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Research Article

Associations of Phthalate Exposure With Adiposity and Metabolic Syndrome in US Adolescents and Adults, NHANES 2013 to 2018

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Abstract

Context: Phthalates are ubiquitous endocrine-disrupting chemicals and suspected obesogens. However, the associations with fat distribution and associated cardiometabolic complications remain unclear.

Objective: We examined the associations between phthalate exposure, body fat (total and distribution patterns), and metabolic syndrome (MetS) among US adolescents and adults.

Methods: We analyzed cross-sectional data from 829 adolescents and 3905 adults in the 2013 to 2018 National Health and Nutrition Examination Survey. Total percentage body fat (%BF), visceral adipose tissue (VAT) mass, and android to gynoid (A/G) ratio were determined using dual-energy x-ray absorptiometry. Associations between molar sums of low molecular weight (∑LMW), high molecular weight (∑HMW), and di(2-ethylhexyl) phthalate (∑DEHP) metabolites, and adiposity indicators and MetS were analyzed with multivariable linear and logistic regressions. Models included sex interaction terms, were stratified by age group, and adjusted for relevant covariates.

Results: ∑HMW and ∑DEHP exposures were positively associated with %BF in males, and all phthalate groups were associated with greater VAT mass and A/G ratio in adolescent males. Five-fold increases in ∑HMW and ∑DEHP metabolites were associated with 21.7% (95% CI, 10.5-33.9) and 18.0% (95% CI, 7.72-29.2) greater VAT mass among adolescent males, respectively. Sex modified the relationship between ∑HMW exposure and A/G ratio among adolescents (interaction P value = .0185). Phthalates were not associated with odds of MetS. When assessing individual MetS components, phthalates were associated with hyperglycemia in adult males.

Conclusion: Greater exposure to phthalates was associated with greater %BF in all males, and with fat distribution in adolescent males; however, phthalates were not linked to MetS.

Key Words: phthalates, endocrine disruption, body fat, fat distribution, metabolic syndrome, NHANES

Abbreviations: %BF, percentage body fat; ∑DEHP, sum of di(2-ethylhexyl) phthalate metabolites; ∑HMW, sum of high molecular weight phthalate metabolites; ∑LMW, sum of low molecular weight phthalate metabolites; A/G ratio, android to gynoid ratio; BMI, body mass index; DEHP, di(2-ethylhexyl) phthalate; DXA, dual-energy x-ray absorptiometry; ETS, environmental tobacco smoke; GM, geometric mean; HDL-C, high-density lipoprotein cholesterol; LOD, limit of detection; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MCNP, monocarboxyisononyl phthalate; MCOP, monocarboxyisooctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MET, metabolic equivalent; MetS, metabolic syndrome; MHBP, mono(3-hydroxy-n-butyl) phthalate; MiBP, monoisobutyl phthalate; NCEP ATP III, National Cholesterol Education Program's Adult Treatment Panel III; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; P_{int}, P value for test of interaction between sex and phthalate group; PIR, income to poverty ratio; PPAR, peroxisome proliferator-activated receptor; VAT, visceral adipose tissue; WC, waist circumference.

The prevalence of obesity in the United States has nearly doubled over the last 4 decades among adults and adolescents [1]. Obesity is closely linked to metabolic syndrome (MetS), a clustering of cardiometabolic risk factors of which the most common is abdominal obesity [2], as determined by waist circumference (WC). Excess visceral adipose tissue (VAT), commonly identified as abdominal obesity, and MetS have been associated with cardiovascular disease risk [3, 4].

Obesity and MetS are complex health conditions linked to genetic and environmental factors [5]. Phthalates are one class of environmental endocrine-disrupting chemicals that have been associated, although inconsistently, with obesity [6] and MetS [7, 8]. Phthalates are used as plasticizers and solvents in polyvinyl chloride, personal care products, food packaging, and more [9]. These chemicals may alter lipid and carbohydrate metabolism and predispose individuals to gain excess weight through several pathways. Activation of

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peroxisome proliferator-activated receptors (PPARs) [10], important regulators of adipogenesis and energy metabolism, is the main pathway posited to link phthalate exposure and metabolic outcomes [11]. Phthalates may also promote obesity by inducing the production of reactive oxygen species, which can disrupt adipogenesis [12]. Further, phthalate exposures have been associated with methylation of environmentally responsive genes, *H19* and *HSD11B2* [13], which regulate growth and adiposity during development.

Epidemiological evidence has demonstrated a link between phthalates and crude indicators of adiposity, like body mass index (BMI), but studies that can better elucidate clinical risk by assessing fat deposition and metabolic dysfunction are needed. Previous studies using nationally representative data have demonstrated associations between exposure to certain phthalate metabolites and increased risk of overweight and obesity in children and adolescents [14-16], and adults [14, 15, 17], based only on BMI. Multiple analyses have also linked phthalate exposures and WC [14, 17, 18]. Three studies have examined associations between phthalates and body fat among adults from the National Health and Nutrition Examination Survey (NHANES) [19-21], but phthalates and dual-energy x-ray absorptiometry (DXA)-derived indicators of fat distribution have received little research attention. Only one prior NHANES analysis has examined the relationship between phthalate exposure and fat distribution using DXA, and the sample was limited to adults with overweight and obesity [20].

Measures of regional body fat distribution may be stronger correlates of cardiometabolic outcomes than total body fat. Android and gynoid fat distributions, and the ratio between the two (A/G ratio), have been associated with adverse cardiometabolic outcomes and increased disease risk [22]. Increased VAT and A/G ratio have been linked with MetS and individual cardiometabolic risk factors [23]. Additionally, some phthalate metabolites have been linked with MetS in some [7, 8, 24], but not all [25] NHANES studies. These studies, however, did not use the most recent NHANES cycles [8, 24, 25], or include age- [8, 24, 25] or sex-restricted [7] populations.

