International Journal of Hygiene and Environmental Health 222 (2019) 195–204

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Urinary phthalate metabolites and metabolic syndrome in U.S. adolescents: Cross-sectional results from the National Health and Nutrition Examination Survey (2003–2014) data

Symielle A. Gaston[a,*,1], Nicolle S. Tulve[b]

[a] ORISE Postdoctoral Participant, U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, 109 T.W. Alexander Drive, Research Triangle Park, NC, 27711, USA

[b] U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, 109 T.W. Alexander Drive, Research Triangle Park, NC, 27711, USA

ARTICLE INFO

Keywords:
Metabolic syndrome
Phthalates
Adolescent
Socioeconomic status

Chemical compounds studied in this article:
Di(2-ethylhexyl phthalate) (PubChem CID 8343)
Mono-(3-carboxypropyl) phthalate (PubChem CID 53435014)
Monobenzyl phthalate (PubChem CID 31736)
Monoethyl phthalate (PubChem CID 75318)
Monoisobutyl phthalate (PubChem CID 92272)
Mono-n-butyl phthalate (PubChem CID 8575)

ABSTRACT

Objective: There is limited research on the association between phthalates and metabolic syndrome (MetS). Among adolescents, phthalate exposure, which can occur from multiple sources, has been linked to several risk factors for MetS. The objective was to investigate the association between urinary phthalate metabolite concentrations (i.e., monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP), mono-(3-carboxylpropyl) phthalate (MCPP), and di(2-ethylhexyl phthalate (DEHP)) and MetS in adolescents aged 12–19 years using the National Health and Nutrition Examination Survey (NHANES) data (2003–2014). A secondary aim was to assess if observed associations varied by a measure of socioeconomic status, economic adversity, which was defined using parental income and educational attainment as well as household food security.

Methods: We used NHANES data which included physical examination, laboratory urinalysis and fasting blood profiles, and self-reported health characteristics and demographics. Physical examination and laboratory data were used to obtain values of MetS components and urinary phthalate metabolites. We created age-, sex-, and survey year-specific tertiles of creatinine-corrected urinary phthalate metabolites. Analysis was performed using appropriate weighting procedures that accounted for NHANES' complex sampling design. After univariate and bivariate analyses, we performed adjusted logistic regressions to test for associations between individual phthalate metabolites and MetS as well as MetS components and number of MetS components, separately, using the lowest tertile as the reference category. A cross-product term (phthalate metabolite*economic adversity) was subsequently added to adjusted models.

Results: Among 918 participants (mean age 16 years, 45% female, 18% with economic adversity), the prevalence of MetS was 5.3%. Prior to adjustment, adolescents with MetS had marginally higher concentrations of phthalate metabolites than adolescents without MetS. There was a suggestive positive association between intermediate concentrations of MnBP and odds of MetS after adjustment (T2: Odds Ratio (OR) = 2.66 (95% confidence interval: 0.98–7.24); T3: OR = 2.11 (0.71–6.27)). Males with higher MnBP concentrations had higher odds of dyslipidemia; however, associations were mostly non-significant for females. Relationships between MiBP concentrations and odds of MetS varied by sex. Males with higher concentrations of MnBP and MiBP had greater odds of having a higher number of MetS components. Relationships between phthalate metabolites and MetS did not vary by economic adversity.

Conclusion: There was a suggestive positive association between MnBP and MetS among adolescents. Associations between phthalate metabolites and MetS as well as MetS components may vary by sex, but may not vary by economic adversity. Further research of the relationships between phthalate exposures, MetS, and potential interactions with socioeconomic factors is warranted.

Abbreviations: CVD, cardiovascular disease; DHHS, Department of Health and Human Services; FBG, fasting blood glucose; FIPR, family income to poverty ratio; HDL, high density lipoprotein; MEC, mobile examination center; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TG, triglycerides

* Corresponding author.
E-mail addresses: symielle.gaston@nih.gov (S.A. Gaston), tulve.nicolle@epa.gov (N.S. Tulve).
[1] Present Address: National Institute of Environmental Health Sciences, 111 T.W. Alexander Drive, Research Triangle Park, NC 27709, (p) 984-287-3724. symielle.gaston@nih.gov

https://doi.org/10.1016/j.ijheh.2018.09.005
Received 6 January 2018; Received in revised form 22 September 2018; Accepted 26 September 2018

1. Introduction

Children and adolescents are manifesting metabolic dysfunction at younger ages making metabolic syndrome (MetS) a condition of concern for all lifestages (Cook et al., 2003; de Ferranti et al., 2004; Dhuper et al., 2007; Eckel et al., 2005; Goodman et al., 2004; Srinivasan et al., 2002; Weiss et al., 2013). MetS is a cluster of risk factors including abdominal obesity, hypertension, dyslipidemia, and hyperglycemia (Eckel et al., 2005; Grundy et al., 2004). It is a strong predictor of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (Eckel et al., 2005; Grundy, 2006; Grundy et al., 2004; Thomsen et al., 2016). Adolescents exhibiting MetS risk factors and MetS at younger ages could have decreased quality of life and premature development of T2DM and CVD as they transition to young and middle adulthood.

Certain phthalates are considered endocrine disrupting chemicals (Furr et al., 2014) and have been linked to a variety of adverse biological processes and health outcomes including hormonal dysregulation and obesity (Elobeid and Allison, 2008; Tijani et al., 2016). Phthalate exposure is ubiquitous due to use in a variety of consumer products such as food packaging, personal care products, medical equipment, and children's toys. Lack of chemical bonding to these products allows phthalates to leach or diffuse into food, materials, or the environment (Giulivo et al., 2016). Thus, people can be exposed to phthalates through the dermal, inhalation, and dietary routes (Giulivo et al., 2016; Phthalates, 2008). Though exposure can occur through different pathways, food is the primary source of phthalate exposure in the general population (Giulivo et al., 2016). Phthalate exposures, whether through food consumption or other environmental pathways, may affect risk of MetS.

There is limited research on the association between phthalates and MetS and findings have been inconsistent. Although individual studies suggest associations between phthalate exposure and several risk factors for MetS, including high blood pressure and obesity (Tang-Peronard et al., 2011; Trasande et al., 2013a), a recent systematic review did not conclude that phthalates act as obesogens among humans (Goodman et al., 2014). Proposed biological mechanisms linking phthalates to metabolic dysfunction include alterations to molecular signaling pathways such as peroxisome proliferator-activated receptors (PPAR) which affect lipid and glucose homeostasis (Benjamin et al., 2017; Goodman et al., 2014). The one cross-sectional study exploring associations between phthalate metabolites and MetS among National Health and Nutrition Examination Survey (NHANES) adult participants found higher concentrations of certain urinary phthalate metabolites (mono-benzyl phthalate (MBzP) and di(2-ethylhexyl phthalate (DEHP)) were associated with greater odds of MetS (James-Todd et al., 2016). However, to our knowledge, there are no nationally representative studies exploring this association among adolescents aged 12–19 years. Further exploration of the association between phthalates and MetS during adolescence is necessary due to the potential impacts of phthalate exposures on cardiometabolic health during a critical period of development prior to adulthood.

Non-chemical stressors in the environments of children and adolescents may interact with chemical stressors and affect subsequent health (Tulve et al., 2016). Two recent reviews describe socioeconomic factors as non-chemical stressors associated with higher risk of childhood obesity and cardiometabolic health outcomes like cardiovascular disease in adulthood (Lichtveld et al., 2017; Suglia et al., 2017). It is plausible that non-chemical stressors like socioeconomic factors may affect the relationships between phthalate exposures and MetS. For instance, compared to higher socioeconomic status (SES) children, lower SES children have been shown to have worse health behaviors like poor dietary patterns (Lichtveld et al., 2017), which can affect both phthalate exposure and MetS risk. However, limited research to date has quantified these potential interactions.

