

# Urinary Phthalates and Increased Insulin Resistance in Adolescents



**WHAT'S KNOWN ON THIS SUBJECT:** Phthalate exposure has been associated with insulin resistance in animal studies and cross-sectional studies of adults, but has not been studied in adolescents.



**WHAT THIS STUDY ADDS:** We detect associations of urinary phthalate metabolites in a cross-sectional study of US adolescents. The association is highly robust to multiple sensitivity analyses, and specific to phthalates commonly found in food. Further longitudinal study of dietary phthalate exposures is needed.

## abstract



**BACKGROUND:** Di-2-ethylhexylphthalate (DEHP) is an environmental chemical commonly found in processed foods. Phthalate exposures, in particular to DEHP, have been associated with insulin resistance in adults, but have not been studied in adolescents.

**METHODS:** Using cross-sectional data from 766 fasting 12- to 19-year-olds in the 2003–2008 NHANES, we examined associations of phthalate metabolites with continuous and categorical measures of homeostatic model assessment of insulin resistance (HOMA-IR).

**RESULTS:** Controlling for demographic and behavioral factors, diet, continuous age, BMI category, and urinary creatinine, for each log (roughly threefold) increase in DEHP metabolites, a 0.27 increase (95% confidence interval 0.14–0.40;  $P < .001$ ) in HOMA-IR was identified. Compared with the first tertile of DEHP metabolite in the study population (14.5% insulin resistant), the third tertile had 21.6% prevalence (95% confidence interval 17.2%–26.0%;  $P = .02$ ). Associations persisted despite controlling for bisphenol A, another endocrine-disrupting chemical commonly found in foods, and HOMA-IR and insulin resistance were not significantly associated with metabolites of lower molecular weight phthalates commonly found in cosmetics and other personal care products.

**CONCLUSIONS:** Urinary DEHP concentrations were associated with increased insulin resistance in this cross-sectional study of adolescents. This study cannot rule out the possibility that insulin-resistant children ingest food with higher phthalate content, or that insulin-resistant children excrete more DEHP. *Pediatrics* 2013;132:e646–e655

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### KEY WORDS

phthalates, insulin resistance

### ABBREVIATIONS

BPA—bisphenol A  
CDC—Centers for Disease Control and Prevention  
CI—confidence interval  
DEHP—di-2-ethylhexylphthalate  
HMW—high molecular weight  
HOMA-IR—homeostatic model assessment of insulin resistance  
IQR—interquartile range  
LMW—low molecular weight  
MBP—mono-n-butyl-phthalate  
MCPP—mono-(3-carboxypropyl) 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  
NCHS—National Centers for Health Statistics  
OR—odds ratio  
PIR—poverty-income ratio  
PPAR—peroxisome proliferator-activated receptor

Drs Blustein and Trasande developed the research question and data analytic plan, jointly provided oversight over the entire analysis, and drafted and revised the paper; Dr Trasande is guarantor; Dr Attina cleaned and analyzed the data; Drs Sathyanarayana and Spanier assisted Dr Trasande in formulating Table 1 and description of the laboratory evidence that spurred the analysis of the NHANES data; and all authors participated in the discussion and interpretation of the results, critically revised the manuscript for intellectual content, and approved the final version.

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Phthalates are esters of ortho-phthalic acid with a diverse array of uses in consumer products, and they can be classified into low-molecular weight (LMW) phthalates, which are frequently added to preserve scent,<sup>1</sup> and high-molecular weight (HMW) phthalates, which are used to produce vinyl plastics for diverse applications ranging from flooring, clear food wrap, and intravenous tubing (Table 1).<sup>2</sup> Within the HMW phthalate category, di-2-ethylhexylphthalate (DEHP) is of particular interest because industrial processes to package food frequently use plastic products containing DEHP.<sup>3</sup> Although medical devices<sup>4</sup> and toys<sup>5</sup> can contain DEHP, dietary intake from contaminated food is the largest contributor to exposure in children.<sup>2,6</sup> While a cross-sectional study of 254 children and adolescents found associations of LMW phthalates in household dust with urinary LMW metabolites, it failed to identify such associations for DEHP.<sup>7</sup> Early life exposure to phthalates has been associated with a variety of adverse effects, particularly involving endocrine processes.<sup>1,8</sup> Although an exploratory, cross-sectional analysis of the 1999–2002 US NHANES did not identify significant associations of urinary phthalate metabolites with BMI

