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Original Article

Gender differences in the associations between urinary bisphenol A and body composition among American children: The National Health and Nutrition Examination Survey, 2003–2006

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ABSTRACT

Background: As an endocrine disruptor, bisphenol A (BPA) exposure has been implicated as a potential risk factor in childhood obesity, which is defined using percentiles of body mass index for age. We aimed to examine the associations between BPA exposure, reflected by urinary BPA concentration, and body composition in American children.

Methods: Data of 1860 children aged 8–19 years who participated in the 2003–2006 National Health and Nutrition Examination Survey (NHANES) were analyzed in this study. Urinary BPA concentration (ng/mL) was used to indicate BPA status in the body. Body composition was measured by dual-energy X-ray absorptiometry (DXA). Multivariate linear regression models were fitted using survey procedures to investigate the associations between urinary BPA level and body composition separately for boys and girls.

Results: After adjusting for demographic and lifestyle covariates, higher quartiled and log-transformed urinary BPA levels were significantly associated with elevated lean body mass index (LBMI) z-scores in boys ($p < 0.05$), and significantly associated with elevated fat mass index (FMI) z-scores in girls ($p < 0.05$). Lower urinary BPA concentration was associated with lower percentage of trunk fat in girls (compared to 1st quartile, 2nd-quartile: $\beta = 2.85$, 95% CI, 0.92–4.78; 3rd-quartile: $\beta = 2.57$, 95% CI, 0.28–4.85; 4th-quartile: $\beta = 2.79$, 95% CI, 0.44–5.14; all $p < 0.05$). Such patterns were not observed in boys.

Conclusions: Higher BPA levels may be associated with elevated LBM in boys, but not in girls, while higher BPA levels may be associated with elevated FM in girls, but not in boys.

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death for men and women of most racial/ethnic groups in the United States.[1] Obesity is a major risk factor for CVD.[1] In addition to traditional risk factors that have been implicated in the development of obesity,[2] emerging evidence has supported a link between obesity and exposure to chemical "obesogens", such as bisphenol A (BPA).[3]

BPA is an endocrine-disrupting chemical produced in large quantities worldwide.[4] It may alter adipocyte proliferation and differentiation by interfering with nuclear hormone receptor signaling pathways.[5] Although cumulative evidence has demonstrated an association of higher BPA levels with higher risk of overweight and obesity in both children and adults,[6–9] existing epidemiological studies have reached inconclusive findings. For instance, Bhandari et al. examined 2664 children and adolescents of the 2003–2008 National Health and Nutrition Examination Surveys (NHANES) and found a significantly positive association between urinary BPA concentration and obesity in boys but not in girls.[6] A study among 1326 Chinese school-age children reported that girls with urinary BPA level ≥2 μg/L had twice the risk of overweight than the low BPA group (<2 μg/L), while a similar association was not observed in boys.[10] Furthermore, the InCHIANTI study on Italian adults showed that urinary BPA concentration was significantly associated with waist size but not with body mass index (BMI).[8]

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The discrepancies in the existing results may be partly explained by different study designs, study populations, or approaches used to evaluate BPA levels.[11,12] However, a potential reason that cannot be ignored is BMI, rather than direct measurement of body composition, has been employed in most previous studies. In these studies, overweight and obesity was defined based on age-sex-specific BMI percentiles or z-scores in children and BMI in adults. Although BMI is the most commonly used indicator of overweight and obesity in epidemiological studies,[13] it does not distinguish between fat mass (FM) and lean body mass (LBM) and is only moderately or weakly correlated with body fat percentage (FP) measured using dual-energy X-ray absorptiometry (DXA), air-displacement plethysmography, or isotope dilution.[14–16] Compared to body composition measurements, the use of BMI values alone may misclassify body weight status[13] and possibly lead to the above-mentioned inconclusive findings.[6,8,9,17–21]