The objective of this cross-sectional analysis was to investigate the association between urinary phthalate metabolite concentrations and MetS among U.S. adolescents using NHANES data for the survey years 2003–2014. Because low SES is often associated with increased obesity, MetS, and chemical exposures (Holben and Taylor, 2015; Hostinar et al., 2017; Shrewsbury and Wardle, 2008; Tyrrell et al., 2013), we also aimed to assess whether observed associations varied by the non-chemical stressor, economic adversity, defined as a combination of low household income, low parental education, and food insecurity (a condition in which there is uncertain or limited access to adequate quality, variety, or quantity of food) (USDA, 2017).

2. Materials and methods

2.1. NHANES data

NHANES data for the years 2003–2014 were used for this analysis. NHANES is an annually administered, cross-sectional survey that employs a complex, multistage probability sampling design with complex weighting schemes in order to ensure representativeness of the resident, noninstitutionalized U.S. population (Curtin et al., 2012, 2013; Johnson et al., 2014). Brief descriptions of the NHANES protocol through these years is described below and has previously been published (Curtin et al., 2012, 2013; Johnson et al., 2014). NHANES protocol involves selection of individuals for a home interview, and a subsample of these individuals for physical examinations that included biologic specimen collection in mobile examination centers (MEC). The National Center for Health Statistics Research Ethics Review Board reviewed and approved NHANES protocols. Our analyses included data from Hispanic, non-Hispanic white, and non-Hispanic black adolescents who fasted at least 6 hours prior to participation in physical examinations/specimen collection, were without physician-diagnosed diabetes, and had viable blood serum/plasma as well as urine samples in which MetS components and phthalate metabolites were measured. Adolescents with physician-diagnosed diabetes were excluded because data limitations resulted in our inability to distinguish between adolescents with type 1 diabetes and T2DM. Additionally, adolescents with either type of diabetes may have had etiologic differences or been more likely to have MetS than those without diagnosed diabetes given that MetS is an identified risk factor for T2DM.

2.2. Outcome: metabolic syndrome

Using data from NHANES MEC physical examinations and laboratory analyses (Zipf et al., 2013), we applied the most widely used pediatric definition of MetS to dichotomize participants as with or without MetS (Cook et al., 2003). This MetS definition is a modified version of the National Cholesterol Education Program Adult Treatment Panel III definition for adolescents (Cook et al., 2003; NCEP, 2002). According to this definition, adolescents aged 12–19 years must have had three or more of the following risk factors to have MetS: abdominal obesity (waist circumference (WC) ≥ 90th percentile for age and sex); elevated blood pressure (systolic blood pressure (BP) or diastolic BP ≥ 90th percentile for age, sex, and height, or current use of antihypertensive drugs); elevated triglycerides (TG) (TG ≥ 110 mg/dL (1.24 mmol/L)); low high-density lipoprotein cholesterol (HDL) (HDL ≤ 40 mg/dL (1.03 mmol/L)); or high fasting blood glucose (FBG) (FBG ≥ 110 mg/dL (6.1 mmol/L)). Like Cook et al. (2003), we calculated age- and sex-WC percentiles specific to the sample population. If possible, at least three BP measurements were taken from participants and we averaged them. For participants with less than three BP measurements (n = 23), we either averaged two measurements or used a single measurement. There were no significant differences in BP between adolescents with three and less than three measurements. We applied Centers for Disease Control and Prevention (CDC) growth charts and National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents blood pressure charts to obtain participants' age-, sex-, and height-specific percentiles for systolic and diastolic BP

(CDC, 2000; NHBPEP, 2004). TG, HDL, and FBG values were obtained from processed blood serum and plasma samples at analytic laboratories in accordance with NHANES quality assurance and control procedures described in detail elsewhere (Zipf et al., 2013).

2.3. Exposure measurement: urinary phthalate metabolites

For a subsample of NHANES participants, urinary phthalate metabolites and other environmental chemicals (e.g., bisphenol A (BPA)) were measured using on-line solid phase extraction coupled with high performance liquid chromatography and tandem mass spectrometry. The detailed protocol is described elsewhere (NCHS, 2011). In this analysis, we included phthalate metabolites in which at least 75% of the concentrations were above the limit of detection (LOD) within the adolescent subsample. These included: monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monoethyl phthalate (MEP), mono-(3-carboxypropyl) phthalate (MCPP), and di(2-ethyhexyl) phthalate (DEHP) metabolites (i.e., mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)). Concentrations below the LOD were assigned a value of LOD/ $\sqrt{2}$ (CDC, 2005). Each metabolite was analyzed individually except DEHP metabolites which grouped together in factor analysis. We calculated a summary measure (ΣDEHP) by calculating the molar sum as done in prior literature (Watkins et al., 2014).

2.4. Economic adversity

We used three variables as indicators of economic adversity which are similar to economic adversity measures used in prior literature (Parks et al., 2013). These variables included annual household income (< $25,000, $25,000-$54,999, $55,000-$74,999, ≥$75,000), highest educational attainment among parents/caregivers (< high school, high school graduate/general equivalency diploma, ≥college), and food insecurity due to its association with both SES and central obesity among adolescents (Holben and Taylor, 2015). A NHANES household food insecurity variable was created based on the number of affirmative responses to eighteen questions that characterized the food security status of the household (Bickel et al., 2000). NHANES original categories included full, marginal, low, and very low food security. We created a dichotomized food insecurity variable: yes (marginal, low, and very low food security) versus no (full food security). We assigned values of one for each indicator variable if participant/caregiver reported annual household income < $25,000, < high school parent/caregiver educational attainment, or food insecurity. A value of zero corresponded to annual household income ≥$25,000, ≥high school parent/caregiver educational attainment, or no food insecurity. To avoid multicollinearity from including each individual SES measure in models, we summed each indicator to create scores (range: 0–3) with a score of three indicating the highest level of adversity. Economic adversity score was correlated (r = −0.66) with the ratio of family's annual income to the federal poverty level in which higher ratios indicated a family income well above the poverty threshold. We dichotomized economic adversity as a score ≥ two versus a score < two.

2.5. Covariates

We considered several covariates for inclusion in adjusted models based on prior literature (James-Todd et al., 2016; Trasande et al., 2013b; Watkins et al., 2014) and construction of directed acyclic graphs (Greenland et al., 1999). Potential covariates included: sex (male/female), race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black), objectively-measured body mass index (BMI) (underweight/normal (BMI < 85th percentile for age and sex), overweight (BMI ≥ 85th percentile and < 95th percentile for age and sex), obese (BMI ≥ 95th percentile for age and sex)), physical activity in the past 30 days (none, moderate, vigorous), total caloric intake per day (kilocalories per day), total fat intake per day (grams per day), age (years), and creatinine (mg/dL). Details regarding the enzymatic method applied to produce a color product to measure creatinine are published in NHANES laboratory manuals (NCHS, 2011). Sex, race/ethnicity, physical activity, total caloric intake, total fat intake, and age were obtained via self-reported information from the sociodemographic, health behavior, and food frequency questionnaires. NHANES calculated and categorized BMI percentiles based on participant height and weight measurements collected during the MEC physical exam using CDC growth charts (CDC, 2000). For physical activity, in the early survey years (2003–2004 and 2005–2006), participants were asked whether they engaged in bicycling (for transportation) or some type of activity (none, moderate, or vigorous) in the past 30 days. In later survey years, more detailed questions captured time spent doing physical activity. To consistently measure physical activity across all survey years, we used the number of minutes engaged in bicycling, moderate, and vigorous activity to group participants as engaging in none (0 minutes of any type of activity), moderate (any bicycling or moderate activity), and vigorous physical activity (any vigorous activity) for survey years 2007–2014 which corresponds to the categorizations in 2003–2006.