We sought to understand the cardiometabolic consequences of phthalates by examining associations between these chemicals, fat mass and distribution, and MetS. Furthermore, given the dynamic industrial use of phthalates, it is critical to use the most recent NHANES data to analyze these associations. Thus, the aims of this study were to investigate the associations of phthalate exposure with (1) adiposity (total percentage and distribution patterns) and (2) MetS in a nationally representative sample of US adolescents and adults. We hypothesized that phthalate exposure would be positively associated with total fat, harmful fat distribution patterns, and MetS, and that associations may differ by sex.

Materials and Methods

Study Population

We analyzed data from the 2013 to 2018 NHANES, a repeated cross-sectional survey of the noninstitutionalized US population. Participants eligible for this study included nonpregnant individuals with available urinary phthalate measurements and at least 1 day of dietary intake data. Additionally, for analyses of the association of phthalate exposure with adiposity, eligible participants included adolescents (aged 12-17 years) and adults (aged 18-59 years) with at least one of the following DXA-derived adiposity outcomes available: total percentage body fat (%BF), VAT mass, or A/G fat ratio (Fig. 1). DXA

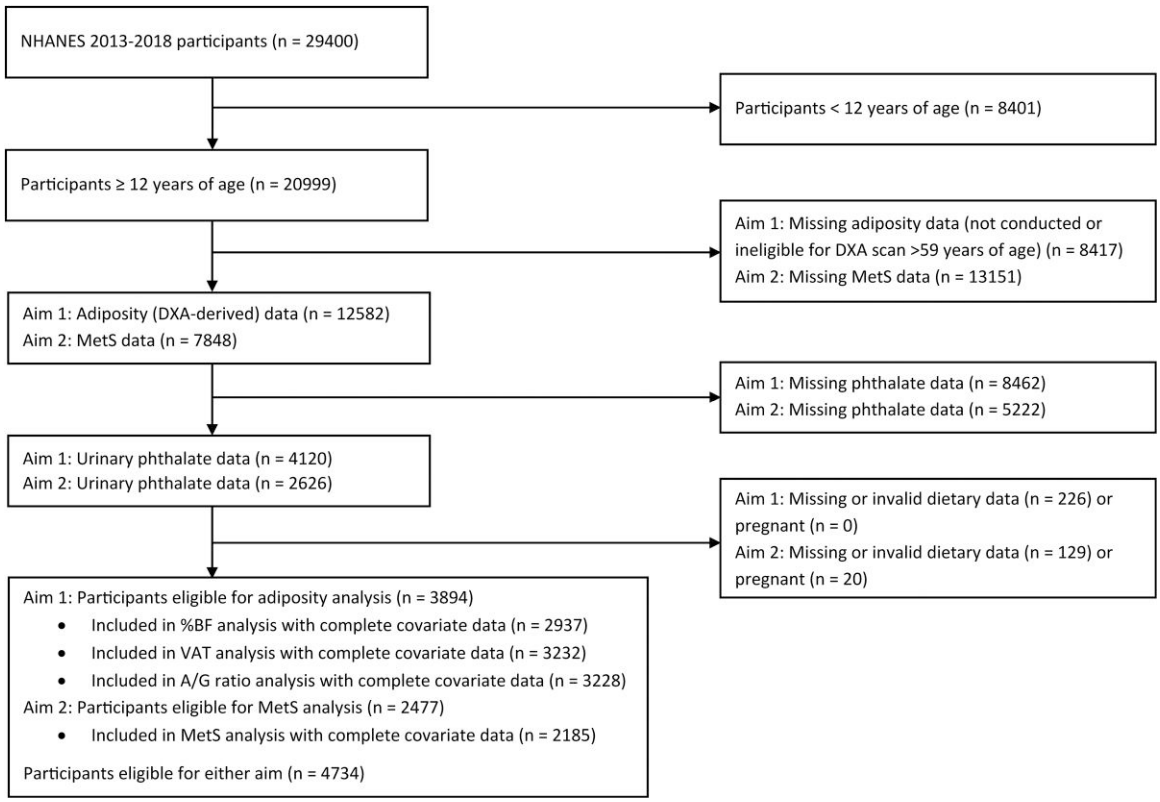

Figure 1. Flow diagram of eligible participants from NHANES 2013 to 2018.

Abbreviations: DXA, dual-energy x-ray absorptiometry; MetS, metabolic syndrome; NHANES, National Health and Nutrition Examination Survey.

scans were not completed on participants older than 59 years. Analyses of the association of phthalate exposure with MetS included individuals at least age 12 years and with valid data available for each MetS component (Fig. 1). Data on MetS components were collected in participants up to age 80 years. NHANES data collection was approved by the National Center for Health Statistics Ethics Review Board, and all NHANES participants provided informed consent.

Measurement of Urinary Phthalates

One-third of NHANES participants were randomly selected for urinary phthalate measurement. Spot urine specimens were frozen at −20 °C until analysis using high-performance liquid chromatography with tandem mass spectroscopy (US Centers for Disease Control and Prevention [26]). The limit of detection (LOD) for each metabolite analyzed was consistent across the 3 NHANES cycles examined (Supplementary Table S1 [27]).

Phthalate metabolites that were measured in all 3 survey cycles and those with at least 70% of sample concentrations above the LOD were included in this analysis: monoethyl phthalate (MEP), monobutyl phthalate (MBP), monoisobutyl phthalate (MiBP), mono(3-hydroxy-n-butyl) phthalate (MHBP), monobenzyl phthalate (MBzP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(3-carboxypropyl) phthalate (MCPP), monocarboxyisooctyl phthalate (MCOP), and monocarboxyisononyl phthalate (MCNP).

We grouped phthalate metabolites based on their parent compound as low molecular weight (LMW), high molecular weight (HMW), or di(2-ethylhexyl) phthalate (DEHP) metabolites. LMW phthalates often function as solvents and stabilizers in personal care products, while HMW phthalates are mainly used as plasticizers [9]. Primary routes of DEHP exposure include fast food [28], high-fat [29], and ultraprocessed foods [28]. In the present analysis, LMW phthalate metabolites included MEP, MBP, MiBP, and MHBP. DEHP metabolites included MEOHP, MEHHP, and MECPP, while HMW phthalate metabolites included the DEHP metabolites and MBzP, MCPP, MCOP, and MCNP. Phthalate metabolite concentrations below the LOD were imputed by NHANES as $LOD/\sqrt{2}$ [30].