In addition, BMI does not reflect fat distribution, which may be a more useful predictor of health outcomes, such as all-cause mortality.[22] In adults, abdominal fat distribution has been consistently shown to be associated with increased risks of type 2 diabetes,[23] arterial stiffness,[24] and CVD,[25] while leg fat appears to be protective.[23–25] In children, higher trunk or lower leg adiposity was associated with greater risks for low high-density lipoprotein cholesterol (HDL-C), high triglycerides, insulin resistance, and high C-reactive protein, while arm adiposity was not associated with these cardiometabolic risk factors.[26] Exploring associations between BPA exposure and regional adiposity may provide new information to help understand the underlying mechanisms of BPA exposure and obesity, examine potential effects of BPA exposure on obesity related diseases, and further identify at-risk populations in general settings.

Studies on exposure to BPA and body composition phenotypes are generally lacking. A recent study in 890 Swedish aging people did not find any significant relationships between serum BPA concentrations and adipose tissue measured by DXA and magnetic resonance imaging (MRI).[27] To our knowledge, such relationships have not been thoroughly examined in children yet.

NHANES provide multi-year data on both urinary BPA concentration and body composition measurements for children. Compared to other population-based data sources, NHANES data have several advantages, such as large sample size, stable and robust sampling strategies, and standardized laboratory techniques.[28] The objective of this study was to investigate the association of urinary BPA levels with body composition in children using multi-year (2003–2006) NHANES data. DXA was used in NHANES to non-invasively estimate lean mass (excluding bone mineral content) and FM of the total body, trunk, arms, and legs. Compared with other methods, such as anthropometric measurements, bioelectrical impedance analysis, computed tomography, and MRI, DXA is accessible, easy to use, carries a low radiation exposure, and has good accuracy and reproducibility even under disease states and growing conditions.[29] Because alterations of body composition occur differently between boys and girls,[30] the abovementioned associations were examined separately by gender.

Methods

Study population

NHANES is a continuous surveillance program administered by the National Center for Health Statistics (NCHS), which is part of Centers for Disease Control and Prevention (CDC). Participants in NHANES received cross-sectional surveys and were sampled from civilian, non-institutionalized Americans using a stratified multistage probability design. The aim of NHANES is to assess the health and nutritional status of the general United States population for both children and adults. The research protocols for NHANES were approved by NCHS Institutional Review Board (IRB). Detailed information on the study designs and data collection procedures has been published elsewhere.[28]

Urinary concentrations of BPA have been measured among representative subsamples of participants aged 6 years and older since the 2003–2004 NHANES. Whole-body DXA scans were administered for participants aged 8 years and older during the 1999–2006 survey years. These yielded our final sample of 1860 children aged 8–19 years old who were enrolled in cross-sectional surveys of the 2003–2006 NHANES and had complete data on both urinary BPA concentration and body composition measurements using DXA.

Urinary BPA

Urinary concentrations of free and conjugated BPA were measured at the Division of Environmental Health Laboratory Sciences (National Center for Environmental Health, CDC, Atlanta, Georgia, USA) using on-line solid phase extraction coupled to high-performance liquid chromatography and tandem mass spectrometry.[31,32] Coefficients of variation for quality control urine samples at low and high concentrations were 19% and 12% in the 2003–2004 cycle and 13% and 11% in the 2005–2006 cycle. The lower limit of detection was 0.36 ng/mL in 2003–2004 and 0.4 ng/mL in 2005–2006. NHANES has assigned BPA concentrations below the level of detection with a value of 0.3 ng/mL. Due to a right-skewed distribution, urinary BPA concentrations were log-transformed, as well as being categorized into quartiles (Q1: 0.30 ng/mL to <1.50 ng/mL, Q2: 1.50 ng/mL to <3.17 ng/mL, Q3: 3.17 ng/mL to <6.06 ng/mL, and Q4: ≥6.06 ng/mL) to examine dose–response relationships.