2.6. Statistical analysis

The analysis was performed using SAS software, Version 9.4 of the SAS System for Windows (Cary, NC), using appropriate weighting procedures that accounted for NHANES' complex sampling design. We adjusted for urine dilution by applying the O'Brien et al. creatinine correction procedure described in detail elsewhere and briefly below (O'Brien et al., 2016). Creatinine concentrations among adolescents have been shown to vary by race/ethnicity, sex, age, and BMI (Barr et al., 2005), so we performed univariate linear regressions on log-transformed creatinine to determine whether to include them as adjustment factors. We used these results to calculate expected values of creatinine in multivariate linear regression models that included significant predictors from the univariate models (race/ethnicity, sex, and age). To obtain creatinine-corrected phthalate metabolite concentrations, we applied covariate-adjustment standardization in which each phthalate metabolite concentration was divided by the ratio of observed creatinine to expected creatinine.

We estimated population characteristics by calculating observed frequencies and weighted percentages for categorical variables and weighted means or geometric means and standard errors for continuous variables. We compared the characteristics of males and females with Rao-Scott Chi-square (χ^2) tests or independent samples t-tests, depending on variable type. Population characteristics were also examined by MetS status among all participants and by sex. Phthalate metabolite concentrations have been shown to vary by sex, age, and survey year (Zota et al., 2014); therefore, after sorting creatinine-corrected phthalate metabolite concentrations by sex, age, and survey year, we created tertiles for each metabolite. We created tertiles because any larger number of categories would have resulted in a very small count of females with MetS in each quantile. Within each tertile, we calculated geometric means and corresponding 95% confidence intervals (CIs) of phthalate metabolite concentrations. To avoid multicollinearity, we chose a single pollutant approach and did not include more than one phthalate metabolite in any model. We performed weighted logistic regression adjusting for urinary creatinine and used the lowest tertile as the reference category to calculate minimally adjusted odds ratios (ORs) and 95% CIs for each individual metabolite (i.e., MEP, MnBP, MiBP, MCPP, ΣDEHP). We added *a priori* covariates described previously and retained those that were associated with creatinine (O'Brien et al., 2016) as well as those that changed any associations by at least 10% in fully-adjusted weighted logistic regression

models. As a result, all fully-adjusted models included the following covariates: creatinine, race/ethnicity, sex (except for models stratified by sex), age, total caloric intake per day, total fat intake per day, and economic adversity. We added a phthalate metabolite*sex cross product term to the fully adjusted models and stratified each model by sex to investigate potential sex differences in ORs. Additionally, we investigated fully-adjusted relationships between tertiles of each individual phthalate metabolite and individual MetS components (e.g., high waist circumference, low HDL cholesterol) and tested for sex interactions in these relationships. Weighted ordinal logistic regression was then used to estimate the fully-adjusted relationship between higher tertiles of phthalate metabolites and the number of MetS components (range:0–4). In ordinal regression models, we limited the sample to adolescents with four or fewer MetS components because there were few adolescents with five components. We then tested for interaction between phthalate metabolites and economic adversity by adding a cross-product term (phthalate metabolite*economic adversity) in fully-adjusted models for MetS among all participants and reported results stratified by economic adversity status (yes vs. no).

We performed two sensitivity analyses. First, we added log-transformed urinary BPA as a covariate in the fully-adjusted weighted logistic regression models for MetS. Dietary ingestion is suggested as the major exposure route for both phthalates and BPA, and each exposure may be associated with insulin resistance and diabetes (Giulivo et al., 2016). Therefore, we adjusted for BPA in the models for MetS to assess any changes in previously observed relationships. Secondly, in separate models, we repeated MetS analyses with additional adjustment for total fasting time. To determine statistical significance, we used two-sided p-values of 0.10 for Wald χ^2 tests for interaction (due to the greater power required to detect interactions) and 0.05 for all other tests for association.

3. Results

3.1. Analytic sample

There was a total of 1140 adolescents that had values for urinary phthalate metabolites and all MetS components (i.e., WC, BP, TG, HDL, FBG). After exclusion of adolescents who fasted less than 6 hours prior to examination (n = 75), had doctor diagnosed diabetes (n = 10), had missing values for covariates included in adjusted models (n = 146), or were of any race/ethnicity other than Hispanic, non-Hispanic White, or non-Hispanic Black (n = 87), the sample consisted of 918 adolescents (some adolescents met more than one of the exclusion criteria).

3.2. Sample characteristics

Observed frequencies and weighted percentages, means, and geometric means describing population characteristics are presented in Table 1. Mean age was 16 years (standard error (SE) 0.10), 63% of adolescents were non-Hispanic white, and 18% met our criteria for economic adversity. Males consumed more calories and fat compared to females, but also reported higher prevalence of moderate and vigorous physical activity. MEP had the highest average corrected concentration (geometric mean 68 ng/mL (SE 4.0) in comparison to other phthalate metabolites. Compared to males, females had higher corrected concentrations of MnBP (females- 20 ng/mL (SE 0.96) vs. males- 17 ng/mL (SE 0.71)) and MiBP (females- 9.1 ng/mL (SE 0.45) vs. males- 7.9 ng/mL (SE 0.40)). Overall, the weighted prevalence of MetS was 5.4%, and MetS prevalence did not vary by sex. The most prevalent individual MetS components were elevated triglycerides (23%) and low HDL cholesterol which was also more prevalent among males (20%) compared to females (12%).

Economic adversity was more prevalent among males with MetS (22%) compared to males without MetS (16%). Conversely, females with MetS had lower prevalence of economic adversity (7.4%) compared to females without MetS (20%). However, given the small sample of females with MetS, results should be interpreted with caution. Overall, except for ΣDEHP, adolescents with MetS had modestly higher urinary phthalate metabolite concentrations compared to adolescents without MetS, and the most notable difference was for MEP concentrations (MetS (yes)- 78 ng/mL (SE 23) vs. MetS (no)- 67 ng/mL (SE 4.0)).

3.3. Associations between phthalate metabolite tertiles and MetS/MetS components

The geometric means within sex, age, and survey year-sorted tertiles for each phthalate metabolite are shown in Supplemental Table 1 and support the necessity of sorting tertiles by sex since within tertile concentrations were often higher among females compared to males. There were suggestive positive associations between MnBP and MetS after minimal (T2: OR = 2.49 (95% CI:0.91–6.79)) and full (T2: OR = 2.66 (0.98–7.24)) adjustment, and although OR's for T3 were weaker, the estimates were in the same direction and the confidence intervals overlapped those for T2 (Table 2). Results were suggestive that relationships between MiBP and MetS, though non-significant, varied by sex: the relationship was positive among males (T2: OR = 1.69 (0.55–5.21); T3: OR = 1.68 (0.48–5.90)) while an inverse relationship was observed among females (T2: OR = 0.26 (0.05–1.36); T3: OR = 0.34 (0.07–1.63), $p_{sex*MiBP} < 0.10$). No other phthalate metabolites were associated with the odds of MetS and no other relationships varied by sex. The sensitivity analysis in which log-transformed urinary BPA was added as a covariate in the fully-adjusted model for MiBP yielded similar, though slightly attenuated results for males, but stronger yet non-significant relationships among females (Supplemental Table 2). Additional adjustment for total fasting time did not affect the observed results (Supplemental Table 3).

MnBP and MiBP were also associated with individual MetS components, and several of the associations varied by sex (Table 3, Supplemental Table 4). Higher concentrations of MnBP were associated with lower odds of elevated blood pressure, and results were similar in direction, but often lacked significance for other phthalate metabolites. While higher concentrations of MnBP were associated with higher odds of elevated triglycerides (T2: OR = 2.86 (1.49–5.48); T3: OR = 3.11 (1.52–6.36)) and low HDL cholesterol (T2: OR = 2.05 (0.90–4.68); T3: OR = 2.34 (1.03–5.34)) among males, relationships were inconsistent among females. Higher concentrations of MnBP (T2: OR = 1.73 (1.01–2.97); T3: OR = 1.85 (1.02–3.36)) and MiBP (T2: OR = 1.70 (1.02–2.82); T3: OR = 1.95 (1.10–3.45)) were associated with higher odds of more MetS components among males, but there was no association observed among females.