Adiposity Assessment

Whole-body DXA scans were administered on Hologic Discovery A densitometers (Hologic Inc.) in a subset of participants aged 8 to 59 years. Total %BF was calculated as fat mass divided by total mass. Scan analysis defined VAT region as the interspace location of the L4 and L5 vertebra. The android and gynoid region lines were automatically placed at locations that have been described previously [31]. A/G ratio was calculated by dividing the android fat mass by the gynoid fat mass.

Metabolic Syndrome Assessment

MetS among adults was defined based on the National Cholesterol Education Program's Adult Treatment Panel III (NCEP) Report [32], while a modified version of the NCEP criteria, similar to that described by Cook et al [33], was adopted for adolescents. The thresholds for the individual MetS components (ie, abdominal obesity, elevated triglycerides, elevated blood pressure, low high-density lipoprotein cholesterol [HDL-C], elevated blood glucose) are provided in Supplementary Table S2 [27].

Assessment of Covariates

Covariates were selected a priori. Sociodemographic data including age, sex, race, ethnicity, education, and family income were self-reported. For adolescents, the educational attainment of an adult household reference person was used. Menopausal status was also self-reported.

Urinary creatinine concentration, determined with fluorescent immunoassay, was included in analyses to account for urinary dilution. Smoking status was classified based on serum cotinine levels as unexposed (<0.5 ng/mL), environmental tobacco smoke exposed (0.5-10 ng/mL), or active smoker (>10 ng/mL). Physical activity was assessed via questionnaires, and these data were summarized as continuous metabolic equivalent minutes for adults and as quartiles for adolescents, due to changes in the questionnaires used for adolescents across survey cycles. Adults self-reported time spent in sedentary activities. Screen time (hours of computer usage outside school and TV/videos watched per day) was used as a proxy for sedentary behavior among adolescents as total sedentary behavior was not assessed consistently across the 3 cycles.

Energy (kcal) and total fat intake (g) were derived from the average of two 24-hour dietary recalls. Fast-food intake (yes/no) was classified as intake of energy-containing food from a fast-food/pizza restaurant, sports/recreation/entertainment setting, or street vendor/vending truck. When only one 24-hour recall was available (13.2% of the eligible sample), it was used for assessment of dietary covariates.

Statistical Analysis

Descriptive data and model estimates were generated using SAS survey procedures to account for the complex sampling design.

Phthalate metabolite concentrations were natural log-transformed to normalize the right-skewed distributions. Weighted geometric means (GMs) were calculated to describe phthalate metabolite concentrations (nmol/mL) and creatinine-adjusted phthalate metabolite concentrations (nmol/mg Cr) in the sample and across levels of covariates and outcomes (Table 1 and Supplementary Table S3 [27], respectively).

We used multivariable linear and logistic regression models to evaluate associations of phthalate metabolites (continuous) with adiposity outcomes (continuous) and MetS (binary), respectively. Because phthalates may exert sex- and age-specific effects [15], we included product terms for sex and stratified by age group (ie, adolescents, adults). We used the augmented product term approach described by Buckley, so that models included a product term between sex and each other covariate, including phthalates [34]. Estimated β coefficients and 95% CIs were generated. Minimal models (model 1) were adjusted for urinary creatinine concentrations (continuous), age (continuous), and sex (male/female) while full models (model 2) were additionally adjusted for race and ethnicity (categorical), family income to poverty ratio (PIR) (continuous), educational attainment (categorical), smoking status (categorical), physical activity (adults: continuous; adolescents: categorical), sedentary behavior (adults; continuous), screen time (adolescents; continuous), energy intake (continuous), menopause status (adults; premenopausal/postmenopausal) and survey cycle (categorical). For logistic regression, the same covariates

Table 1. Geometric mean urinary molar concentrations of phthalates among US adolescents and adults included in analyses, NHANES 2013 to 2018

