n (%)	903 (35.5)
LMW phthalate metabolite concentration, molar, median (IQR)	0.884 (0.425–1.989)
HMW phthalate metabolite concentration, molar, median (IQR)	0.491 (0.243–0.972)
DEHP metabolite concentration, molar, median (IQR)	0.337 (0.166–0.704)

GED, General Education Development.

Table II

Mean urinary molar concentration of metabolites of the 3 phthalate families, by sample characteristics (n = 2447)

	Mean urinary LMW metabolite molar concentration	<i>P</i> value *	Mean urinary HMW metabolite molar concentration	<i>P</i> value *	Mean urinary DEHP metabolite molar concentration	<i>P</i> value *
Sex						
Male	0.564	Reference	0.456	Reference	0.315	Reference
Female	0.732	<.001	0.510	.070	0.359	.048
Age, y						
6–11	0.792	Reference	0.785	Reference	0.532	Reference
12–19	0.847	.188	0.450	<.001	0.326	<.001
Race/ethnicity						
Hispanic-Mexican American	0.982	Reference	0.492	Reference	0.351	Reference
Hispanic-other Hispanic	1.267	.033	0.579	.210	0.419	.186
Non-Hispanic white	0.742	<.001	0.560	.055	0.395	.110
Non-Hispanic black	1.067	.181	0.497	.885	0.353	.948
Other	0.625	<.001	0.482	.875	0.350	.979
Poverty–income ratio						
First quartile (<0.83)	0.942	Reference	0.598	Reference	0.432	Reference
Second quartile (0.83–1.59)	0.937	.937	0.521	.135	0.361	.078
Third quartile (1.60–3.09)	0.819	.049	0.533	.182	0.371	.116
Fourth quartile (3.1)	0.735	<.001	0.523	.139	0.375	.157
Missing	0.869	.618	0.551	.636	0.398	.652
Parent/caregiver education						
Less than 9th grade	1.005	Reference	0.514	Reference	0.368	Reference
9th–12th grade	1.026	.851	0.537	.664	0.368	.981
High school or GED	0.894	.283	0.538	.686	0.375	.878
Some college	0.803	.040	0.543	.598	0.385	.678
College or greater	0.673	.001	0.555	.413	0.408	.337
Missing	0.771	.177	0.461	.496	0.327	.529
Serum cotinine						
<0.015 ng/mL	0.704	Reference	0.478	Reference	0.341	Reference
0.015–1.9 ng/mL	0.856	.021	0.568	.026	0.403	.048
2.0 ng/mL	0.885	.025	0.470	.863	0.329	.738
Missing	0.807	.167	0.598	.020	0.453	.044
Television watching						
<2 h/d	0.816	Reference	0.561	Reference	0.400	Reference
2 h/d	0.870	.296	0.578	.601	0.401	.956
Missing	0.768	.520	0.449	.054	0.329	.105
Caloric intake compared with active child needs for age and sex						
Appropriate	0.822	Reference	0.504	Reference	0.356	Reference

	Mean urinary LMW metabolite molar concentration	<i>P</i> value *	Mean urinary HMW metabolite molar concentration	<i>P</i> value *	Mean urinary DEHP metabolite molar concentration	<i>P</i> value *
Excessive	0.841	.761	0.631	.001	0.453	.001
Missing	0.881	.534	0.602	.342	0.428	.339
BP						
<90th percentile	0.817	Reference	0.541	Reference	0.384	Reference
90th percentile	1.002	.051	0.509	.394	0.359	.405
Overweight status						
Not overweight	0.825	Reference	0.544	Reference	0.371	Reference
Overweight	0.835	.825	0.529	.713	0.352	.51

All percentages are weighted using population weights for the sample in which phthalates were measured. The total number of subjects from some variables do not total to 2447 owing to missing data. See the text.

* Derived using regression of log molar concentration of urinary phthalate against characteristic, adjusted for urinary creatinine. Mean urinary phthalate represents retransformed mean from log base.