3.4. Interactions between phthalate metabolite tertiles and economic adversity

Results stratified by economic adversity and *p*-values for interaction terms are presented in Table 4. Interactions were not significant. Although models for adolescents with economic adversity failed to converge due to small sample sizes, among adolescents without economic adversity, associations between MnBP and MetS were stronger than those in Table 2. The odds of MetS were over four-fold higher for higher concentrations of MnBP (T2: OR = 4.22 (1.24–14.25); T3: OR = 4.21 (0.97–18.31)) compared to T1. Models were additionally stratified by sex for MiBP due to potential sex interaction, and relationships between MiBP and odds of MetS did not vary by economic adversity ($p_{MiBP*economic\ adversity} = 0.33$ for males and $p_{MiBP*economic\ adversity}$non-estimable for females, Supplemental Table 5). Nonetheless, higher concentrations of MiBP were associated with almost three-fold higher (T2: OR = 2.95 (1.40–6.23)) and eleven-fold higher odds (T3: OR = 10.66 (3.22–35.29)) of MetS among males with economic adversity.

Table 1
Overall Population Characteristics and Population Characteristics Stratified by Sex and Metabolic Syndrome Status among Adolescents aged 12–19 years, National Health and Nutrition Examination Survey (NHANES), 2003–2014 (N = 918).

	Overall			Males			Females			P[a]
	N = 918			n = 501 (54.5%)			n = 417 (45.5%)			
	All	MetS (yes)	MetS (no)	All	MetS (yes)	MetS (no)	All	MetS (yes)	MetS (no)	
		n = 45 (5.44%)	n = 873 (94.6%)		n = 31 (6.68%)	n = 470 (93.3%)		n = 14 (3.95%)	N = 403 (96.0%)	
	n (%) or mean (SE)									
Age (years)	15.7 (0.100)	15.7 (0.524)	15.8 (0.102)	15.9 (0.127)	16.1 (0.595)	15.9 (0.134)	15.6 (0.136)	15 (0.988)	16 (0.119)	0.049
Sex										
Male	501 (54.5)	31 (66.9)	470 (53.8)	501 (100)	31 (100)	470 (100)	–	–	–	0.56
Female	417 (45.5)	14 (33.1)	403 (46.2)	–	–	–	417 (100)	14 (100)	403 (100)	
Race/Ethnicity										
Hispanic	361 (21.9)	19 (22.9)	342 (21.8)	190 (21.6)	15 (28.9)	175 (21.0)	171 (22.3)	4 (10.9)	167 (22.7)	0.34
Non-Hispanic White	280 (63.3)	16 (67.4)	264 (63.1)	159 (64.6)	10 (62.7)	149 (64.7)	121 (61.9)	6 (76.7)	115 (61.2)	
Non-Hispanic Black	277 (14.8)	10 (9.70)	267 (15.1)	152 (13.9)	6 (8.40)	146 (14.3)	125 (15.9)	4 (12.3)	121 (16.0)	
Annual Household Income										
< $25,000	275 (20.8)	14 (18.2)	261 (20.9)	138 (19.6)	11 (18.6)	127 (19.6)	137 (22.2)	3 (17.2)	134 (22.4)	0.75
$25,000-$54,999	328 (31.7)	20 (40.2)	308 (31.2)	183 (30.5)	11 (25.5)	172 (30.9)	145 (33.1)	9 (69.9)	136 (31.6)	
$55,000-$74,999	88 (10.6)	3 (10.3)	85 (10.7)	49 (9.79)	2 (14.1)	47 (9.49)	39 (11.6)	1 (2.53)	38 (12.0)	
≥$75,000	230 (36)	8 (31.3)	219 (37.2)	131 (40.1)	7 (41.8)	124 (40.0)	96 (33.0)	1 (10.3)	95 (33.9)	
Highest Educational Attainment in Household										
< High School	211 (13.4)	10 (12.0)	201 (13.4)	117 (14.2)	9 (17.1)	108 (13.9)	94 (12.4)	1 (1.44)	93 (12.8)	0.79
High School	527 (58.3)	31 (76.6)	496 (57.2)	287 (57.1)	20 (71.9)	267 (56.0)	240 (59.7)	11 (86.1)	229 (58.6)	
≥ College	180 (28.4)	4 (11.4)	176 (29.3)	97 (28.8)	2 (10.9)	95 (30.0)	83 (27.9)	2 (12.5)	81 (28.5)	
Food Insecurity										
Yes	351 (29.6)	17 (33.4)	334 (29.4)	186 (30.1)	14 (44.7)	172 (29.1)	165 (29.1)	3 (10.4)	162 (29.8)	0.29
No	567 (70.4)	28 (66.6)	539 (70.6)	315 (69.9)	17 (55.3)	298 (70.9)	252 (70.9)	11 (89.6)	241 (70.2)	
Economic Adversity [b]										
Yes	251 (17.8)	13 (17.4)	238 (17.8)	125 (16.6)	11 (22.3)	114 (16.2)	126 (19.3)	2 (7.40)	124 (19.8)	< 0.0001
No	667 (82.2)	32 (82.6)	635 (82.2)	376 (80.7)	20 (77.7)	356 (83.8)	291 (80.7)	12 (92.6)	279 (80.2)	
Total Caloric Intake (kcal per day)	2.13 (0.0389)	2.14 (0.143)	2.13 (0.0391)	2.47 (0.0500)	2.41 (0.118)	2.47 (0.0503)	1.72 (0.0414)	1.59 (0.224)	1.72 (0.0415)	< 0.0001
Total Fat Intake (grams per day)	79.6 (1.72)	79.7 (4.60)	79.6 (1.76)	93 (2.3)	92.5 (4.64)	92.7 (2.18)	64 (1.8)	53.7 (5.74)	64.4 (1.82)	0.51
Body Mass Index Category										
Underweight/Normal	578 (64.7)	3 (4.22)	575 (68.2)	314 (62.6)	2 (1.23)	312 (67.0)	264 (67.3)	1 (10.3)	263 (69.6)	0.0006
Overweight	169 (16.8)	3 (8.98)	166 (17.2)	101 (18.3)	0 (0)	101 (19.6)	68 (14.9)	3 (27.1)	65 (14.4)	
Obese	171 (18.5)	39 (86.8)	132 (14.6)	86 (19.0)	29 (98.8)	57 (13.3)	85 (17.9)	10 (62.6)	75 (16.0)	
Physical Activity Reported (past 30 days)										
None	76 (6.75)	6 (11.0)	70 (6.51)	32 (3.76)	5 (11.4)	27 (3.21)	44 (10.3)	1 (10.3)	43 (10.3)	0.075
Moderate	753 (84.4)	33 (66.9)	720 (85.4)	412 (86.2)	21 (60.4)	391 (88.1)	341 (82.2)	12 (80.0)	329 (82.3)	
Vigorous	89 (8.85)	6 (22.1)	83 (8.09)	57 (10.0)	5 (28.1)	52 (8.72)	32 (7.47)	1 (9.96)	31 (7.36)	
Creatinine (mg/dL), GM (SE)	119 (4.12)	123 (17.9)	119 (4.21)	125 (4.71)	130 (25.7)	125 (4.87)	112 (6.07)	109 (15.9)	112 (6.25)	
Creatinine-corrected urinary phthalate metabolites, GM (SE) [c]										
MEP (ng/mL)	67.5 (3.96)	77.9 (23.3)	66.9 (3.97)	61.5 (4.42)	73.3 (27.7)	60.7 (4.13)	75.5 (6.23)	88.1 (40.8)	75.0 (6.07)	0.047
MnBP (ng/mL)	17.8 (0.575)	18.6 (2.97)	17.8 (0.586)	16.5 (0.707)	16.1 (3.18)	16.6 (0.649)	19.5 (0.959)	25.1 (5.70)	19.3 (0.930)	0.016

(*continued on next page*)

Table 1 (*continued*)