Characteristic	N (weighted %)	GM (SE), nmol/mL		
		∑LMW metabolites	∑HMW metabolites	∑DEHP metabolites
All	4734	0.285 (0.009)	0.141 (0.004)	0.056 (0.001)
Sex				
Male	2331 (50.1)	0.275 (0.009)	0.151 (0.006)	0.060 (0.002)
Female	2403 (49.9)	0.295 (0.013)	0.131 (0.004)	0.053 (0.001)
Age, y				
12-17	829 (11.2)	0.292 (0.019)	0.167 (0.008)	0.065 (0.003)
18-59	3190 (75.1)	0.281 (0.009)	0.140 (0.005)	0.055 (0.002)
≥60	715 (13.8)	0.300 (0.019)	0.125 (0.006)	0.055 (0.003)
Race and ethnicity				
Hispanic	1271 (17.2)	0.361 (0.022)	0.147 (0.008)	0.062 (0.003)
Non-Hispanic Black	1069 (11.7)	0.557 (0.026)	0.179 (0.010)	0.071 (0.003)
Non-Hispanic White	1632 (62.1)	0.240 (0.008)	0.136 (0.005)	0.053 (0.001)
Non-Hispanic Asian	549 (5.0)	0.227 (0.019)	0.112 (0.006)	0.050 (0.002)
Other, including multiracial	213 (4.0)	0.307 (0.043)	0.131 (0.014)	0.056 (0.005)
Poverty-income ratio[a]				
<1.3	1446 (22.6)	0.359 (0.020)	0.169 (0.008)	0.067 (0.002)
1.3-1.84	556 (10.5)	0.305 (0.020)	0.151 (0.010)	0.063 (0.004)
1.85-3.49	1029 (24.1)	0.302 (0.018)	0.151 (0.008)	0.058 (0.002)
3.5+	1263 (42.8)	0.234 (0.010)	0.121 (0.006)	0.048 (0.002)
Education level[b]				
<HS degree	966 (13.4)	0.364 (0.019)	0.160 (0.007)	0.066 (0.002)
HS/Some college/AA degree	2591 (55.8)	0.296 (0.011)	0.146 (0.006)	0.058 (0.002)
≥College graduate	1138 (30.8)	0.240 (0.014)	0.123 (0.006)	0.049 (0.002)
Serum cotinine, ng/mL				
Unexposed, <0.5	3213 (70.9)	0.271 (0.011)	0.134 (0.005)	0.053 (0.001)
ETS exposed, 0.5-10	318 (6.1)	0.356 (0.035)	0.180 (0.013)	0.074 (0.005)
Active smoker, >10	1014 (23.1)	0.306 (0.017)	0.148 (0.008)	0.059 (0.003)
Adolescent physical activity				
Q1	219 (27.4)	0.268 (0.031)	0.154 (0.012)	0.061 (0.005)
Q2	181 (21.9)	0.313 (0.050)	0.164 (0.019)	0.062 (0.006)
Q3	223 (27.7)	0.296 (0.038)	0.165 (0.016)	0.066 (0.006)
Q4	194 (23.0)	0.300 (0.030)	0.191 (0.018)	0.075 (0.006)
Adult physical activity				
Q1	974 (21.6)	0.281 (0.020)	0.131 (0.007)	0.054 (0.002)
Q2	986 (25.5)	0.271 (0.017)	0.149 (0.008)	0.058 (0.003)
Q3	967 (28.5)	0.303 (0.013)	0.126 (0.007)	0.051 (0.002)
Q4	977 (24.4)	0.279 (0.015)	0.147 (0.006)	0.058 (0.003)
Adolescent screen time				
Q1	210 (26.5)	0.284 (0.031)	0.169 (0.016)	0.067 (0.005)
Q2	185 (21.2)	0.298 (0.027)	0.184 (0.014)	0.070 (0.005)
Q3	201 (24.6)	0.293 (0.045)	0.159 (0.019)	0.057 (0.006)
Q4	222 (27.7)	0.295 (0.030)	0.159 (0.011)	0.068 (0.005)
Sedentary behavior, min/wk				
Q1	941 (21.7)	0.300 (0.014)	0.134 (0.007)	0.056 (0.002)
Q2	953 (25.1)	0.285 (0.018)	0.130 (0.007)	0.053 (0.002)
Q3	1155 (29.8)	0.297 (0.018)	0.140 (0.007)	0.055 (0.002)
Q4	835 (23.4)	0.257 (0.013)	0.147 (0.010)	0.056 (0.003)

(*continued*)

Table 1. Continued

Characteristic	N (weighted %)	GM (SE), nmol/mL		
		∑LMW metabolites	∑HMW metabolites	∑DEHP metabolites
Total % body fat[c]				
Obesity	1766 (51.1)	0.307 (0.013)	0.149 (0.007)	0.058 (0.002)
No obesity	1737 (48.9)	0.251 (0.011)	0.135 (0.006)	0.053 (0.002)
Visceral adipose tissue mass[c]				
Above optimal	1497 (42.8)	0.293 (0.017)	0.152 (0.007)	0.059 (0.002)
Optimal	2347 (57.2)	0.271 (0.011)	0.137 (0.005)	0.054 (0.002)
Android/gynoid ratio				
>1.0 (males) or >0.8 (females)	2600 (68.7)	0.288 (0.012)	0.145 (0.006)	0.057 (0.002)
≤1.0 males or ≤0.8 (females)	1239 (31.3)	0.266 (0.011)	0.141 (0.006)	0.055 (0.002)
Metabolic syndrome[d]				
Yes	846 (34.3)	0.310 (0.018)	0.155 (0.009)	0.061 (0.003)
No	1631 (65.7)	0.297 (0.012)	0.143 (0.006)	0.056 (0.002)

Abbreviations: ΣDEHP, sum of di(2-ethylhexyl) phthalate metabolites; ΣHMW, sum of high molecular weight phthalate metabolites; ΣLMW, sum of low molecular weight phthalate metabolites; GM, geometric mean; NHANES, National Health and Nutrition Examination Survey.
[a]Poverty to income ratio compares family income to US census-defined poverty levels; a value of 1.0 indicates the federal poverty threshold and above 1.0 indicates family income above poverty.
[b]Education level refers to an individual's educational attainment for participants aged 20 years and older, or as the educational attainment of the head of household for participants younger than 20 years.
[c]Obesity and optimal/above optimal categorizations were based on total percentage fat and visceral adipose tissue cut points published by the Obesity Medicine Association.
[d]Metabolic syndrome was defined by the National Cholesterol Education Program's Adult Treatment Panel III criteria (adults), or a modified version of these criteria (adolescents).

were included in the models for adults and estimated odds ratios (ORs) and 95% CIs were generated. Due to the limited number of eligible adolescents with MetS, categorical covariates were modified to reach model convergence and generate valid maximum likelihood estimates. Namely, education was removed as a covariate and levels of the remaining categorical variables were collapsed. Model fit was assessed using the Akaike information criterion and through visual inspection of residuals.

An exploratory post hoc analysis was performed to assess the relationship between phthalates and the presence of individual MetS components among adults. Multivariable logistic regression models were constructed as described earlier. The Benjamini-Hochberg procedure with a false discovery rate of 0.1 was used to adjust for multiple comparisons [35].

We conducted sensitivity analyses to evaluate the potential for confounding by dietary fat (continuous) or fast-food intake (binary), given that high-fat [29] and fast foods [28] are important sources of phthalate exposure and associated with excess adiposity and MetS.

All hypothesis tests were 2-tailed, and those with P values less than .05 were considered statistically significant. All statistical analyses were conducted with SAS v9.4 (SAS Institute Inc).