among children,<sup>9</sup> other analyses, including an analysis of 2003–2008 NHANES data, have found an association of LMW, but not HMW or DEHP, phthalates with childhood obesity.<sup>10,11</sup> Mono-(2-ethylhexyl) phthalate (MEHP), a DEHP metabolite, activates peroxisome proliferator-activated receptor (PPAR)  $\gamma$  transcription more selectively than rosiglitazone,<sup>12</sup> a drug used to treat type 2 diabetes by increasing insulin sensitivity.<sup>13</sup> This selective upregulation appears to explain the differential effects of rosiglitazone and MEHP, in which MEHP produces a phenotype of insulin resistance in cellular models<sup>14,15</sup> and in vivo.<sup>16</sup> Given that PPAR plays key roles in lipid and carbohydrate metabolism,<sup>17</sup> these findings provide biological plausibility for DEHP metabolites in insulin resistance. Only 2 studies have examined phthalate-insulin resistance relationships, 1 identifying strong correlations of HMW and DEHP metabolites with insulin resistance in adult men in the 1999–2002 NHANES,<sup>18</sup> and the other associating phthalate metabolites with prevalent diabetes among women in the 2001–2008 NHANES.<sup>19</sup> In the context of increasing diabetes in youth globally,<sup>20,21</sup> and absent changes of genetic predisposition over the same time period,

concern about environmental exposures as a possible contributor is warranted.

We therefore performed a cross-sectional analysis of the 2003–2008 NHANES to examine associations of urinary phthalate metabolites with insulin resistance in adolescents, for each of the 3 categories (LMW, HMW, and DEHP), examined separately, as well as for individual metabolites.

## METHODS

NHANES is a continuous, 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 questionnaire, laboratory, diet, and physical examination components were used in the present analysis, for which data are available in biennial groupings. Written consent, and child assent as appropriate, was obtained after approval by the National Center for Health Statistics Research Ethics Review Board. The New York University School of Medicine Institutional Review Board exempted this study from review because it is based on previously collected and de-identified data.

**TABLE 1** Widely Produced Phthalates, Their Common Uses and Metabolites

Phthalate Parent Compound	Metabolite	Potential Sources of Exposure	Category
Diethyl phthalate	Mono-ethyl phthalate (MEP)	Cosmetics, nail polish, deodorant, perfumes/cologne, lotions, aftershave, pharmaceuticals/herbal coating, insecticide	LMW
Di-n-butyl phthalate and di-isobutyl phthalate	MBP	Nail polish, make-up, aftershave, perfumes, pharmaceuticals/herbal coating, chemiluminescent glow sticks	LMW
Di-n-butyl phthalate	Mono-isobutyl phthalate (MiBP)	Medicines, cosmetics, cellulose acetate plastics, latex adhesives, in nail polish and other cosmetic products, as a plasticizer in cellulose plastics, as a solvent for certain dyes	LMW
Di-n-butyl phthalate	MBP	Medicines, cosmetics, cellulose acetate plastics, latex adhesives, in nail polish and other cosmetic products, as a plasticizer in cellulose plastics, as a solvent for certain dyes	LMW
Butyl benzyl phthalate	Monobenzyl phthalate (MBzP)	Vinyl flooring, adhesives, sealants, food packaging, furniture upholstery, vinyl tile, carpet tiles, and artificial leather and is also used in certain adhesives	HMW
Di-n-octyl phthalate	MCPP	Soft plastics	HMW
DEHP	MEHP	Polyvinyl chloride-containing medical tubing, blood storage bags, medical devices, food packaging, plastic toys, wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, some toys, shoes, automobile upholstery and tops, packaging film and sheets	DEHP (also HMW)
	MECPP	bags, medical devices, food packaging, plastic toys, wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, some toys, shoes, automobile upholstery and tops, packaging film and sheets	DEHP (also HMW)
	MEHHP	coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, some toys, shoes, automobile upholstery and tops, packaging film and sheets	DEHP (also HMW)
	MEOHP	shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, some toys, shoes, automobile upholstery and tops, packaging film and sheets	DEHP (also HMW)

## Measures of Insulin Resistance

We calculated homeostatic model assessment of insulin resistance (HOMA-IR) by multiplying fasting glucose in mmol/L by fasting insulin in  $\mu\text{U/mL}$  and dividing by 22.5.<sup>22</sup> It has strong correlation with the gold standard hyperinsulinemic-euglycemic patch-clamp test.<sup>22,23</sup> HOMA-IR was log (base e)-transformed to account for skewed distribution, with results presented after retransformation to the original scale. To assess insulin resistance as a categorical outcome, we used the cut point of 4.39 ( $>2$  SD above mean HOMA-IR for normal-weight adolescents with normal fasting glucose in NHANES 1999–2002).<sup>24</sup> Our primary study outcome was insulin resistance, though we examined continuous HOMA-IR as an outcome in secondary analyses.