	Overall			Males			Females			P[a]
	N = 918			n = 501 (54.5%)			n = 417 (45.5%)			
	All	MetS (yes)	MetS (no)	All	MetS (yes)	MetS (no)	All	MetS (yes)	MetS (no)	
		n = 45 (5.44%)	n = 873 (94.6%)		n = 31 (6.68%)	n = 470 (93.3%)		n = 14 (3.95%)	N = 403 (96.0%)	
	n (%) or mean (SE)									
MiBP (ng/mL)	8.40 (0.331)	8.61 (1.16)	8.39 (0.334)	7.87 (0.395)	8.90 (1.63)	7.80 (0.383)	9.07 (0.4481)	8.03 (1.41)	9.12 (0.487)	0.039
MCPP (ng/mL)	3.21 (0.147)	4.45 (1.34)	3.15 (0.140)	3.29 (0.170)	3.35 (0.713)	3.29 (0.178)	3.12 (0.216)	7.90 (5.17)	3.00 (0.166)	0.48
MBzP (ng/mL)	10.7 (0.432)	14.5 (3.22)	10.5 (0.436)	10.2 (0.574)	14.4 (3.77)	9.96 (0.580)	11.2 (0.560)	14.6 (5.32)	11.1 (0.531)	0.18
ΣDEHP (nmol/mL)	0.203 (0.0111)	0.155 (0.0282)	0.206 (0.0115)	0.214 (0.0158)	0.138 (0.0335)	0.220 (0.0166)	0.191 (0.0125)	0.194 (0.0375)	0.191 (0.0124)	0.16
Meets Cook et al. (2003) Criteria for MetS (yes)	45 (5.44)	45 (100)	–	31 (6.68)	31 (100)	–	14 (3.95)	14 (100)	–	0.22
Meets Cook et al. (2003) Criteria for Individual MetS Risk Factors										
High Waist Circumference (yes)	101 (11.0)	39 (89.0)	62 (6.55)	52 (11.0)	28 (97.1)	24 (4.79)	49 (11.1)	11 (72.5)	38 (8.61)	0.95
Elevated Blood Pressure (yes)	57 (5.07)	16 (21.9)	41 (4.10)	29 (3.97)	8 (10.5)	21 (3.51)	28 (6.38)	8 (45.2)	20 (4.79)	0.14
Elevated Triglycerides (yes)	199 (23.4)	40 (96.8)	159 (19.2)	109 (23.8)	28 (97.4)	81 (18.6)	90 (22.8)	12 (95.8)	78 (19.8)	0.78
Low High-Density Lipoprotein Cholesterol (yes)	145 (16.5)	39 (92.4)	106 (12.1)	96 (20.2)	27 (92.7)	69 (15.0)	49 (12.1)	12 (91.9)	37 (8.80)	0.0079
High Fasting Blood Glucose (yes)	18 (1.32)	8 (7.97)	10 (0.938)	15 (1.99)	7 (8.38)	8 (1.54)	3 (0.513)	1 (7.15)	2 (0.240)	0.069

Abbreviations: SE (standard error); kcal (kilocalories); mg (milligram); dL (deciliter); GM (geometric mean); MEP (monoethyl phthalate); ng (nanogram); mL (milliliter); MnBP (mono-n-butyl phthalate); MiBP (monoisobutyl phthalate); MCPP (mono-(3-carboxypropyl) phthalate; MBzP (monobenzyl phthalate); ΣDEHP (di(2-ethylhexyl) phthalate [molar sum of mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)]); nmol (nanomol); MetS (Metabolic Syndrome).

Note: Data presented are actual frequencies and weighted percentages. Percentages and means were weighted to account for the sampling design. Percentages may not sum to 100 due to rounding.

[a] P-value for Rao-Scott $\chi 2$ test for differences in proportions or *t*-test for differences in the means/geometric means between overall samples of males and females.

[b] Economic adversity defined as at least two of the following: annual household income ≤$25,000, highest household educational attainment < high school, or food insecurity (household not having enough food to eat).

[c] Creatinine adjustment procedures are described in O'Brien et al. (2016).

Table 2
Prevalence Odds Ratios for MetS for Each Tertile of Urinary Phthalate Metabolite Concentrations among Adolescents aged 12–19 years, National Health and Nutrition Examination Survey (NHANES), 2003–2014 (N = 918).

n with MetS	Tertile	Overall (N = 918)		Males (n = 501)	Females (n = 417)
		45		31	14
		Model 1[a]	Model 2[b]	Model 3[c]	Model 3[c]
MEP	T1	reference	reference	reference	reference
	T2	1.03 (0.34–3.14)	1.07 (0.31–3.67)	0.45 (0.11–1.78)	5.01 (0.92–27.27)*
	T3	1.39 (0.52–3.69)	1.55 (0.56–4.31)	1.29 (0.36–4.66)	3.36 (0.64–17.62)
MnBP	T1	reference	reference	reference	reference
	T2	2.49 (0.91–6.79)*	2.66 (0.98–7.24)*	3.11 (0.96–10.13)*	2.79 (0.43–18.11)
	T3	2.13 (0.73–6.20)	2.11 (0.71–6.27)	2.55 (0.68–9.58)	2.46 (0.31–19.76)
MiBP[d]	T1	reference	reference	reference	reference
	T2	0.82 (0.30–2.22)	0.84 (0.31–2.27)	1.69 (0.55–5.21)	0.26 (0.05–1.36)
	T3	0.84 (0.32–2.25)	0.87 (0.33–2.31)	1.68 (0.48–5.90)	0.34 (0.07–1.63)
MCPP	T1	reference	reference	reference	reference
	T2	1.10 (0.37–3.25)	1.05 (0.36–3.04)	0.83 (0.25–2.74)	3.93 (0.87–17.81)*
	T3	1.60 (0.42–5.91)	1.52 (0.42–5.43)	1.17 (0.25–2.74)	6.00 (0.81–44.60)*
MBzP	T1	reference	reference	reference	reference
	T2	1.34 (0.41–4.44)	1.42 (0.46–4.45)	1.11 (0.25–4.90)	2.05 (0.32–13.33)
	T3	1.22 (0.31–4.81)	1.27 (0.32–4.95)	1.51 (0.31–7.38)	0.79 (0.09–6.64)
ΣDEHP	T1	reference	reference	reference	reference
	T2	1.41 (0.51–3.92)	1.36 (0.51–3.67)	1.21 (0.36–4.11)	2.07 (0.37–11.47)
	T3	0.52 (0.13–2.04)	0.52 (0.14–2.00)	0.53 (0.09–3.15)	0.68 (0.11–4.35)

Abbreviations: MetS (Metabolic Syndrome); MEP (monoethyl phthalate); MnBP (mono-n-butyl phthalate); MiBP (monoisobutyl phthalate); MCPP (mono-(3-carboxypropyl) phthalate; MBzP (monobenzyl phthalate); ΣDEHP (di(2-ethylhexyl) phthalate [molar sum of mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)]).
*P < 0.10 **P < 0.05.
[a] Adjusted for urinary creatinine.
[b] Model 1 additionally adjusted for race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black), total caloric intake (kcal/day), fat intake (g), economic adversity (yes, no), age (years), and sex (male, female).
[c] Model 3 adjusted for all the parameters in Model 2 except for sex.
[d] Cross-product term (*phthalate*sex*) significant at two-side p-value = 0.10.

Table 3
Prevalence Odds Ratios for Individual MetS Components and Number of Components for Each Tertile of Urinary Phthalate Metabolite Concentrations among Adolescents aged 12–19 years, National Health and Nutrition Examination Survey (NHANES), 2003–2014 (N = 918).