Results

Phthalate Exposure

The final eligible sample for either aim included 829 adolescents and 3905 adults, yielding a total of 4734 participants (Fig. 1). Nine out of 11 metabolites were detected in more than 90% of participants (Supplementary Table S1 [27]). GMs of phthalate metabolite concentrations (nmol/mL) among the overall eligible sample were highest for ∑LMW (GM = 0.285, SE = 0.009), followed by ∑HMW (GM = 0.141, SE = 0.004), and ∑DEHP (GM= 0.056, SE = 0.001) (Table 1). Higher concentrations of ∑HMW phthalates and ∑DEHP metabolites were observed among adolescents compared with adults. Non-Hispanic Black participants appeared to have higher exposure levels than Hispanic, White, and Asian participants for all phthalate groups. Participants with the lowest socioeconomic status, as indicated by PIR and education level, appeared to have the greatest exposures to all phthalate groups.

Associations Between Phthalate Exposure and Adiposity

A total of 814 adolescents and 3080 adults met the inclusion criteria for our analysis of phthalate exposure and adiposity. Based on Obesity Medicine Association guidelines, 51.1% of participants had obesity according to total %BF (females: ≥35%; males: ≥30%), while 42.8% of participants had above optimal VAT (≥1 pound) [36]. More than two-thirds (68.7%) of participants had A/G ratios greater than 1.0 (males) or greater than 0.8 (females) (Table 1).

To convert regression results to interpretable measures, we computed unit increases in total %BF and A/G ratio, and percentage increases in VAT mass for 5-fold increases in the exposures. A 5-fold increase in exposure to ∑HMW phthalates was associated with 2.86 (95% CI, 0.69-5.03) and 1.23 (95% CI, 0.47-1.99) unit increases in total %BF in adolescent and adult males, respectively (Fig. 2A; Supplementary Table S4 [27]). Similar increases were seen for DEHP, as 5-fold increases in ∑DEHP exposures were associated with 2.69 (adolescent males; 95% CI, 0.66-4.72) and 1.03 (adult males; 95% CI, 0.27-1.79) unit increases in total %BF (Fig. 2A). When assessing phthalate exposure and fat distribution, a 5-fold increase in ∑HMW phthalate exposure was associated with 21.7%

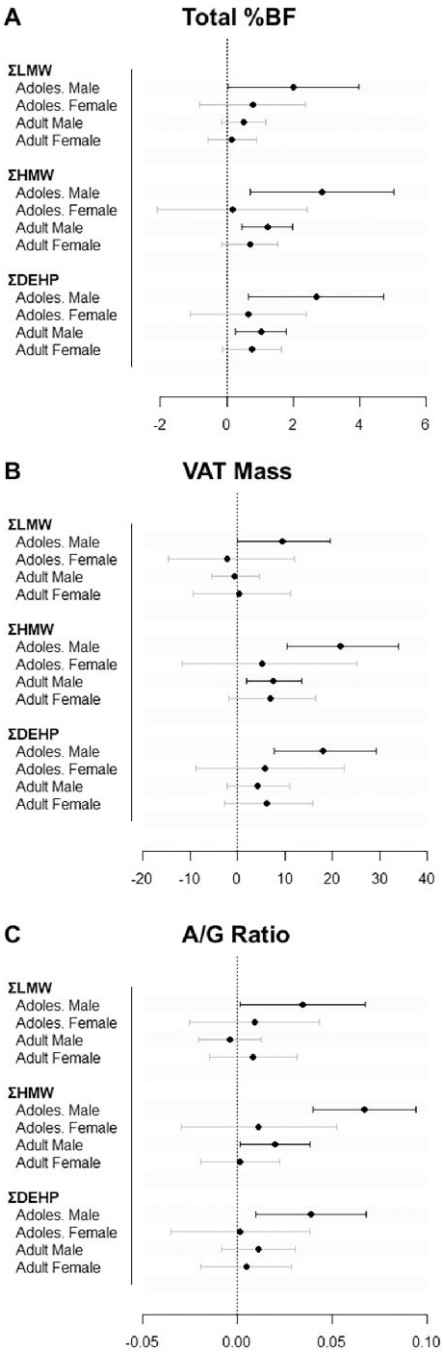

Figure 2. Adjusted associations (β [95% CI]) for A, total percentage body fat; B, visceral adipose tissue mass (% change); and C, android to gynoid ratio per 5-fold increases in urinary phthalate metabolites (ΣLMW, ΣHMW, ΣDEHP), NHANES 2013 to 2018. Multivariable regression models adjusted for urinary creatinine (continuous), age (continuous), sex (male/female), poverty income ratio (continuous), educational attainment (<high school, high school/some college/associates degree, ≥college graduate), energy intake (continuous), physical activity (adults: continuous; adolescents: categorical), sedentary behavior (adults; continuous), screen time (adolescents; continuous), race and ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Non-Hispanic Asian, Other (including multiracial)), smoking status (unexposed, ETS exposed, active smoker), menopause status (adults; premenopausal/postmenopausal), and survey year (2013-2014, 2015-2016, 2017-2018).

Abbreviations: β, regression coefficient; ΣDEHP, sum of di(2-ethylhexyl) phthalate metabolites; ΣHMW, sum of high molecular weight phthalate metabolites; ΣLMW, sum of low molecular weight phthalate metabolites; %BF, percentage body fat; A/G, android to gynoid fat ratio; ETS, environmental tobacco smoke; NHANES, National Health and Nutrition Examination Survey; *P*-int, *P* value for test of interaction between sex and phthalate group; VAT, visceral adipose tissue.

(adolescent males; 95% CI, 10.5-33.9) and 7.51% (adult males; 95% CI, 1.81-13.5) increases in VAT mass (Fig. 2B), and with 0.07 (adolescent males; 95% CI, 0.04-0.09) and 0.02 (adult males; 95% CI, 0.00-0.04) unit increases in A/G ratio (Fig. 2C). Five-fold increases in ∑DEHP exposure were also associated with statistically significant percentage increases in VAT mass (β = 18.0; 95% CI, 7.72-29.2) (Fig. 2B) and A/G ratio (β = 0.04; 95% CI, 0.01-0.07) (Fig. 2C) in adolescent males. Associations between ∑LMW phthalate metabolites and adiposity were detected only among adolescent males (%BF: β = 2.01; 95% CI, 0.05-3.98) (Fig. 2A); (VAT: β = 9.38; 95% CI, 0.01-19.6) (Fig. 2B); and (A/G ratio: β = 0.03; 95% CI, 0.00-0.07) (Fig. 2C). No statistically significant associations were observed among adolescent or adult females in the fully adjusted models. However, there was a significant sex interaction between ∑HMW phthalate metabolites and A/G ratio (P_{int} = .0185) among adolescents (Supplementary Table S4).