Table III

Linear and logistic regression analysis of cardiometabolic outcomes associated with urinary phthalate metabolites

BP outcome (n = 2447)	z-score increment, SBP	z-score increment, DBP	OR, BP 90th Percentile
LMW Metabolites	+0.03 (−0.02, +0.07)	+0.02 (−0.04, +0.07)	1.19 (0.96, 1.47)
HMW Metabolites	+0.04 (−0.002, +0.08)	+0.004 (−0.04, +0.04)	0.94 (0.82, 1.09)
DEHP Metabolites	+0.04 (+0.001, +0.08)*	−0.005 (−0.04, +0.03)	0.94 (0.82, 1.08)

Triglyceride outcome (n = 705)	OR, elevated triglycerides	Increment, triglycerides
LMW Metabolites	0.85 (0.71, 1.01)	−0.22 (−4.40, +0.07)
HMW Metabolites	1.06 (0.90, 1.24)	−0.28 (−2.55, +2.06)
DEHP Metabolites	1.05 (0.90, 1.22)	−0.34 (−2.47, +1.85)

HDL outcome (n = 2539)	OR, low HDL	Increment, HDL
LMW Metabolites	1.00 (0.87, 1.15)	+0.13 (−0.60, +0.85)
HMW Metabolites	0.93 (0.80, 1.07)	+0.42 (−0.31, +1.15)
DEHP Metabolites	0.94 (0.82, 1.08)	+0.40 (−0.25, +1.06)

Increases are per log unit in urinary LMW/HMW/DEHP metabolite concentration. See Methods for calculation. Models control for sex, caloric intake, television watching, poverty:income, parental education, serum cotinine, urinary creatinine, BMI category, race/ethnicity, and age categories. Results using weighted modeling are presented here.

* $P < .05$.

Table IV

Associations of individual urinary phthalate metabolites with BP outcomes in linear and logistic regression analyses

Increment/OR (n = 2447)	SBP z-score	DBP z-score	BP 90th percentile
MEP	+0.02 (−0.02, +0.06)	+0.02 (−0.03, +0.06)	1.20 (1.01, 1.43) *
MEHP	+0.05 (+0.01, +0.09) *	−0.02 (−0.06, +0.03)	1.01 (0.89, 1.15)
MBP	+0.06 (+0.001, +0.12) *	+0.02 (−0.03, +0.07)	1.05 (0.82, 1.35)
MEHHP	+0.04 (+0.01, +0.08) *	−0.002 (−0.04, +0.03)	0.96 (0.86, 1.09)
Monobenzylphthalate	+0.03 (−0.02, +0.08)	+0.03 (−0.02, +0.09)	1.12 (0.87, 1.44)
Mono-isobutyl phthalate	+0.03 (−0.02, +0.08)	−0.02 (−0.09, +0.04)	1.00 (0.74, 1.35)
MCPP	+0.02 (−0.03, +0.07)	+0.03 (−0.04, +0.10)	0.80 (0.61, 1.05)
MEOHP	+0.04 (+0.01, +0.08) *	−0.004 (−0.04, +0.03)	0.94 (0.82, 1.08)
MECPP	+0.04 (−0.01, +0.08)	−0.01 (−0.04, +0.03)	0.93 (0.81, 1.08)

MCPP, mono-(3-carboxypropyl) phthalate.

Increases are per log unit in urinary LMW/HMW/DEHP metabolite concentration. See Methods for calculation. All models control for sex, caloric intake, television watching, poverty–income ratio, parental education, serum cotinine, urinary creatinine, BMI, race/ethnicity, and age categories. Results using unweighted modeling are presented.

* $P < .05$.

Table V

Stratified linear and logistic regression analysis of SBP z-score against urinary phthalates