Measurements of body composition by DXA

After urine specimen collection, DXA scans were conducted during the examination sessions on the same day. Participants aged 8 years or older at examination were eligible for DXA scans. Whole-body DXA scans were undertaken in the NHANES mobile examination centers using the Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, MA, USA) with Hologic software version 8.26:a3* till mid-2005.[33] The acquisition software was upgraded to Hologic Discovery v12.4 in 2005. Participants were excluded from DXA exams if they: 1) had a positive pregnancy test at the time of the examination; 2) stated that they were pregnant; 3) weighed over 300 lbs (136 kg); or 4) were taller than 6′5″ (195 cm).

The QDR-4500A densitometers overestimated lean mass and underestimated FM by 5%.[34] Therefore, NHANES decreased DXA lean mass by 5% and an equivalent weight (in kilograms) was added to the FM so that the total mass remained the same.[35] To account for nonrandom missing DXA data, multiple imputation was performed by the National Center for Health Statistics (NCHS) to create five imputed data sets using a sequential regression multivariate imputation method.[36] Detailed information on the rationale and methods for multiple imputation has been described in the NHANES DXA data file documents.[35]

The percentage of body fat of each region and the total body was estimated using DXA scans. Fat mass index (FMI) and lean body mass index (LBMI) were calculated as FM (kg) or LBM (kg), respectively, divided by the square of height (m). LBM did not include bone mineral content. To facilitate comparisons of FMI and LBMI across age, gender, and race/ethnicity, FMI and LBMI z-scores were calculated based on a newly published fat and lean BMI

reference curve for American children.[37] Peripheral fat mass (kg) or lean body mass (kg) was estimated by summing up FM or LBM from arms and legs. Trunk:peripheral fat ratio was calculated by dividing trunk fat mass (kg) by peripheral fat mass (kg).

Statistical methods

All analyses were weighted for the complex cluster sample design and conducted using Proc Survey in SAS Version 9.3 (SAS Institute, Cary, NC, USA). Distributions of selected demographic and lifestyle characteristics were described using unweighted frequencies and weighted proportions. Weighted means and standard errors of urinary BPA concentrations were calculated and compared across those demographic and lifestyle covariates.

Weighted means and standard errors of body composition measurements were calculated for the whole sample and compared by age and gender (i.e., 8–11 years old vs. 12–19 years old and boys vs. girls). The associations of urinary BPA concentration with body composition measurements were examined using multivariate linear regression models. Urinary BPA was categorized using weighted quartiles. Urinary BPA was also analyzed as a continuous variable using log-transformation. Body composition measurements were treated as continuous outcome variables.

Measurement of potential confounders that were adjusted for in linear regression models is described in supplementary material (eAppendix 1). Linear regression models were fitted using 4-year waves of NHANES from 2003 to 2006. In order to investigate whether the associations of urinary BPA concentration and body composition measurements differed by gender, linear regression models were fitted separately for boys and girls.

All regression analyses were repeatedly performed for each of the five imputed data sets. Final results were generated by combining five sets of regression coefficients using Rubin's combining rules (SAS procedure: PROC MIANALYZE). $p < 0.05$ was considered to be statistically significant in all analyses.

Results

Urinary BPA concentration by selected demographic variables

A total of 1860 children participated in the 2003–2006 NHANES, donated urine samples, and completed DXA exams (Table 1). Approximately 67.5% of the participants were older than 12 years. Slightly more than half (51.5%) were boys. The weighted mean urinary BPA level was 5.61 ng/mL (standard error: 0.25 ng/mL). Although urinary BPA concentration did not significantly differ by age, gender, body weight status, caregiver's education, family income:poverty ratio, or sedentary behaviors, BPA concentration varied statistically significantly by race/ethnicity, serum cotinine, and survey year ($p < 0.05$).

Comparisons of body composition measurements by age and gender

Body composition measurements are presented for all subjects and by age-sex subgroups in Table 2. Compared to the participants aged 8–11 years old, children 12–19 years of age had statistically significantly greater FM, LBM, and trunk:peripheral fat ratio ($p < 0.05$). Younger children had statistically significantly greater FP of the arms, legs, and total body ($p < 0.05$).