The associations between phthalate exposure and adiposity were robust to the addition of fast food (Supplementary Table S5 [27]), total fat (Supplementary Table S6 [27]), or both of these dietary factors (Supplementary Table S7 [27]) to the models.

Associations Between Phthalate Exposure and Metabolic Syndrome

We assessed associations of phthalate exposures with MetS among 324 adolescents and 2153 adults. The overall prevalence of MetS was 34.3% (Table 1). Phthalate exposure was not associated with MetS among adults in any fully adjusted model (Table 2), and there was no evidence of interaction by sex (P_{int} > .05). Additional adjustment for fast food and/or total fat intake did not modify these associations (Supplementary Table S8 [27]). However, the post hoc analysis revealed statistically significant associations between certain phthalates and some MetS components (Table 3).

Positive associations between ∑LMW phthalate and ∑DEHP metabolites and hyperglycemia in adult males (OR: 1.55; 95% CI, 1.14-2.11 for ∑LMW; OR: 1.96; 95% CI, 1.33-2.88 for ∑DEHP) and an inverse association between ∑LMW phthalate metabolites and hypertriglyceridemia in adult males (OR: 0.58; 95% CI, 0.39-0.86) remained statistically significant after adjustment for multiple comparisons (Table 3). Positive associations between ∑HMW phthalate exposure and hyperglycemia (OR: 1.60; 95% CI, 1.06-2.43) and ∑DEHP exposure and abdominal obesity (OR: 1.60; 95% CI, 1.03-2.48) in adult males, and between ∑HMW phthalate metabolites and hypertriglyceridemia in adult females (OR: 1.58; 95% CI, 1.09-2.30) did not remain statistically significant after Benjamini-Hochberg correction (Table 3). Sensitivity analyses revealed that associations between phthalate metabolites and MetS components were not altered by the inclusion of additional dietary covariates (Supplementary Tables S9-S13 [27]). Among adults, associations between ∑LMW phthalate metabolites and hypertriglyceridemia and hyperglycemia were modified by sex (P_{int} = .0070; P_{int} = .0323, respectively) (Table 3).

The analysis of MetS in adolescents, which relied on a small number of MetS cases and used a reduced and collapsed set of covariates, suggested that a 5-fold increase in ∑LMW exposure was positively associated with MetS among adolescent males (OR: 2.99; 95% CI, 1.11-8.05) (Supplementary Table S14 [27]). Five-fold increases in ∑HMW and ∑DEHP exposures

Table 2. Associations between 5-fold increases in natural log-transformed urinary phthalate metabolite concentrations and metabolic syndrome (odds ratio [95% CI]) among US adults, NHANES 2013 to 2018

	Model 1[a]	Sex P_{int}	Model 2[b]	Sex P_{int}
Adult male	N = 1027 (LMW); N = 1053 (HMW/DEHP)		N = 928 (LMW); N = 952 (HMW/DEHP)	
∑LMW metabolites	0.91 (0.66-1.26)	.3606	0.95 (0.68-1.33)	.4134
∑HMW metabolites	1.31 (0.90-1.90)	.6930	1.30 (0.89-1.89)	.8639
∑DEHP metabolites	1.39 (0.89-2.17)	.9389	1.27 (0.79-2.03)	.7695
Adult female	N = 1070 (LMW); N = 1099 (HMW/DEHP)		N = 908 (LMW); N = 934 (HMW/DEHP)	
∑LMW metabolites	1.11 (0.83-1.47)		1.14 (0.82-1.59)	
∑HMW metabolites	1.44 (1.02-2.03)*		1.36 (0.92-2.02)	
∑DEHP metabolites	1.36 (0.91-2.02)		1.15 (0.73-1.80)	

Abbreviations: ΣDEHP, sum of di(2-ethylhexyl) phthalate metabolites; ΣHMW, sum of high molecular weight phthalate metabolites; ΣLMW, sum of low molecular weight phthalate metabolites; NHANES, National Health and Nutrition Examination Survey.
*$P < .05$.
[a]Model 1 was adjusted for urinary creatinine (continuous), age (continuous), and sex (male/female).
[b]Model 2 was adjusted for urinary creatinine (continuous), age (continuous), sex (male/female), poverty income ratio (continuous), educational attainment (<high school, high school/some college/associates degree, ≥college graduate), energy intake (continuous), physical activity (continuous), sedentary behavior (continuous), race and ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Non-Hispanic Asian, Other [including multi-racial]), smoking status (unexposed, ETS exposed, active smoker), menopause status (premenopausal/postmenopausal), and survey year (2013-2014, 2015-2016, 2017-2018).

were associated with lower odds of MetS in adolescent females (∑HMW: OR: 0.04; 95% CI, 0.00-0.76; ∑DEHP: OR: 0.10; 95% CI, 0.02-0.50), but similar patterns were not observed among adolescent males (∑HMW: $P_{int} = .0089$; ∑DEHP: $P_{int} = .0058$) (Supplementary Table S14 [27]).

Discussion

In this cross-sectional analysis, we observed positive associations between phthalate exposures and total %BF, VAT mass, and A/G ratio, primarily in adolescent males. Although phthalate exposures were not significantly associated with MetS in adults, phthalates were associated with some individual MetS components, particularly hyperglycemia among adult males. Associations observed between phthalate exposure and MetS in adolescents should be interpreted with caution due to the small number of cases and the model covariate limitations required to achieve model convergence.