Increment in SBP z-score	LMW phthalate	HMW phthalate	DEHP phthalate
Male (n = 1275)	+0.01 (−0.05, +0.07)	+0.07 (+0.01, +0.12) [*]	+0.06 (+0.01, +0.11) [*]
Female (n = 1171)	+0.05 (−0.03, +0.12)	+0.02 (−0.04, +0.07)	+0.02 (−0.03, +0.08)
Child (n = 724)	+0.06 (−0.02, +0.15)	+0.07 (+0.01, +0.13) [*]	+0.08 (+0.02, +0.13) [†]
Adolescent (n = 1722)	+0.01 (−0.05, +0.07)	+0.03 (−0.03, +0.09)	+0.03 (−0.03, +0.08)
Hispanic (n = 880)	+0.03 (−0.05, +0.12)	+0.07 (+0.01, +0.13) [*]	+0.06 (+0.002, +0.11) [*]
White (n = 688)	+0.03 (−0.03, +0.09)	+0.03 (−0.03, +0.09)	+0.03 (−0.03, +0.08)
Black (n = 780)	+0.01 (−0.06, +0.07)	+0.05 (−0.03, +0.13)	+0.06 (−0.01, +0.13)
Poor (n = 1182)	+0.01 (−0.06, +0.08)	+0.06 (−0.02, +0.14)	+0.06 (−0.02, +0.13)
Not poor (n = 1154)	+0.03 (−0.04, +0.10)	+0.04 (−0.02, +0.09)	+0.04 (−0.02, +0.09)
Low cotinine level (n = 1862)	+0.04 (−0.01, +0.10)	+0.05 (+0.001, +0.10) [*]	+0.05 (−0.001, +0.09)
High cotinine level (n = 355)	+0.01 (−0.10, +0.13)	+0.07 (+0.004, +0.13) [*]	+0.06 (−0.002, +0.12)
Low caregiver education (n = 1321)	+0.04 (−0.02, +0.11)	+0.05 (−0.02, +0.12)	+0.05 (−0.02, +0.12)
High caregiver education (n = 1019)	+0.01 (−0.06, +0.08)	+0.04 (−0.02, +0.10)	+0.04 (−0.01, +0.09)
Appropriate caloric intake (n = 1775)	+0.01 (−0.04, +0.07)	+0.04 (−0.01, +0.10)	+0.04 (−0.01, +0.10)
Excessive caloric intake (n = 671)	+0.06 (−0.04, +0.15)	+0.04 (−0.02, +0.10)	+0.04 (−0.02, +0.11)
TV watching <2 h/d (n = 1123)	+0.06 (−0.01, +0.13)	+0.04 (−0.02, +0.09)	+0.03 (−0.02, +0.08)
TV watching >2 h/d (n = 1323)	−0.01 (−0.06, +0.04)	+0.05 (−0.02, +0.12)	+0.05 (−0.01, +0.12)
<85th percentile BMI (n = 1543)	+0.04 (−0.02, +0.09)	+0.06 (+0.004, +0.11) [*]	+0.05 (+0.001, +0.11) [*]
85th percentile BMI (n = 903)	+0.01 (−0.07, +0.10)	+0.02 (−0.05, +0.08)	+0.02 (−0.04, +0.09)

Increases are per log unit in urinary LMW/HMW/DEHP metabolite concentration. See Methods for calculation. All models control for sex, caloric intake, television watching, poverty-income ratio, parental education, serum cotinine, urinary creatinine, BMI, race/ethnicity, and age categories.

^{*} $P < .05$.

[†] $P < .01$.

Table VI

Unweighted linear and logistic regression analysis of BP outcomes associated with urinary phthalate metabolites (n = 2446)

	Model A	Model B	Model C
z-score increment, SBP			
LMW metabolites	+0.04 (+0.001, +0.07) [*]	+0.03 (−0.002, +0.07)	0.02 (−0.01, +0.06)
HMW metabolites	+0.06 (+0.02, +0.09) [†]	+0.06 (+0.02, +0.09) [†]	0.04 (+0.01, +0.08) [*]
DEHP metabolites	+0.05 (+0.02, +0.09) [†]	+0.05 (+0.02, +0.08) [†]	0.04 (+0.01, +0.08) [†]
z-score increment, DBP			
LMW metabolites	−0.01 (−0.06, +0.03)	−0.02 (−0.06, +0.02)	−0.03 (−0.07, +0.02)
HMW metabolites	+0.02 (−0.02, +0.06)	+0.02 (−0.02, +0.06)	+0.03 (−0.01, +0.07)
DEHP metabolites	+0.02 (−0.02, +0.06)	+0.02 (−0.02, +0.06)	+0.02 (−0.02, +0.06)
OR, BP 90th percentile			
LMW metabolites	1.12 (0.65, 1.29)	1.10 (0.95, 1.28)	1.08 (0.93, 1.27)
HMW metabolites	1.01 (0.86, 1.16)	0.99 (0.86, 1.15)	1.01 (0.86, 1.17)
DEHP metabolites	1.01 (0.88, 1.16)	1.01 (0.88, 1.16)	1.02 (0.88, 1.17)

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

Model A controls for urinary creatinine. Model B controls for urinary creatinine and BMI category. Model C controls for sex, caloric intake, television watching, poverty–income ratio, parental education, serum cotinine, urinary creatinine, BMI category, race/ethnicity, and age categories.

^{*} $P < .05$.

[†] $P < .01$.