Among 8–11 year olds, girls had significantly lower arm LBM, but significantly greater trunk:peripheral fat ratio, and significantly greater total and regional FPs than boys ($p < 0.05$). Within the group of 12–19 year olds, girls had significantly lower LBM, but significantly higher FM, and significantly greater total and regional FPs compared to their same-aged male counterparts ($p < 0.05$). FMI z-scores and LBMI z-scores did not significantly differ by age and gender ($p > 0.05$).

The associations between urinary BPA concentration and body composition measurements in boys

Body composition measurements are presented by quartiles of urinary BPA concentration for boys in Table 3. Using multiple linear regression analysis after controlling for demographic and lifestyle covariates, the trunk FM of boys in the second ($\beta = 1.38$, 95% CI, 0.32–2.43) and third ($\beta = 1.03$, 95% CI, 0.16–1.89) quartiles, but not in the highest quartile, were significantly higher than that in the lowest quartile of urinary BPA concentration ($p < 0.05$). LBM of all regions (arms, legs, and trunk) were ubiquitously significantly higher in the second and fourth quartiles compared to the lowest quartile of urinary BPA level ($p < 0.05$). Correspondingly, trunk:peripheral fat ratio was significantly greater in the second ($\beta = 0.064$, 95% CI, 0.025–0.103), third ($\beta = 0.061$, 95% CI, 0.027–0.094), and fourth ($\beta = 0.041$, 95% CI, 0.007–0.075) quartiles compared to the lowest quartile of urinary BPA concentration ($p < 0.05$). Neither FPs nor FMI z-scores were significantly associated with BPA concentration. However, LBMI z-scores were significantly higher in the second ($\beta = 0.436$, 95% CI, 0.137–0.735) and fourth ($\beta = 0.406$, 95% CI, 0.200–0.611) quartiles. Using log-transformed urinary BPA to substitute BPA quartiles, significantly positive associations were found between log-transformed urinary BPA levels and LBM ($\beta = 0.10$, 95% CI, 0.02–0.17 for arms and $\beta = 0.24$, 95% CI, 0.02–0.45 for legs), and between LBMI z-score ($\beta = 0.109$, 95% CI, 0.030–0.188).

The associations between urinary BPA concentration and body composition measurements in girls

Table 4 shows changes in body composition measurements by quartiles of urinary BPA concentration in girls. After adjusting for demographic and lifestyle covariates, arm FM was significantly higher in the second ($\beta = 0.24$, 95% CI, 0.02–0.46) quartile than in the lowest quartile of urinary BPA concentration, and trunk FM was significantly greater in the second ($\beta = 1.12$, 95% CI, 0.15–2.09) and fourth ($\beta = 1.32$, 95% CI, 0.24–2.40) quartiles ($p < 0.05$). Trunk:peripheral fat ratio was significantly greater in the third ($\beta = 0.049$, 95% CI, 0.003–0.096) and fourth ($\beta = 0.056$, 95% CI, 0.011–0.102) quartiles compared to the lowest quartile of urinary BPA concentration ($p < 0.05$). FP of the arms, trunk, and total body was ubiquitously statistically significantly increased in the second and third quartiles ($p < 0.05$). Neither LBM nor LBMI z-scores had statistically significant changes with elevated BPA concentration. However, FMI z-scores were significantly increased in the second ($\beta = 0.294$, 95% CI, 0.064–0.524), third ($\beta = 0.295$, 95% CI, 0.022–0.567), and fourth ($\beta = 0.293$, 95% CI, 0.037–0.549) quartiles. Similarly, log-transformed urinary BPA levels were positively associated with trunk FP ($\beta = 0.81$, 95% CI, 0.02–1.61) and FMI z-score ($\beta = 0.090$, 95% CI, 0.003–0.177).