		High Waist Circumference	Elevated Blood Pressure	Elevated Triglycerides	Low HDL Cholesterol	High FBG	Number of Components
	n with component/n without component	101/817	57/861	199/719	145/773	18/900	–
MEP	T1	reference	reference	reference	reference	reference	reference
	T2	0.62 (0.26–1.44)	0.49 (0.22–1.09)	1.11 (0.66–1.88)	1.02 (0.54–1.93)	0.36 (0.05–2.63)	0.84 (0.53–1.35)
	T3	1.13 (0.53–2.41)	1.52 (0.70–3.29)	1.15 (0.61–2.17)	1.28 (0.69–2.41)	1.70 (0.37–7.76)	1.37 (0.84–2.23)
MnBP [EBP, ET, LHDL, NC]	T1	reference	reference	reference	reference	reference	reference
	T2	**2.17 (1.10–4.32)****	**0.36 (0.17–0.77)****	1.34 (0.83–2.14)	1.81 (0.93–3.50)*	**0.27 (0.07–0.99)****	1.24 (0.80–1.92)
	T3	1.72 (0.81–3.65)	**0.32 (0.12–0.87)****	**1.86 (1.16–2.99)****	1.63 (0.80–3.33)	0.64 (0.12–3.25)	1.44 (0.92–2.25)
MiBP [ET, NC]	T1	reference	reference	reference	reference	reference	reference
	T2	0.89 (0.42–1.79)	0.57 (0.25–1.30)	0.93 (0.58–1.48)	1.63 (0.91–2.89)*	0.83 (0.11–6.00)	1.08 (0.73–1.60)
	T3	1.66 (0.89–3.10)	0.46 (0.20–1.05)*	1.21 (0.71–2.06)	1.20 (0.66–2.17)	2.03 (0.38–10.95)	1.26 (0.83–1.91)
MCPP [EBP, ET]	T1	reference	reference	reference	reference	reference	reference
	T2	1.06 (0.51–2.21)	0.86 (0.40–1.82)	1.13 (0.70–1.83)	0.99 (0.55–1.78)	3.25 (0.86–12.25)*	1.01 (0.67–1.53)
	T3	1.30 (0.60–2.81)	**0.33 (0.13–0.83)****	0.87 (0.48–1.60)	1.74 (0.92–3.30)*	3.22 (0.95–10.93)*	1.03 (0.62–1.73)
MBzP [ET]	T1	reference	reference	reference	reference	reference	reference
	T2	1.67 (0.78–3.55)	0.64 (0.25–1.62)	1.02 (0.61–1.71)	1.37 (0.76–2.47)	0.68 (0.16–2.95)	1.08 (0.70–1.65)
	T3	1.53 (0.59–3.97)	0.54 (0.22–1.36)	1.06 (0.59–1.93)	1.43 (0.73–2.83)	0.52 (0.10–2.67)	1.10 (0.63–1.91)
ΣDEHP	T1	reference	reference	reference	reference	reference	reference
	T2	1.56 (0.77–3.17)	0.57 (0.28–1.16)	1.21 (0.71–2.05)	0.98 (0.52–1.85)	1.56 (0.26–9.29)	1.11 (0.73–1.68)
	T3	0.84 (0.33–2.17)	0.89 (0.39–2.05)	1.05 (0.63–1.75)	0.84 (0.44–1.60)	0.62 (0.08–4.91)	1.05 (0.66–1.65)

Abbreviations: MetS (Metabolic Syndrome); HDL (high density lipoprotein); FBG (fasting blood glucose); MEP (monoethyl phthalate); MnBP (mono-n-butyl phthalate); MiBP (monoisobutyl phthalate); MCPP (mono-(3-carboxypropyl) phthalate; MBzP (monobenzyl phthalate); ΣDEHP (di(2-ethylhexyl) phthalate [molar sum of mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)]).
Note: All models adjusted for urinary creatinine, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black), total caloric intake (kcal/day), fat intake (g), economic adversity (yes, no), age (years), and sex (male, female). Dichotomous logistic regression models were applied to estimate prevalence odds ratios of individual MetS components. Ordinal logistic regression models were applied to estimate prevalence odds ratios for the number of MetS components. Number of MetS components ranged from 0 to 4.
The following indicate $p_{sex*phthalate\ metabolite} < 0.10$ for specific MetS components: [HWC] high waist circumference; [EBP] elevated blood pressure; [ET] elevated triglycerides; [LHDL] low HDL cholesterol; [HFBG] high blood glucose; and [NC] number of MetS components. Models in which cross-product terms were not estimable include: MBzP- high fasting blood glucose; MiBP- high fasting blood glucose; ΣDEHP- high fasting blood glucose.
*P < 0.10 **P < 0.05.

Table 4
Prevalence Odds Ratios for MetS for Each Tertile of Urinary Phthalate Metabolite Concentrations Stratified by Childhood Economic Adversity among Adolescents aged 12–19 years, National Health and Nutrition Examination Survey (NHANES), 2003–2014 (N = 918).

		Overall		
		Economic Adversity (yes)	Economic Adversity (no)	$p_{economicadversity*phthlate\ metabolite}$
		n = 251	n = 667	
	n with MetS	13	32	
MEP	T1	reference	reference	0.67
	T2	NE	1.54 (0.56–4.26)	
	T3	NE	1.97 (0.60–6.45)	
MnBP	T1	reference	reference	0.53
	T2	NE	**4.22 (1.25–14.25)****	
	T3	NE	4.21 (0.97–18.31)*	
MiBP[a]	T1	reference	reference	0.39
	T2	NE	0.90 (0.36–2.21)	
	T3	NE	0.66 (0.19–2.33)	
MCPP	T1	reference	reference	0.40
	T2	NE	0.79 (0.24–2.61)	
	T3	NE	1.63 (0.39–6.74	
MBzP	T1	reference	reference	0.34
	T2	NE	1.90 (0.48–7.59)	
	T3	NE	2.14 (0.37–12.35)	
ΣDEHP	T1	reference	reference	0.54
	T2	NE	1.58 (0.56–4.42)	
	T3	NE	0.64 (0.12–3.54)	

Abbreviations: MetS (Metabolic Syndrome); MEP (monoethyl phthalate); NE (non-estimable); MnBP (mono-n-butyl phthalate); MiBP (monoisobutyl phthalate); MCPP (mono-(3-carboxypropyl) phthalate; MBzP (monbenzyl phthalate); ΣDEHP (di(2-ethylhexyl) phthalate [sum of mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)]).
Note: All models adjusted for urinary creatinine, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black), total caloric intake (kcal/day), fat intake (g), age (years), and sex (male, female).
*$P < 0.10$ **$P < 0.05$.
[a] Cross-product term (*phthalate*sex*) significant at two-side p-value = 0.10.

4. Discussion

Our objective was to investigate cross-sectional relationships between urinary phthalate metabolites and MetS among U.S. adolescents. A secondary objective was to assess whether these relationships varied by economic adversity (a non-chemical stressor describing socioeconomic status). Results supported a suggestive positive association between MnBP and MetS: adolescents with intermediate concentrations of MnBP had over two-fold higher odds of MetS than adolescents with the lowest concentrations. Higher MnBP concentrations were also associated with higher odds of MetS components including elevated waist circumference, elevated triglycerides, and low HDL cholesterol, particularly among males. Relationships between MiBP concentrations and odds of MetS may also vary by sex. Despite the lack of statistical significance, females with higher MiBP concentrations had lower odds of MetS; conversely, males with higher MiBP concentrations had higher odds of MetS. Both higher MnBP and higher MiBP concentrations were associated with higher odds of having more MetS components among males. Relationships between phthalate metabolites and MetS did not vary by economic adversity.

Although our study found no strong associations between phthalate metabolites and MetS, certain phthalates were associated with MetS components. MnBP and MiBP were the two phthalate metabolites that showed consistent relationships with MetS components. Concentrations of MnBP were similar but concentrations of MiBP were higher than those found in adult NHANES participants (James-Todd et al., 2016); however, adolescents may have dissimilar exposures than adults. Higher concentrations of MnBP were associated with marginally higher odds of MetS and higher concentrations of both MnBP and MiBP were associated with higher odds of a number of MetS components among adolescents and adolescent males, respectively, which is comparable to prior literature. A recent review supports a positive association between phthalates and adolescent obesity, a strong risk factor for MetS, which may partially explain associations with MetS (Lichtveld et al., 2017).