Our results build on previous NHANES analyses examining associations of phthalate exposure with total body fat [19, 21] and abdominal fat indices [20] in US adults. Consistent with our findings, Wang et al [19] detected positive associations between DEHP metabolites and bioelectrical impedance analysis–derived estimates of fat mass and %BF. Corbasson et al [21] found positive associations between MEP and MBzP and DXA-derived %BF, but found no associations in fully adjusted models with MEHP, the sole DEHP metabolite examined. In US adults with overweight and obesity, Shi and colleagues [20] reported positive associations between MBzP and total abdominal fat index in females, while ∑DEHP metabolites were linked to higher total abdominal and visceral fat indices in males. The present findings expand on previous NHANES analyses linking specific phthalate metabolites to crude body fat approximations, including BMI and WC in children and adolescents [14, 16] and adult males [14, 17]. These studies generally demonstrated more consistent positive associations among HMW (eg, MBzP, MEHHP) compared to LMW (eg, MBP) phthalate metabolites.

Several studies conducted outside the United States have also observed positive associations between phthalates and obesity in adults [37, 38] and children and adolescents [39, 40], yet not all detected statistically significant associations [41]. MEP [14, 17, 40], MBzP [14, 17], and MEHHP [14, 17] are among the metabolites most consistently linked with obesity, classified using BMI. A minority of studies have evaluated relationships of phthalate exposure with more direct adiposity measures [37, 39, 42-44]. Zhang et al [42] found positive associations between MBP and LMW phthalate metabolites and %BF among Chinese children, while Silva et al [44] reported higher di-n-octyl phthalate metabolites were associated with greater fat mass index in Dutch children. Contrary to our analysis, which observed phthalate-adiposity associations only among males, in a longitudinal study of midlife women, phthalate exposure was associated with faster increases in %BF [43].

This is one of the first studies to investigate associations between phthalate exposure and DXA-derived regional adipose tissue deposition in a nationally representative sample of adolescents and adults. One previous study restricted to Swedish 70-years-olds investigated the relationship between phthalate exposure and fat distribution using DXA and magnetic resonance imaging [37]. In women, MiBP was associated with greater total and trunk fat, while MMP was linked to greater trunk fat and trunk fat to leg fat ratio. Significant positive associations between MEP and VAT were reported in males. Similarly, we found that phthalate exposure was associated with greater A/G ratio and VAT, particularly among adolescent males.

There are several mechanisms through which phthalate exposure may be linked to obesity, including activation of PPARs [10], dysregulation of sex and thyroid hormones [45], promotion of oxidative stress, and epigenetic changes (eg, DNA methylation) [13]. Many phthalate metabolites activate PPARα and PPARγ [10], nuclear receptors that serve key roles in the regulation of lipid and glucose metabolism, adipogenesis, and lipid accumulation [11]. Specific phthalate monoesters (ie, MBP, MEHP, MBzP) activate PPARγ [10] and promote lipid storage in preadipocytes. Inappropriate PPAR activation can impair the metabolism of sex hormones [46] and alter the physiological function of the hormones, contributing to increased adiposity.

In vitro, in vivo, and cross-sectional studies provide evidence of the antiandrogenic effects of phthalates. Phthalate diesters with moderate-length side chains (ie, 3-6 C) demonstrated human androgen receptor–mediated antiandrogenic activities

Table 3. Associations between 5-fold increases in natural log-transformed urinary phthalate metabolite concentrations and metabolic syndrome components (odds ratio [95% CI]) among US adults, NHANES 2013 to 2018[a]

	Abdominal obesity[b]	Sex P_{int}	Hypertriglyceridemia[c]	Sex P_{int}	Hypertension[d]	Sex P_{int}	Low HDL-C[e]	Sex P_{int}	Hyperglycemia[f]	Sex P_{int}
Adult male N = 928 (LMW); N = 952 (HMW/DEHP)										
∑LMW metabolites	1.25 (0.95-1.65)	.4790	0.58 (0.39-0.86)[h]	.0070	1.22 (0.86-1.73)	.6488	0.92 (0.68-1.25)	.8591	1.55 (1.14-2.11)[h]	.0323
∑HMW metabolites	1.37 (0.91-2.07)	.5564	0.92 (0.65-1.32)	.0577	1.27 (0.76-2.13)	.2802	1.11 (0.77-1.60)	.4869	1.60 (1.06-2.43)[g]	.2873
∑DEHP metabolites	1.60 (1.03-2.48)[g]	.6026	0.85 (0.56-1.27)	.2939	1.42 (0.80-2.54)	.2041	1.04 (0.66-1.64)	.6627	1.96 (1.33-2.88)[h]	.1988
Adult female N = 908 (LMW); N = 934 (HMW/DEHP)										
∑LMW metabolites	1.06 (0.76-1.48)		1.29 (0.85-1.95)		1.09 (0.74-1.62)		0.89 (0.67-1.18)		0.96 (0.67-1.39)	
∑HMW metabolites	1.65 (0.97-2.80)		1.58 (1.09-2.30)[g]		0.87 (0.55-1.36)		1.31 (0.86-1.98)		1.19 (0.77-1.83)	
∑DEHP metabolites	1.35 (0.81-2.24)		1.21 (0.75-1.95)		0.81 (0.47-1.40)		1.19 (0.72-1.99)		1.30 (0.80-2.10)	

Abbreviations: ΣDEHP, sum of DEHP metabolites; ΣHMW, sum of high molecular weight phthalate metabolites; ΣLMW, sum of low molecular weight phthalate metabolites; HDL-C, high-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey.

[a]Models were adjusted for urinary creatinine (continuous), age (continuous), sex (male/female), poverty income ratio (continuous), educational attainment (less than high school, high school/some college/associates degree, college graduate or above), energy intake (continuous), physical activity (continuous), sedentary behavior (continuous), race and ethnicity (Hispanic, Non-Hispanic Black, Non-Hispanic White, Non-Hispanic Asian, Other [including multi-racial]), smoking status (unexposed, ETS exposed, active smoker), menopause status (premenopausal/postmenopausal), and survey year (2013-2014, 2015-2016, 2017-2018).

[b]Abdominal obesity was defined as waist circumference greater than or equal to 102 cm in males or greater than or equal to 88 cm in females.