Discussion

This study used a multi-year nationally representative sample of American children to examine the associations of urinary BPA concentration with body composition measurements, such as FM, LBM, and body FP. To our knowledge, this may be the first study to investigate the associations in a large-scale population-based sample of young people. Moderate associations between high urinary BPA concentration (both quartiled and log-transformed) and body mass accumulation were identified using regression models, even after controlling for traditional demographic and lifestyle covariates. However, the contribution of urinary BPA concentration

Table 1
Weighted mean urinary bisphenol A concentration of the study participants (8–19 years old) by selected demographic characteristics, National Health and Nutrition Examination Survey (NHANES) 2003–2006.

Characters	All[a]	Urinary bisphenol A level (ng/mL)[b]	*p* value[c]
		Mean (SE)	
N	1860	5.61 (0.25)	
Age, years, n (%)			0.116
8–11	448 (32.48)	6.43 (0.70)	
12–19	1412 (67.52)	5.22 (0.20)	
Sex, n (%)			0.221
Male	950 (51.49)	6.04 (0.52)	
Female	910 (48.51)	5.16 (0.33)	
Race/ethnicity, n (%)			0.001
Non-Hispanic white	495 (61.54)	5.40 (0.33)	
Non-Hispanic black	631 (15.56)	6.23 (0.42)	
Mexican American	592 (12.20)	4.09 (0.33)	
Other Hispanic	50 (3.86)	7.11 (2.69)	
Other	92 (6.84)	8.00 (2.19)	
Body weight status			0.445
Underweight	70 (3.56)	6.39 (1.00)	
Normal weight	1096 (62.42)	5.67 (0.39)	
Overweight	314 (17.21)	5.07 (0.41)	
Obesity	380 (16.81)	5.78 (0.44)	
Caregiver education, n (%)			0.487
Less than high school	572 (19.06)	5.21 (0.48)	
High school, GED or equivalent	418 (25.33)	5.97 (0.39)	
More than high school	782 (55.61)	5.59 (0.39)	
Family income:poverty ratio, n (%)			0.419
<1	550 (20.47)	6.11 (0.36)	
1–4	1065 (64.43)	5.59 (0.33)	
≥5	171 (15.10)	4.96 (0.83)	
Serum cotinine, ng/mL, n (%)			0.010
Low to moderate (<2 ng/mL)	1433 (84.09)	5.02 (0.27)	
High (≥2 ng/mL)	263 (15.91)	6.86 (0.53)	
Television/video watching, hours/day, n (%)			0.489
<2 h/day	573 (34.85)	5.93 (0.53)	
≥2 h/day	1242 (65.15)	5.48 (0.30)	
Computer use, n (%)			0.270
Non-use	434 (18.94)	6.23 (0.51)	
Use	1380 (81.06)	5.50 (0.31)	
Survey year, n (%)			0.037
2003–2004	918 (49.31)	6.17 (0.18)	
2005–2006	942 (50.69)	5.07 (0.47)	

GED, general equivalency diploma; SE, standard error.
[a] Unweighted frequencies and weighted proportions are presented.
[b] Weighted means and SE are presented.
[c] Survey linear regression models were used to compare urinary bisphenol A concentration for each of the selected demographic characteristics.

to body weight was undertaken through different pathways between boys and girls. Specifically, high levels of urinary BPA concentration were statistically significantly associated with an increase in LBM among boys but an increase in FM among girls.

The "environmental obesogen hypothesis" proposes that exposure to environmental obesogenic chemicals may predispose some individuals to the development of obesity and associated health conditions, such as type 2 diabetes, CVDs, hypertension, and dyslipidemia.[3] BPA is one of the most common obesogens, with the majority of daily exposure to BPA coming from our diet.[4] As a synthetic estrogen, BPA could imitate the actions of estradiol and disrupt nuclear hormone receptor signaling pathways involved in adipogenesis, lipid metabolism, and energy balance.[5,38,39]