There are limited studies to compare our current results. Authors of a prior study of children and adolescents aged 6–19 years (NHANES, 2003–2008) grouped phthalate metabolites by concentration (low molecular weight, high molecular weight, DEHP) and found no associations between either low molecular weight and high molecular weight phthalate metabolites and elevated blood pressure, triglyceride levels, or HDL levels (Trasande et al., 2013a). They also found no relationship between MiBP and elevated blood pressure; however, in contrast to our study, phthalates were not investigated individually for other cardiometabolic health outcomes and sex-specific associations were not described. In a study of NHANES (2001–2010) adult participants, the authors found no association between quartiles of MnBP concentrations and MetS (James-Todd et al., 2016); however, we found that adolescents with intermediate concentrations (in the second tertile) of MnBP had marginally higher odds of MetS than adolescents with the lowest concentrations of MnBP. Our results may differ due to measurement differences. Furthermore, unlike James-Todd and colleagues' findings of associations between DEHP concentrations and MetS for adults, we found no association between DEHP and MetS for adolescents. In a recent literature review assessing the association between phthalates and obesity, authors found that results depended on which phthalate metabolites were being investigated, sex and age of population studied, and level of exposure (Tang-Peronard et al., 2011). The differences in our study results and those of other studies could also be due to these factors, which highlight the need for future studies to continue to explore phthalate exposures and MetS, as well as individual MetS components, across all lifestages.

There are several exposure pathways that may contribute to the associations observed in this analysis. MnBP is a metabolite of the low molecular weight parent compound, di-n-butyl phthalate, which is commonly used in some plastics, cosmetics, personal care products, and solvents for some dyes (Crinnion, 2010; Heudorf et al., 2007). MiBP is a metabolite of the low molecular weight parent compound, di-isobutyl phthalate, which is also used in personal care products as well as pharmaceuticals. Due to their uses, exposure to MnBP and MiBP can occur through non-dietary routes. Because the most consistent relationships were observed for phthalate metabolites in which dietary exposure is not likely the primary route, other factors, including the surrounding school and home environment as well as personal care product usage, may contribute to phthalate exposure and the risk for MetS. Future research should consider these environmental and behavioral risk factors along with phthalate metabolite measurement in future studies of MetS and other cardiometabolic health outcomes.

Potential biological mechanism may mediate the pathways from phthalate exposure to MetS as well as cardiovascular disease. Phthalate exposure may alter signaling pathways for cells responsible for lipid metabolism and homeostasis which can lead to lipid accumulation and possible vulnerability to CVD (Benjamin et al., 2017; Goodman et al., 2014). Although we did not observe variation in phthalate metabolites and MetS associations in this study, lower SES is associated with increased psychosocial and neighborhood stressors that may affect vulnerability to cardiometabolic health and cardiovascular disease later in life (Lichtveld et al., 2017; Suglia et al., 2017). Further research throughout the lifecourse is necessary to explore this proposed mechanism and potential interaction among diverse populations at different lifestages.

There are several limitations. We are unable to infer causality and highlight reverse causality as a possibility due to the cross-sectional study design. It is possible that adolescents' MetS status preceded their phthalate exposure. The concentrations of urinary phthalates are a measure of recent phthalate exposure and not exposure over time, which results in the possibility of exposure misclassification. However, a recent longitudinal study of adolescent females over a three-year period showed that although phthalate concentrations changed over time, categories of concentrations remained consistent (Wolff et al., 2017). Furthermore, given the ubiquitous often continuous exposure to phthalates, it is possible that there is minor variation in exposure. Nonetheless, misclassification is likely non-differential and affects all adolescents regardless of MetS status. Non-differential misclassification results in estimates biased towards the null, so associations may be stronger than the results observed in the current analysis. There were also a small number of adolescents with MetS which affected the power to detect associations and the stability of the estimates, especially among females. The small numbers of adolescents with MetS in each phthalate exposure category, in addition to the opposite directions of associations observed for individual MetS components (e.g., inverse associations between phthalate metabolites and blood pressure, positive associations with elevated trigylcerides), may have also contributed to the lack of dose-response associations observed. Future research, such as prospective studies with large sample sizes of higher risk groups like obese adolescents, are warranted. Additionally, tertiles of phthalate metabolites do not imply clinical significance and may not be the threshold at which effects are seen, which also may contribute to the lack of dose-response relationships for MetS. Nonetheless, odds of individual MetS components across tertiles were either similar or increased/decreased incrementally as tertiles increased. Additionally, we did not employ multiple comparison procedures due to the exploratory nature of this study. The results may be due to chance. Although we thoroughly assessed which covariates to include in our models, residual confounding due to unmeasured confounders remains a possibility and could affect results by either attenuating or overestimating associations. For instance, the childhood adversity measure cut-points may not uniformly indicate adversity across all regions of the U.S. Furthermore, there is possible residual confounding due to the potential measurement error of self-reported covariates in the models. Despite these limitations, this exploratory analysis supports that further research is needed to better understand the association between phthalate exposure and MetS among adolescents.

There are several strengths of this work. NHANES employs thorough quality control and quality assurance procedures to ensure the validity of the data. Secondly, due to the use of NHANES data and appropriate weighting procedures, results of this study are generalizable to the noninstitutionalized population of Hispanic, white, and black U.S. adolescents. Thirdly, we adjusted for BPA in a sensitivity analysis, which strengthens our findings of the potential effects of phthalates beyond those of a widely recognized endocrine disrupting chemical. Fourthly, we also assessed potential sex differences which are important given the endocrine disrupting properties of phthalates. Lastly, we explored this question among a diverse population across different SES levels, and our results highlight that future research may require consideration of potential interactions between non-chemical stressors and chemical exposures like phthalates.

5. Conclusions

In this cross-sectional analysis, our results suggested that MnBP and MiBP may be associated with increased odds of MetS as well as individual MetS components among U.S. adolescents. Phthalates are widely used in consumer products and food packaging, thus exposure is ubiquitous. Given ubiquitous exposure, the increase in obesity and metabolic dysfunction observed among adolescents in recent years, and our results, it is important to continue research of phthalate exposures and MetS. We observed no variation in relationships between phthalate metabolites and MetS by economic adversity, a non-chemical stressor reflective of socioeconomic status, among adolescents. Nonetheless, further research of the relationships between phthalate exposures and metabolic syndrome, as well as how non-chemical stressors may interact with phthalate exposures is warranted.

Conflicts of interest

The authors declare no actual or competing financial interests.

Acknowledgements

This project was supported by an appointment to the Internship/Research Participation Program at the U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, Systems Exposure Division, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and EPA. The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2018.09.005.

References

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113, 192–200.
Benjamin, S., Masai, E., Kamimura, N., Takahashi, K., Anderson, R.C., Faisal, P.A., 2017. Phthalates impact human health: epidemiological evidences and plausible mechanism of action. J. Hazard Mater. 340, 360–383.
Bickel, G., Nord, M., Price, C., Hamilton, W., Cook, J., 2000. Guide to Measuring Household Food Security, Revised 2000. US Department of Agriculture, Food, and Nutrition Service, Alexandria, VA.
CDC, 2000. CDC Growth Charts. National Center for Health Statistics.
CDC, 2005. Third National Report on Human Exposure to Environmental Chemicals Centers for Disease Control and Prevention.
Cook, S., Weitzman, M., Auinger, P., Nguyen, M., Dietz, W.H., 2003. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch. Pediatr. Adolesc. Med. 157, 821–827.
Crinnion, W.J., 2010. Toxic effects of the easily avoidable phthalates and parabens. Altern. Med. Rev. 15, 190–197.
Curtin, L.R., Modhadjer, L.K., Dohrmann, S.M., et al., 2013. National Health and Nutrition Examination Survey: Sample Design 2007-2010 2 Vital Health Stat.
Curtin, L.R., Mohandjer, L., Dohrmann, S., et al., 2012. The National Health and Nutrition Examination Survey: Sample Design, 1999-2006 2 Vital Health Stat.
de Ferranti, S.D., Gauvreau, K., Ludwig, D.S., Neufeld, E.J., Newburger, J.W., Rifai, N., 2004. Prevalence of the metabolic syndrome in american adolescents: findings from the third national health and nutrition examination survey. Circulation 110, 2494–2497.
Dhuper, S., Cohen, H.W., Daniel, J., Gumidyala, P., Agarwalla, V., St Victor, R., Dhuper, S., 2007. Utility of the modified ATP III defined metabolic syndrome and severe obesity as predictors of insulin resistance in overweight children and adolescents: a cross-sectional study. Cardiovasc. Diabetol. 6, 4.
Eckel, R.H., Grundy, S.M., Zimmet, P.Z., 2005. The metabolic syndrome. Lancet 365, 1415–1428.
Elobeid, M.A., Allison, D.B., 2008. Putative environmental-endocrine disruptors and obesity: a review. Curr. Opin. Endocrinol. Diabetes Obes. 15, 403–408.
Furr, J.R., Lambright, C.S., Wilson, V.S., Foster, P.M., Gray Jr., L.E., 2014. A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicol. Sci.: Off. Publ. Soc. Toxicol. 140, 403–424.
Giulivo, M., Lopez de Alda, M., Capri, E., Barcelo, D., 2016. Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ. Res. 151, 251–264.
Goodman, E., Daniels, S.R., Morrison, J.A., Huang, B., Dolan, L.M., 2004. Contrasting prevalence of and demographic disparities in the world health organization and national cholesterol education Program adult treatment Panel III definitions of metabolic syndrome among adolescents. J. Pediatr. 145, 445–451.
Goodman, M., LaKind, J.S., Mattison, D.R., 2014. Do phthalates act as obesogens in humans? A systematic review of the epidemiological literature. Crit. Rev. Toxicol. 44, 151–175.