## Measurement of Urinary Phthalates

Phthalates were measured in 1 spot urine sample, and analyzed by using high-performance liquid chromatography and tandem mass spectroscopy. More extensive methodological description is provided elsewhere.<sup>25</sup> For phthalate concentrations below the level of detection (5.1% for MEHP,  $<1\%$  for all other metabolites), we substituted the limit of detection divided by the square root of 2, following common practice.<sup>11</sup> To adjust for dilution, we included urinary creatinine as a covariate in all analyses, as suggested by CDC.<sup>26</sup> To assess possible systematic bias introduced by a change in the urinary creatinine measurement method in 2007, we added a categorical variable representing NHANES wave to final models as part of a sensitivity analysis.

We grouped urinary biomarkers according to their use in product categories, calculating molar sums for LMW, HMW, and DEHP metabolites (after the stratification as presented in Table 1), and log (base e)-transforming to

account for skewed distribution. Our primary exposure variables were the log-transformed total molar concentrations of LMW, HMW, and DEHP metabolites, although secondary analyses also examined tertiles of metabolite groupings, and analyzed individual metabolites.

## Potential Confounders

Information on height and weight was based on measures taken by trained health technicians, who used data recorders and used standardized procedures. We derived BMI z-scores from 2000 CDC norms, incorporating height, weight, and gender; overweight and obese were categorized as BMI z-score  $\geq 1.036$  and  $\geq 1.64$ .<sup>27</sup>

Other measures came from surveys and laboratory assessments. 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). Calorie intake was examined as a continuous variable. Because exposure to tobacco smoke is a risk factor for metabolic syndrome in adolescence, we included serum cotinine in multivariable models. We categorized into low ( $<0.015$  ng/mL), medium ( $<2$  and  $\geq 0.015$  ng/mL), and high ( $\geq 2$  ng/mL) categories.<sup>28</sup>

Race/ethnicity was categorized into Mexican American, other Hispanic, Non-Hispanic white, non-Hispanic black, and other, based on self-report by 17- to 19-year-olds and caregiver report in 12- to 16-year-olds. Caregiver education was categorized as  $<9$ th grade, 9th to 12th grade, high school/graduate equivalency diploma, some college, and college or greater. Poverty-income ratio (PIR; family income divided by the federal poverty line for family size) was categorized into quartiles. To maximize sample size in multivariable analysis, “missing” categories were created for all potential confounders, except BMI

category ( $n = 6$ ). Except for serum cotinine (9.6%),  $<5\%$  of values were missing for any confounding variable.

## Statistical Analysis

We conducted univariate and multivariate analyses, by using Stata 12.0 (Stata Corp, College Station, TX), and following NCHS guidelines.<sup>29</sup> Fasting samples and urinary phthalate measurements are collected from partially overlapping subsamples in NHANES. Although there are subsample weights for each, NCHS advises against use of either subsample weight, because sample sizes may get small when combining subsamples and weighted analyses may result in unstable and unreliable statistical estimates (R. Paulose, PhD, CDC, NCHS, personal communication). We therefore followed the practice of Stahlhut et al,<sup>18</sup> performing unweighted analyses as our base analytic approach, and performed a series of sensitivity analyses.

LMW/HMW/DEHP urinary metabolite concentrations were log-transformed to account for skewed distribution, and divided into tertiles within the population with available phthalate and HOMA-IR data. We performed univariate regressions of logs of the molar concentrations of metabolite groups against HOMA-IR, insulin resistance, and each of the demographic, dietary, anthropometric, and the other covariates. We used multivariable linear regression analysis to model HOMA-IR, and logistic regression to model insulin resistance in separate models. In nested multivariable models we sequentially added (1) urinary creatinine, (2) BMI category and continuous age, (3) demographic and exposure characteristics (race/ethnicity, caregiver education, PIR, gender, serum cotinine), and (4) caloric intake.

As part of this exploratory analysis of phthalate–insulin resistance associations, we assessed heterogeneity of association by performing regressions

of phthalate metabolites with HOMA-IR and insulin resistance, controlling for urinary creatinine, in strata defined by each of the potential confounding categorical variables described previously. For these stratified analyses, we collapsed categories to ensure meaningful sample size in each group. As a further test of heterogeneity, we added stratum-phthalate interaction terms to whole-sample regression models controlling for all covariates to statistically test those interactions for statistical significance. When interaction terms had  $P < .05$ , we interpreted this to confirm a stratum-specific effect.

### Sensitivity Analysis

We assessed the robustness of our analysis by reprising (1) multivariable analyses using fasting weights, (2) multivariable analyses using environmental sample weights, and (3) multivariable analyses adding variables used in determining sample weights as covariates to the full multivariable model. The third approach is noted to enhance statistical efficiency, especially when analyses are intended to determine associations rather than estimate prevalence of a condition or mean for an outcome (such as HOMA-IR).<sup>30</sup> We also applied multiple imputation techniques,<sup>31</sup> to generate randomly replacement values for each missing categorical variable, based on race/ethnicity-specific rates identified in the NHANES sample. We performed 20 imputations for the imputed variable following common practice.<sup>32</sup> These multiply imputed models examined a smaller number of covariates (substituting log-transformed cotinine for categorical cotinine, continuous PIR for PIR category, and BMI z-score for categorical BMI), which reduced potential for multicollinearity and overfitting of logistic models, which can decrease power and increase type 1 error.