No randomized controlled trials have been conducted to examine the associations between BPA exposure and obesity because of ethical concerns, while cross-sectional, case–control, and prospective epidemiological studies have provided mixed findings. Non-significant associations were found between birth weight of offspring and BPA concentration of mothers.[12] A prospective cohort study of 297 mother-child pairs from the HOME Study found that prenatal and early-life exposure to BPA was not associated with an increase in BMI at 2–5 years of age.[17] However, a number of other studies have reported significant associations between BPA levels and body weight (or BMI) in children, adults, and polycystic ovary syndrome patients.[9,11,18–21,40]

BMI has been widely used in previous studies to measure adiposity of their subjects, which may partly explain such discrepancies. Trasande et al. analyzed the data of 2838 children aged 6–19 years from the 2003–2008 NHANES and observed positive associations between urinary BPA and BMI z-scores in both boys and girls.[9] A study in eastern China found no difference in urinary BPA concentrations between normal weight and overweight/obese school children.[41] Eng et al. examined children aged 6–18 years from the 2003–2010 NHANES and found that urinary BPA was significantly associated with obesity and waist circumference:height ratio but not associated with other chronic disease risk factors, including body FP.[7] Although BMI is commonly used as a proxy for obesity, it has been noted that BMI does not distinguish between adipose tissue and lean mass and gives an imperfect estimate of body FP.[13] Factors such as age, race/ethnicity, and physical activity may confound the relationship between BMI and adiposity status.[42]

The major finding of this study is that we observed urinary BPA concentration differentially associated with body composition measurements between boys and girls aged 8–19 years old. Boys at higher levels of urinary BPA concentration had significantly greater LBM, reflected by LBMI z-scores, while girls with higher BPA concentration had significantly greater FM, reflected by FMI z-scores, as well as FP of the arms, trunk, and total body. It is unclear why BPA may "target" body compartments (i.e., fat and lean mass) differently in boys and girls. We speculate that the underlying mechanism may be related to different sex hormonal reactions to BPA exposure by gender. LBM growth is promoted by testosterone in boys.[43] The data on the BPA association with testosterone concentration are scarce in boys. However, Galloway et al. examined the relationship between BPA excretion and sex hormone levels in Italian men.[8] They found no association between urinary BPA concentration and 17β-estradiol but a highly significant association between BPA and total testosterone concentration, even after adjusting for covariates ($\beta = 0.046$, 95% CI, 0.015–0.076). Increased FM in girls may be due to the estrogen-like effects of BPA. Girls with higher BPA concentration are more likely to develop early onset of puberty, which is usually concurrent with childhood obesity.[44] Future research is needed to confirm this postulation and further examine the relationships between BPA exposure, sex hormone levels, and body composition changes.

Our results did not show an obvious dose–response relationship between urinary BPA concentration and body composition measurements in boys and girls. A large body of cell culture, animal, and epidemiological studies support this observation, and demonstrate low-dose effects and nonmonotonic dose–response curves of endocrine-disrupting chemicals (e.g., BPA) on adipose tissue.[9,18,38,45,46] For instance, BPA suppressed adiponectin release from mature adipocytes of human tissue and showed a U-shaped relationship.[45,46] In female mice, low-dose but not high-dose exposure to BPA increased adipose tissue weight and serum leptin concentrations, while low-dose but not high-dose BPA exposure increased serum triacylglycerol and glucose in male mice.[38] Both children and adult epidemiological studies reported nonmonotonic associations between urinary BPA and obesity.[9,18] The effects at low doses of BPA cannot be predicted by the effects at high doses. This may be explained by different endocrine-disrupting pathways that low-dose BPA activates via interfering with estrogen receptors, other nuclear and nonnuclear receptors, hormone metabolism, and epigenetic regulation.[47]

Our data suggested a variation in locations of body composition changes that were related to BPA exposure. BPA-related LBM

Table 2
Body composition measurements of the study participants (8–19 years old), National Health and Nutrition Examination Survey (NHANES) 2003–2006.[a]

