Urinary Phthalates Are Associated with Higher Blood Pressure in Childhood

Leonardo Trasande, MD, MPP[1,2,3,4,5], Sheela Sathyanarayana, MD, MPH[6], Adam J. Spanier, MD, PhD, MPH[7], Howard Trachtman, MD[1], Teresa M. Attina, MD, PhD, MPH[1], and Elaine M. Urbina, MD, MS[8]

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. *(J Pediatr 2013;163:747-53)*.

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-n-isobutylphthalate) 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, butylbenzylphthalate) 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

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

From the Departments of [1]Pediatrics, [2]Environmental Medicine, and [3]Population Health, New York University School of Medicine; [4]Wagner School of Public Service, and [5]Steinhardt School of Culture, Education, and Human Development, New York University, New York, NY; [6]Department of Pediatrics, Seattle Children's Research Institute, University of Washington, Seattle, WA; [7]Department of Pediatrics, Penn State University, Hershey, PA; and [8]Division of Preventive Cardiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Supported by the KiDS of NYU Foundation. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.03.072

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 ≥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 (<2 and ≥0.015 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