We also tested the robustness of our results, by including doctor-diagnosed diabetes and prediabetes covariates, and reprising multivariable results excluding adolescents with diabetes and/or prediabetes. Because liver function may alter phthalate metabolism,<sup>33</sup> we examined associations of metabolites with alanine aminotransferase in multivariable models to rule out confounding by differences in liver function. Finally, we added quartiled urinary concentrations of bisphenol A (BPA), a known contaminant of diet, which has been associated with obesity in children and adolescents.<sup>34</sup>

### RESULTS

Of the 5829 children ages 12 to 19 who participated, urinary phthalate metabolites were measured in 1832 non-pregnant participants. Of these, fasting insulin/glucose were measured in 766. Median urinary LMW, HMW, and DEHP metabolites were 0.83 (interquartile range [IQR] 0.40–1.89, SE 0.25), 0.50 (IQR 0.25–0.98, SE 0.07), and 0.34 (IQR 0.17–0.71, SE 0.07) micromolar. Median HOMA-IR was 2.24 (SE 0.15; IQR 1.43–3.66); 17.6% were insulin-resistant (HOMA-IR  $\geq 4.39$ ). Six reported doctor-diagnosed diabetes, and 3 reported doctor-diagnosed prediabetes.

Descriptive analyses identified significantly higher levels of LMW, HMW, and DEHP metabolites among girls (Table 2). Whites had significantly lower LMW metabolite concentrations, whereas other Hispanics had higher HMW and DEHP metabolite concentrations. Adolescents from higher-income households, and with high school/graduate equivalency diploma or college/greater-educated caregivers had lower LMW metabolite concentrations. Adolescents with higher urinary cotinine concentrations also had higher concentrations for LMW, HMW, and DEHP. HMW and DEHP metabolites were highest among those with excessive caloric intake.

### Associations of Phthalate Metabolites With Insulin-Resistance Outcomes

Table 3 examines the association of LMW, HMW, and DEHP metabolites with insulin resistance (defined as HOMA-IR  $> 4.39$ ) and HOMA-IR as a continuous measure, using logistic and linear regression modeling, controlling for urinary creatinine only. In the entire sample, no significant associations are identified with insulin resistance in the entire sample, controlled for urinary creatinine. However, for each log unit (roughly threefold) increase in HMW metabolites, a 0.20 increase in HOMA-IR is identified ( $P = .007$ ), whereas for each log unit increase in DEHP metabolites, a 0.19 increase in HOMA-IR ( $P = .005$ ) is identified. Stratified modeling (Supplemental Table 6) exhibited stronger associations of HMW and DEHP metabolites with HOMA-IR among girls, Hispanic and non-Hispanic black individuals, and adolescents living in households with poverty-income quartile  $< 1.3$ . Significant associations are also identified for LMW phthalates in relationship to HOMA-IR among girls and non-Hispanic black individuals, in contrast to other subpopulations. Interaction with race is confirmed with HOMA-IR as the outcome, with significant increments among Mexican American ( $P = .001$  for HMW and DEHP) and non-Hispanic black ( $P = .002$  for HMW and DEHP) individuals but not among white individuals ( $P \geq .74$ ). When insulin resistance is the outcome, significantly increased odds among Mexican American individuals are identified in relationship to HMW and DEHP (both  $P = .02$ ), but not among other subgroups ( $P \geq .17$ ). No significant interaction with gender ( $P \geq .79$ ), poverty ( $P \geq .20$ ), or body mass category ( $P \geq .51$ ) is identified.

Nested, multivariable models that controlled incrementally for BMI category and continuous age variables,

**TABLE 2** Comparison of Urinary Phthalate Metabolites in Study Population With Fasting Insulin and Glucose Data in Pooled 2003–2008 NHANES (n = 766)