	All	8-11 years	12-19 years	*p* value	8-11 years			12-19 years		
	Mean (SE)	Mean (SE)	Mean (SE)		Boys	Girls	*p* value	Boys	Girls	*p* value
					Mean (SE)	Mean (SE)		Mean (SE)	Mean (SE)	
Fat mass, kg										
Arm	2.01 (0.05)	1.51 (0.05)	2.25 (0.06)	<0.001	1.44 (0.10)	1.59 (0.06)	0.207	1.99 (0.07)	2.52 (0.06)	<0.001
Leg	7.07 (0.15)	5.31 (0.16)	7.91 (0.17)	<0.001	5.03 (0.27)	5.61 (0.20)	0.112	6.94 (0.19)	8.94 (0.17)	<0.001
Trunk	6.94 (0.19)	4.76 (0.19)	7.98 (0.22)	<0.001	4.40 (0.32)	5.15 (0.21)	0.065	7.03 (0.28)	8.99 (0.24)	<0.001
Lean body mass, kg										
Arm	4.17 (0.07)	2.68 (0.05)	4.88 (0.07)	<0.001	2.77 (0.07)	2.58 (0.05)	0.030	5.81 (0.08)	3.88 (0.04)	<0.001
Leg	12.54 (0.17)	8.29 (0.16)	14.56 (0.17)	<0.001	8.41 (0.24)	8.17 (0.17)	0.382	16.39 (0.20)	12.60 (0.13)	<0.001
Trunk	18.01 (0.23)	11.89 (0.22)	20.92 (0.19)	<0.001	12.08 (0.33)	11.70 (0.22)	0.324	22.92 (0.27)	18.79 (0.15)	<0.001
Trunk:peripheral fat ratio	0.726 (0.005)	0.667 (0.007)	0.754 (0.006)	<0.001	0.653 (0.011)	0.683 (0.010)	0.041	0.753 (0.010)	0.755 (0.010)	0.714
Fat percentage										
Arm	30.64 (0.39)	32.86 (0.52)	29.58 (0.49)	<0.001	31.18 (0.94)	34.68 (0.69)	0.011	23.58 (0.51)	35.99 (0.37)	<0.001
Leg	34.25 (0.34)	36.35 (0.38)	33.25 (0.45)	<0.001	34.83 (0.71)	37.99 (0.53)	0.004	27.74 (0.43)	39.14 (0.33)	<0.001
Trunk	25.61 (0.35)	25.98 (0.46)	25.43 (0.43)	0.332	24.32 (0.81)	27.77 (0.61)	0.004	21.36 (0.48)	29.78 (0.46)	<0.001
Total body fat percentage	29.25 (0.32)	30.40 (0.39)	28.70 (0.40)	0.002	28.92 (0.71)	32.00 (0.52)	0.004	24.20 (0.42)	33.51 (0.34)	<0.001
FMI z-score	0.018 (0.037)	0.066 (0.053)	−0.004 (0.041)	0.202	0.138 (0.092)	−0.012 (0.077)	0.277	−0.006 (0.056)	−0.002 (0.046)	0.893
LBMI z-score	0.157 (0.048)	0.141 (0.063)	0.165 (0.053)	0.652	0.127 (0.104)	0.155 (0.070)	0.823	0.127 (0.062)	0.205 (0.060)	0.272

FMI, fat mass index; LBMI, lean body mass index; SE, standard error.
[a] Survey linear regression models were used to compare body composition measurements by age and gender.