[c]Hypertriglyceridemia was defined as plasma triglycerides of 150 mg/dL or greater, or taking medication to manage high triglycerides.

[d]Hypertension was defined as systolic blood pressure of 130 mm Hg or greater, or diastolic blood pressure 85 mm Hg or greater, or taking medication to manage high blood pressure.

[e]Low HDL-C was defined as HDL-C less than 40 mg/dL in males or less than 50 mg/dL in females.

[f]Hyperglycemia was defined as fasting plasma glucose of 100 mg/dL or greater, or taking medication to manage elevated glucose.

[g]Statistically significant ($P < .05$) without correction.

[h]Statistically significant with Benjamini-Hochberg correction.

[47]. Some phthalates (dicylohexyl phthalate, benzylbutyl phthalate, dipentyl phthalate, diisohexyl phthalate, dihexyl phthalate, and diisoheptyl phthalate) demonstrated both antiandrogenic and weakly estrogenic properties [47]. Phthalates inhibited testosterone biosynthesis in vitro in human testis [48]. In vivo, phthalates can decrease testosterone levels and alter sexual differentiation [49]. Epidemiological studies have also demonstrated associations between androgen dysregulation, particularly decreased testosterone, and obesity and MetS in men [50]. These antiandrogenic effects of phthalates, coupled with the differences in levels of endogenous sex hormones, may explain some of the male-only associations of phthalate exposures with adiposity observed in this analysis. Differences by sex have been observed in some [14, 15], but not all [16, 40], prior epidemiological studies. Buser et al [15] reported a similar pattern of sex-specific associations for LMW metabolites whereby LMW metabolites were associated with obesity in adolescent males, but not among adolescent females. However, others have observed significant positive [14, 39, 40] and inverse associations [14] among younger female populations. Methodological differences related to age, metabolites assessed, and categorization of metabolites may have contributed to these discrepancies. Furthermore, the small size of the adolescent female sample in our study may have also contributed to the null findings in this group.

Although phthalate exposure was positively associated with VAT in the present study and individuals with elevated VAT are prone to cardiometabolic complications [3], phthalate exposure was not associated with MetS prevalence in adults. However, our findings suggested a possible association between phthalate exposure and higher odds of MetS in adolescents and positive and negative associations with hyperglycemia and hypertriglyceridemia, respectively, among adults. We may have observed the inverse association between ∑LMW metabolites and hypertriglyceridemia in males because some LMW phthalates, like MBP, can activate PPARγ [10], which can increase triglyceride clearance [51]. Gaston and Tulve [25] observed no significant associations between phthalate metabolites and MetS prevalence, but similarly found associations between certain phthalate metabolites and individual MetS components, although the analysis was conducted among adolescents from NHANES 2003 to 2014. Two other studies linked ΣDEHP exposure with increased odds of MetS, but only among subsets of the populations analyzed, namely males [8] and White males [24]. Dubey et al [7] conducted an analysis of females in NHANES and found that exposure to the highest tertile of some HMW phthalate metabolites (MECPP, MEOHP, MEHHP, and MBzP) was associated with MetS, but not after adjusting for multiple comparisons. James-Todd et al [8] also found higher levels of MBzP to be associated with a greater odds of MetS in the overall analysis, but only in females when stratifying by sex. Furthermore, in contrast to these previous analyses [7, 8, 24, 25], which categorized phthalate exposure in quantiles, our study used continuous phthalate measurements. Overall, significant findings in previous analyses have been largely limited to certain individual phthalate metabolites and exposure quantiles, lacking consistent evidence of dose-dependent associations.

The present study has several limitations. The cross-sectional nature of this analysis limits our ability to assess the temporality and causality of the relationship between phthalate exposure and adiposity. Additionally, phthalate exposure assessment relied on a single spot-urine collection. Repeated measurements would be optimal for assessing usual exposure. However, single urine samples can predict 3-month average exposure assessed via repeated urine sampling [52]. Nonetheless, it is possible that nondifferential misclassification of phthalate exposure may have occurred, potentially resulting in bias toward the null. Residual confounding may also affect our results. For example, we were unable to include participant occupation given the lack of these data in the latest NHANES cycles. Job-related physical activity (or inactivity) may be linked to the outcomes examined. However, the physical activity covariate included in our analyses included adults' work-related and recreational activities. Furthermore, the lack of comprehensive dietary data may confound the association between phthalate exposure and adiposity.

Despite these limitations, our study has several strengths. First, this study was unique in that we explored the association between phthalate exposures and multiple DXA-derived adiposity outcomes in a nationally representative sample of adolescents and adults. The few studies that have assessed phthalate exposure and specific adiposity distribution outcomes have been limited to specific groups of children and women in Europe [37, 44] and Asia [39, 42]. These regional and total adiposity measurements, which are known to be associated with adverse cardiometabolic outcomes, may provide a more nuanced understanding of the relationship between phthalates and obesity compared to BMI-based assessments. Additionally, the ascertainment of MetS components in the present study was rigorous; we used the comprehensive measurement, biomarker, and medication data collected in NHANES and applied special criteria for adolescents compared to adults.

In this cross-sectional analysis, exposure to certain phthalate metabolites was associated with increased adipose tissue and with adverse patterns of fat distribution, marked by increased VAT and A/G ratio. The strongest associations were observed for HMW phthalate metabolites and DEHP metabolites among adolescent males. Among adults, we also found associations between phthalate exposure and some components of MetS, yet phthalates were not associated with overall MetS prevalence. Future prospective studies are needed to corroborate the association between phthalate exposure and the development of harmful adipose distribution patterns.

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Author Contributions

M.D.W.: methodology, software, formal analysis, writing—original draft, visualization, and writing—review and editing; J.W.P.: methodology and writing—review and editing; D.B.D.: methodology and writing—review and editing; J.C.T.: writing—review and editing; S.S.: writing—review and editing; and M.M.M.: conceptualization, methodology, writing—review and editing, supervision.

Disclosures

The authors have nothing to disclose.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in "References."

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