	Total, n (%)	Mean Urinary LMW Metabolite, $\mu\text{M}$	P Value <sup>a</sup>	Mean Urinary HMW Metabolite, $\mu\text{M}$	P Value <sup>a</sup>	Mean Urinary DEHP Metabolite, $\mu\text{M}$	P Value <sup>a</sup>
Gender							
Boys	424 (55.4)	0.508	Reference	0.313	Reference	0.224	Reference
Girls	342 (44.6)	0.729	<.001	0.380	.008	0.273	.01
Race/ethnicity							
Hispanic: Mexican American	228 (29.8)	0.891	Reference	0.368	Reference	0.264	Reference
Hispanic: other Hispanic	49 (6.4)	1.167	.16	0.503	.05	0.373	.04
Non-Hispanic white	208 (27.1)	0.662	.002	0.442	.06	0.320	.06
Non-Hispanic black	250 (32.6)	1.010	.18	0.421	.16	0.303	.18
Other	31 (4.0)	0.945	.30	0.463	.24	0.322	.34
PIR							
First quartile (<0.83)	190 (24.8)	0.982	Reference	0.457	Reference	0.334	Reference
Second quartile (0.83–1.59)	178 (23.2)	0.945	.71	0.379	.08	0.267	.05
Third quartile (1.60–3.09)	159 (20.8)	0.782	.03	0.383	.10	0.271	.08
Fourth quartile (at least 3.1)	202 (26.4)	0.727	.003	0.443	.76	0.323	.76
Missing	37 (4.8)	0.888	.57	0.395	.42	0.297	.55
Parent/caregiver education							
<9th grade	104 (13.6)	1.033	Reference	0.395	Reference	0.277	Reference
9th–12th grade	115 (15.0)	1.016	.90	0.390	.93	0.304	.64
High school or graduate equivalency diploma	176 (23.0)	0.769	.02	0.408	.80	0.317	.47
Some college	227 (29.6)	0.868	.14	0.459	.21	0.324	.41
College or greater	109 (14.2)	0.729	.01	0.383	.82	0.275	.97
Missing	35 (4.6)	0.788	.08	0.439	.59	0.506	.05
Serum cotinine							
<0.015 ng/mL	133 (17.4)	0.777	Reference	0.353	Reference	0.253	Reference
0.015–1.9 ng/mL	490 (64.0)	0.840	.43	0.421	.08	0.306	.08
≥2.0 ng/mL	141 (18.4)	1.041	.02	0.468	.02	0.330	.04
Missing	2 (0.3)	0.371	.30	0.284	.24	0.242	.95
Caloric intake compared with needs in active child of age/gender							
Appropriate	538 (70.2)	0.841	Reference	0.376	Reference	0.269	Reference
Excessive	199 (26.0)	0.861	.78	0.517	.005	0.378	<.001
Missing	29 (3.8)	1.211	.06	0.564	.24	0.415	.04
Overweight status							
Not overweight (<85th percentile)	509 (67.0)	0.833	Reference	0.405	Reference	0.312	Reference
Overweight (≥85th percentile)	251 (33.0)	0.914	.23	0.466	.16	0.275	.13
Insulin status							
Not resistant	631 (87.9)	0.844	Reference	0.405	Reference	0.291	Reference
Insulin resistant	135 (17.6)	0.928	.32	0.466	.15	0.340	.48

Total number of subjects from some variables do not total to 766 because of missing data. See text.

<sup>a</sup> 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 Insulin Resistance Outcomes Associated With Urinary Phthalate Metabolites

	Model A, <i>n</i> = 766	Model B, <i>n</i> = 766	Model C, <i>n</i> = 760	Model D, <i>n</i> = 758 <sup>a</sup>
OR, insulin resistance				
Log-transformed LMW metabolite	1.10 (0.91, 1.32)	1.00 (0.79, 1.25)	0.92 (0.72, 1.19)	0.92 (0.71, 1.19)
Log-transformed HMW metabolite	1.14 (0.95, 1.37)	1.34 (1.07, 1.69) <sup>c</sup>	1.38 (1.08, 1.75) <sup>c</sup>	1.45 (1.13, 1.87) <sup>d</sup>
Log-transformed DEHP metabolite	1.14 (0.96, 1.34)	1.33 (1.08, 1.66) <sup>d</sup>	1.36 (1.09, 1.71) <sup>d</sup>	1.44 (1.14, 1.82) <sup>d</sup>
Increment, HOMA-IR <sup>b</sup>				
Log-transformed LMW metabolite	+0.06 (−0.21, +0.19)	+0.001 (−0.13, +0.13)	−0.06 (−0.16, +0.04)	−0.07 (−0.18, +0.04)
Log-transformed HMW metabolite	+0.20 (+0.05, +0.35) <sup>d</sup>	+0.30 (+0.15, +0.46) <sup>e</sup>	+0.24 (+0.11, +0.37) <sup>e</sup>	+0.26 (+0.13, +0.40) <sup>e</sup>
Log-transformed DEHP metabolite	+0.19 (+0.06, +0.33) <sup>d</sup>	+0.31 (+0.16, +0.47) <sup>e</sup>	+0.24 (+0.12, +0.37) <sup>e</sup>	+0.27 (+0.14, +0.40) <sup>e</sup>

Model A controls for urinary creatinine; Model B adds continuous age and BMI category to Model A; Model C adds gender, PIR, parental education, serum cotinine, and race/ethnicity to Model B; and Model D adds caloric intake to Model C. Results using unweighted modeling are presented.

<sup>a</sup> No participants with missing poverty-income cotinine data were insulin resistant, and these were excluded from logistic models to permit convergence.