Greenland, S., Pearl, J., Robins, J.M., 1999. Causal diagrams for epidemiologic research. Epidemiology 10, 37–48.
Grundy, S.M., 2006. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J. Am. Coll. Cardiol. 47, 1093–1100.
Grundy, S.M., Brewer, H.B., Cleeman, J.I., Smith, S.C., Lenfant, C., 2004. Definition of metabolic syndrome. Report of the national heart. In: Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition 109. pp. 433–438.
Heudorf, U., Mersch-Sundermann, V., Angerer, J., 2007. Phthalates: toxicology and exposure. Int. J. Hyg Environ. Health 210, 623–634.
Holben, D.H., Taylor, C.A., 2015. Food insecurity and its association with central obesity and other markers of metabolic syndrome among persons aged 12 to 18 Years in the United States. J. Am. Osteopath. Assoc. 115, 536–543.
Hostinar, C.E., Ross, K.M., Chen, E., Miller, G.E., 2017. Early-life socioeconomic disadvantage and metabolic health disparities. Psychosom. Med. 79, 514–523.
James-Todd, T.M., Huang, T., Seely, E.W., Saxena, A.R., 2016. The association between phthalates and metabolic syndrome: the national health and nutrition examination survey 2001-2010. Environ. Health : a global access science source 15, 52.
Johnson, C., Dohmann, S., Burt, V., Modhadjer, L., 2014. In: Statistics, N.C.f.H. (Ed.), National Health and Nutrition Examination Survey: Sample Design, 2011-2014.
Lichtveld, K., Thomas, K., Tulve, N.S., 2017. Chemical and non-chemical stressors affecting childhood obesity: a systematic scoping review. J. Expo. Sci. Environ. Epidemiol. 28, 1.
NCEP, 2002. Third report of the national cholesterol education Program (NCEP) expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III) final report. Circulation 106, 3143–3421.
NCHS, 2011. Laboratory Procedures Manual, National Health and Nutrition Examination Survey (NHANES).
NHBPEP, 2004. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114, 555–576.
O'Brien, K.M., Upson, K., Cook, N.R., Weinberg, C.R., 2016. Environmental chemicals in urine and blood: improving methods for creatinine and lipid adjustment. Environ. Health Perspect. 124, 220–227.
Parks, C.G., D'Aloisio, A.A., DeRoo, L.A., Huiber, K., Rider, L.G., Miller, F.W., Sandler, D.P., 2013. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood. Ann. Rheum. Dis. 72, 350–356.
Phthalates, N.R.C.U.C.o.t.H.R.o, 2008. Phthalate Exposure Assessment in Humans, Phthalates and Cumulative Risk Assessment: the Tasks Ahead. National Academies Press (US), Washington (DC).
Shrewsbury, V., Wardle, J., 2008. Socioeconomic status and adiposity in childhood: a systematic review of cross-sectional studies 1990-2005. Obesity 16, 275–284.
Srinivasan, S.R., Myers, L., Berenson, G.S., 2002. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. Diabetes 51, 204–209.
Suglia, S.F., Koenen, K.C., Boynton-Jarrett, R., Chan, P.S., Clark, C.J., Danese, A., Faith, M.S., Goldstein, B.I., Hayman, L.L., Isasi, C.R., Pratt, C.A., Slopen, N., Sumner, J.A., Turer, A., Turer, C.B., Zachariah, J.P., 2017. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the american heart association. Circulation 137, e15–e28.
Tang-Peronard, J.L., Andersen, H.R., Jensen, T.K., Heitmann, B.L., 2011. Endocrine-disrupting chemicals and obesity development in humans: a review. Obes. Rev. : an official journal of the International Association for the Study of Obesity 12, 622–636.
Thomsen, M.R., Nayga, R.M., Alviola, P.A., Rouse, H.L., 2016. The effect of food deserts on the body mass index of elementary schoolchildren. Am. J. Agric. Econ. 98, 1–18.
Tijani, J.O., Fatoba, O.O., Babajide, O.O., Petrik, L.F., 2016. Pharmaceuticals, endocrine disruptors, personal care products, nanomaterials and perfluorinated pollutants: a review. Environ. Chem. Lett. 14, 27–49.
Trasande, L., Sathyanarayana, S., Spanier, A.J., Trachtman, H., Attina, T.M., Urbina, E.M., 2013a. Urinary phthalates are associated with higher blood pressure in childhood. J. Pediatr. 163, 747–753 e741.
Trasande, L., Spanier, A.J., Sathyanarayana, S., Attina, T.M., Blustein, J., 2013b. Urinary phthalates and increased insulin resistance in adolescents. Pediatrics 132, e646–655.
Tulve, N.S., Ruiz, J.D.C., Lichtveld, K., Darney, S.P., Quackenboss, J.J., 2016. Development of a conceptual framework depicting a child's total (built, natural, social) environment in order to optimize health and well-being. J Environ Health Sci 2, 1–8.
Tyrrell, J., Melzer, D., Henley, W., Galloway, T.S., Osborne, N.J., 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. Environ. Int. 59, 328–335.
USDA, 2017. In: Agriculture, U.S.D.o. (Ed.), Definitions of Food Security.
Watkins, D.J., Eliot, M., Sathyanarayana, S., Calafat, A.M., Yolton, K., Lanphear, B.P., Braun, J.M., 2014. Variability and predictors of urinary concentrations of phthalate metabolites during early childhood. Environ. Sci. Technol. 48, 8881–8890.
Weiss, R., Bremer, A.A., Lustig, R.H., 2013. What is metabolic syndrome, and why are children getting it? Ann. N. Y. Acad. Sci. 1281, 123–140.
Wolff, M.S., Pajak, A., Pinney, S.M., Windham, G.C., Galvez, M., Rybak, M., Silva, M.J., Ye, X., Calafat, A.M., Kushi, L.H., Biro, F.M., Teitelbaum, S.L., 2017. Associations of urinary phthalate and phenol biomarkers with menarche in a multiethnic cohort of young girls. Reprod. Toxicol. 67, 56–64.
Zipf, G., Chiappa, M., Porter, K.S., et al., 2013. National Health and Nutritional Examination Survey: Plan and Operations, 1999-2010. National Center for Health Statistics.
Zota, A.R., Calafat, A.M., Woodruff, T.J., 2014. Temporal trends in phthalate exposures: findings from the national health and nutrition examination survey, 2001-2010. Environ. Health Perspect. 122, 235–241.