<sup>b</sup> HOMA-IR categorized using cut point of 4.39 (>2 SD above mean HOMA-IR for normal-weight adolescents with normal fasting glucose in NHANES 1999–2002).

<sup>c</sup> *P* < .05.

<sup>d</sup> *P* < .01.

<sup>e</sup> *P* < .001.

sociodemographic factors, and caloric intake in the entire sample identified increasingly stronger relationships of HMW and DEHP urinary metabolites with insulin resistance outcomes. In the final multivariable model (Model D), insulin resistance was significantly associated with log-transformed urinary HMW (odds ratio [OR] 1.45, *P* = .003) and DEHP (OR 1.44, *P* = .002), but not urinary LMW metabolites. For each log unit (roughly threefold) increase in HMW and DEHP metabolite, 0.26 and 0.27 increases in HOMA-IR (both *P* < .001) were identified.

When the study population was categorized into tertiles (Table 4), adolescents with the highest HMW (0.34, 95% confidence interval [CI] 0.10–0.61; *P* = .004) and DEHP (0.38, 95% CI 0.14–0.64; *P* = .001) had higher HOMA-IR than the others. Compared with the first tertile of HMW (14.3% adjusted prevalence), the third tertile is associated with a 21.3% prevalence (95% CI 16.8%–25.8%; *P* = .021) of insulin resistance. Similarly, compared with the first tertile of DEHP (14.5% adjusted prevalence), the third tertile had 21.6% prevalence (95% CI 17.2%–26.0%; *P* = .017).

Within-category analyses of insulin resistance outcomes (Table 5) suggested that associations of HOMA-IR and insulin resistance were absent for LMW

metabolites, and stronger for DEHP than non-DEHP metabolites. Log-transformed urinary concentrations of 4 DEHP metabolites, MEHP (*P* = .006), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP; *P* < .001), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP; *P* < .001), and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP; *P* < .001) were all significantly associated with increases in HOMA-IR. Associations were also identified for 2 of the LMW phthalate metabolites, mono-isobutyl phthalate (*P* = .007) and mono-*n*-butylphthalate (MBP; *P* = .04), and 1 of the non-DEHP HMW metabolites, mono-(3-carboxypropyl) phthalate (MCPHP; *P* < .001). Log-transformed MEHHP (OR 1.51, *P* < .001), MEOHP (OR 1.49, *P* = .001), MECPP (OR 1.36, *P* = .01), MCPHP (OR 1.47, *P* = .008), mono-isobutyl phthalate (OR 1.57, *P* = .002), and MBP (OR 1.55, *P* = .01) were significantly associated with insulin resistance.

Associations of HOMA-IR and insulin resistance were robust to the following: weighting and addition of primary sampling unit and strata; addition of NHANES wave; multiple imputation; categorization of age into 12–15 and 16–19 year old groups; exclusion of adolescents previously diagnosed with prediabetes or diabetes; and addition of prediabetes and diabetes covariates (data not shown). No significant

association of phthalate metabolites was identified in association with continuous/categorized alanine aminotransferase (Supplemental Table 7). When quartiled urinary BPA was added to regression models, associations of HMW and DEHP with HOMA-IR remained unchanged, and urinary BPA quartiles were not associated with HOMA-IR (Supplemental Table 8), although the highest BPA quartile was associated with insulin resistance.

## DISCUSSION

This is the first study to identify associations of an environmental chemical with insulin resistance in adolescents. The association is confirmed both when HMW and DEHP metabolites are modeled as continuous or categorical variables. Chemically similar LMW metabolites were not associated, suggesting specificity of association, and the findings are robust to simultaneous examination of another endocrine disrupting chemical, BPA. Our analyses include a rich set of information about demographics, exposures, and lifestyle variables, thus providing more convincing evidence for nonspuriousness. Our findings are also consistent with the previous cross-sectional study in adults, although we did not find significant differences in association by gender, which the previous study's

**TABLE 4** Linear and Logistic Regression Analysis of Insulin Resistance Outcomes Associated With Urinary Phthalate Metabolites (Tertiled)

	LMW Metabolites	HMW Metabolites	DEHP Metabolites
Increment, HOMA-IR, <i>n</i> = 760			
Predicted HOMA-IR			
First tertile	Reference 2.44 (2.25 to 2.65)	Reference 2.15 (2.00 to 2.32)	Reference 2.15 (1.99 to 2.31)
Second tertile	-0.18 (-0.35 to 0.02) 2.21 (2.06 to 2.37)	0.10 (-0.10 to 0.32) 2.26 (2.10 to 2.43)	0.07 (-0.12 to 0.29) 2.22 (2.07 to 2.39)
Third tertile	-0.11 (-0.31 to 0.10) 2.29 (2.13 to 2.46)	0.34 (0.10 to 0.61) <sup>b</sup> 2.54 (2.35 to 2.73)	0.38 (0.14 to 0.64) <sup>b</sup> 2.58 (2.39 to 2.77)
OR, insulin resistance, <i>n</i> = 758 <sup>a</sup>			
Prevalence			
First tertile	Reference 19.6% (14.9% to 24.2%)	Reference 14.3% (10.8% to 17.7%)	Reference 14.5% (11.0% to 17.9%)
Second tertile	0.67 (0.35 to 1.32) 16.1% (12.4% to 19.8%)	1.57 (0.84 to 2.95) 18.0% (14.3% to 21.7%)	1.43 (0.76 to 2.69) 17.4% (13.7% to 21.0%)
Third tertile	0.77 (0.38 to 1.56) 17.2% (13.5% to 20.8%)	2.22 (1.13 to 4.40) <sup>c</sup> 21.3% (16.8% to 25.8%)	2.25 (1.16 to 4.38) <sup>c</sup> 21.6% (17.2% to 26.0%)

Increases are per log unit in urinary LMW/HMW/DEHP metabolite concentration. See methods for calculation. Tertiles for LMW as follows: <0.528 molar (*n* = 233); 0.528–1.34 molar (*n* = 247); ≥1.34 molar (*n* = 286). Tertiles for HMW as follows: <0.319 molar (*n* = 274); 0.319–0.74 molar (*n* = 241); ≥0.74 molar (*n* = 251). Tertiles for DEHP as follows: <0.215 molar (*n* = 268); 0.215–0.516 molar (*n* = 240); ≥0.516 molar (*n* = 258). All models control for continuous urinary creatinine, age (measured continuously), and caloric intake, as well as gender, PIR, parental education, serum cotinine, BMI, and race/ethnicity categories. Results using unweighted modeling are presented.

<sup>a</sup> No participants with missing poverty-income cotinine data were insulin resistant, and these were excluded from logistic models to permit convergence.

<sup>b</sup> *P* < .01.

<sup>c</sup> *P* < .05.

**TABLE 5** Associations of Individual Urinary Phthalate Metabolites With Insulin Resistance Outcomes in Linear and Logistic Regression Analyses

Increment/OR	Increment, HOMA-IR, <i>n</i> = 760	OR, Insulin Resistance, <i>n</i> = 758 <sup>a</sup>
LMW phthalates		
Log-transformed mono-ethyl phthalate	-0.07 (-0.16, +0.03)	0.89 (0.71, 1.11)
Log-transformed MBP	+0.13 (+0.01, +0.26) <sup>b</sup>	1.55 (1.11, 2.16) <sup>b</sup>
Log-transformed mono-isobutyl phthalate	+0.15 (+0.04, +0.26) <sup>c</sup>	1.57 (1.18, 2.09) <sup>c</sup>
HMW metabolites (non-DEHP)		
Log-transformed monobenzylphthalate	+0.02 (-0.08, +0.13)	1.26 (0.97, 1.63)
Log-transformed MCPP	+0.20 (+0.08, +0.32) <sup>c</sup>	1.47 (1.10, 1.95) <sup>c</sup>
HMW metabolites of DEHP		
Log-transformed MEHP	+0.11 (+0.04, +0.20) <sup>c</sup>	1.13 (0.91, 1.40)
Log-transformed MEHHP	+0.20 (+0.12, +0.29) <sup>d</sup>	1.51 (1.21, 1.88) <sup>d</sup>
Log-transformed MEOHP	+0.20 (+0.11, +0.29) <sup>d</sup>	1.49 (1.19, 1.87) <sup>c</sup>
Log-transformed MECPP	+0.16 (+0.07, +0.25) <sup>d</sup>	1.36 (1.08, 1.73) <sup>b</sup>

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

All models control for continuous urinary creatinine, age (measured continuously), and caloric intake as well as gender, PIR, parental education, serum cotinine, BMI, and race/ethnicity categories. Results using unweighted modeling are presented.

<sup>a</sup> No participants with missing poverty-income cotinine data were insulin resistant, and these were excluded from logistic models to permit convergence.

<sup>b</sup> *P* < .05.

<sup>c</sup> *P* < .01.

<sup>d</sup> *P* < .001.

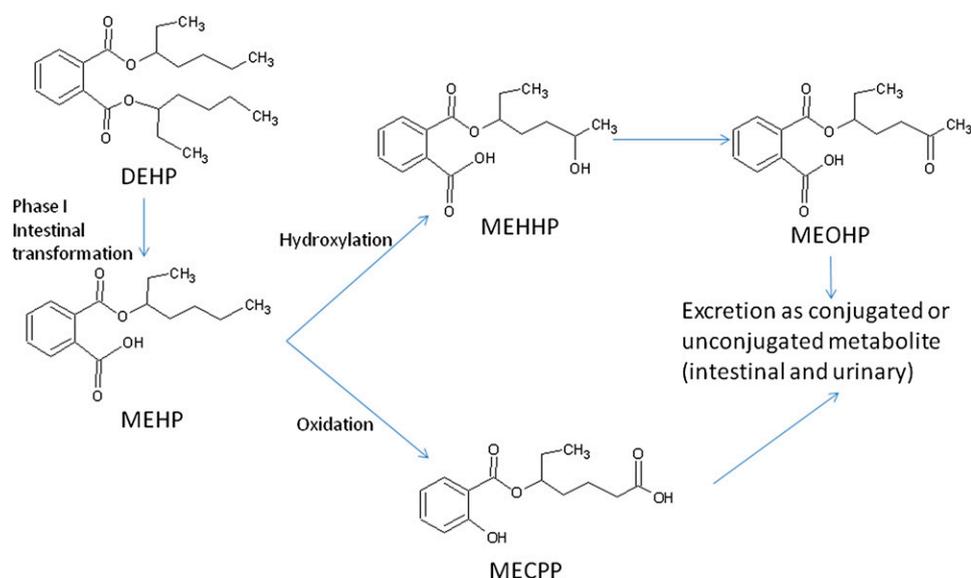
authors documented, and we identified stronger associations with DEHP metabolites (more consistent with the putative biological mechanism), whereas associations were identified with MBP, monobenzylphthalate, and

mono-ethyl phthalate in adults (less consistent with the putative biological mechanism).<sup>18</sup> Yet even when coupled with a potential mechanism (selective upregulation of PPAR expression),<sup>17</sup> causation cannot be inferred from

a cross-sectional study. Many potential confounders were unmeasured, including pubertal status, which is not assessed in the NHANES; future studies should account for this important and potential confounder. Phthalates may affect pancreatic function earlier in life than the adolescent period we examined in the current study, and longitudinal studies of prenatal and infant exposure are needed. Another alternative explanation would be that insulin-resistant children have unhealthy eating behaviors, including more packaged food consumption, and thus have higher urinary levels.

Relationships between phthalate (including DEHP) intake and urinary metabolites are complex. We know of no pharmacokinetic studies in children/adolescents. In animals, studies suggest that DEHP is hydrolyzed into MEHP, and then rapidly transformed to MECPP, MEHHP, and MEOHP, the primary metabolites identified in human studies (see Fig 1).<sup>35,36</sup> Butylbenzylphthalate and di-n-octylphthalate are most typically metabolized to MBP and MCPP, respectively<sup>37</sup>; yet, we could not examine all of the >15 metabolites of DEHP that have been identified. While dietary sources are likely to be the chief source of exposure, given the uses of DEHP in other products, we cannot rule out nondietary sources as contributors to the associations identified here. Given that LMW, but not HMW/DEHP metabolites, have been associated with obesity among children and adolescents,<sup>10,11</sup> DEHP exposures may act independently of increased body mass to produce insulin resistance, but further research is needed to interrogate mechanisms.

Phthalate exposure is measured at 1 time point in this analysis, and monoesters of phthalates are more typically known to have half-lives of 12 to 48 hours,<sup>38</sup> yet phthalates are known to deposit in fat, thereby

**FIGURE 1**

Metabolites of DEHP associated with insulin resistance, and pathways of metabolism and excretion.

lengthening half-life beyond that identified in the few adult pharmacokinetic studies.<sup>39</sup> Urinary phthalates are more likely to represent current as opposed to chronic exposure, although a single sample has moderate sensitivity (56% to 67%) and high specificity (83% to 87%) for MEHP, monobenzylphthalate, mono-ethyl phthalate, and MBP to estimate exposure tertile over a 3-month period.<sup>40</sup> Even if current urinary phthalates are weak indices of exposure, our estimates of association should be biased toward the null for dichotomous outcomes.<sup>41</sup>

Knowledge gaps also persist in understanding food contamination with

DEHP. A comprehensive review suggests that most studies are dated and may not represent current exposures.<sup>42</sup> Although further studies are needed, it should be noted that alternatives to DEHP include wax paper and aluminum wrap; indeed, a dietary intervention that introduced fresh foods that were not canned or packaged in plastic reduced DEHP metabolites by 53% to 56%.<sup>43</sup> Fresh fruit consumption may also reduce DEHP exposure, given reduced contact of plastic before consumption. Among 6- to 85-year-olds participating in NHANES 2003–2004, consumption of an additional ounce equivalent of fruit was associated with a 0.052

log unit decrease in DEHP metabolites.<sup>44</sup>

## CONCLUSIONS

We have identified a cross-sectional association of DEHP metabolite exposure with increased insulin resistance in a large sample of US children. Additional, longitudinal studies are needed, both to confirm the association and elaborate the different potential mechanisms involved.

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