Table 3
Associations between urinary bisphenol A concentration and body composition measurements among boys (8–19 years old), National Health and Nutrition Examination Survey (NHANES) 2003–2006.[a]

	Concentration quartiles									Log BPA		
	Q1 (0.30 ng/mL to <1.50 ng/mL)	Q2 (1.50 ng/mL to <3.17 ng/mL)			Q3 (3.17 ng/mL to <6.06 ng/mL)			Q4 (≥6.06 ng/mL)			Beta estimate	95% CI	
	Beta estimate	Beta estimate	95% CI		Beta estimate	95% CI		Beta estimate	95% CI				
Fat mass, kg													
Arm	Reference	0.24	−0.05	0.53	0.19	−0.03	0.42	0.27	−0.07	0.61	0.09	−0.03	0.21
Leg	Reference	0.43	−0.34	1.20	0.16	−0.51	0.84	0.45	−0.53	1.43	0.13	−0.20	0.46
Trunk	Reference	*1.38*	*0.32*	*2.43*	*1.03*	*0.16*	*1.89*	1.21	−0.07	2.50	0.39	−0.08	0.87
Lean body mass, kg													
Arm	Reference	*0.33*	*0.09*	*0.58*	*0.21*	*0.01*	*0.41*	*0.28*	*0.05*	*0.50*	*0.10*	*0.02*	*0.17*
Leg	Reference	*0.67*	*0.04*	*1.31*	0.51	−0.06	1.08	*0.75*	*0.11*	*1.38*	*0.24*	*0.02*	*0.45*
Trunk	Reference	*1.23*	*0.22*	*2.24*	0.65	−0.13	1.43	*0.95*	*0.11*	*1.78*	0.28	−0.02	0.59
Trunk:peripheral fat ratio	Reference	*0.064*	*0.025*	*0.103*	*0.061*	*0.027*	*0.094*	*0.041*	*0.007*	*0.075*	0.014	−0.001	0.030
Fat percentage													
Arm	Reference	0.27	−2.16	2.69	−0.06	−2.13	2.00	0.14	−2.58	2.86	0.06	−0.85	0.96
Leg	Reference	0.16	−1.75	2.08	−0.62	−2.51	1.27	−0.40	−2.73	1.92	−0.15	−0.93	0.62
Trunk	Reference	1.61	−0.42	3.64	1.12	−0.63	2.88	1.04	−1.42	3.49	0.36	−0.51	1.24
Total body fat percentage	Reference	0.80	−1.03	2.63	0.28	−1.36	1.92	0.37	−1.86	2.60	0.13	−0.63	0.88
FMI z-score	Reference	0.155	−0.095	0.405	0.013	−0.218	0.243	0.072	−0.200	0.344	0.020	−0.077	0.117
LBMI z-score	Reference	*0.436*	*0.137*	*0.735*	0.213	−0.039	0.464	*0.406*	*0.200*	*0.611*	*0.109*	*0.030*	*0.188*

The significance level is $p < 0.05$.
BPA, bisphenol A; CI, confidence interval; FMI, fat mass index; LBMI, lean body mass index.
[a] Survey linear regression models were adjusted for age (months), ethnicity/race, height, caregiver's education, family income:poverty ratio, serum cotinine level, daily calorie intake, television/video watching, computer use, survey year, and urinary creatinine (log-transformed).

Table 4
Associations between urinary bisphenol A concentration and body composition measurements among girls (8–19 years old), National Health and Nutrition Examination Survey (NHANES) 2003–2006.[a]

	Concentration quartiles								Log BPA	
	Q1 (0.30 ng/mL to <1.50 ng/mL)	Q2 (1.50 ng/mL to <3.17 ng/mL)		Q3 (3.17 ng/mL to <6.06 ng/mL)		Q4 (≥6.06 ng/mL)		Beta estimate	95% CI
	Beta estimate	Beta estimate	95% CI	Beta estimate	95% CI	Beta estimate	95% CI		
Fat mass, kg									
Arm	Reference	*0.24*	*0.02* *0.46*	0.21	−0.05 0.47	0.27	−0.01 0.55	0.09	−0.02 0.19
Leg	Reference	0.63	−0.03 1.29	0.47	−0.37 1.32	0.69	−0.12 1.50	0.23	−0.06 0.52
Trunk	Reference	*1.12*	*0.15* *2.09*	0.84	−0.21 1.89	*1.32*	*0.24* *2.40*	0.35	−0.05 0.75
Lean body mass, kg									
Arm	Reference	0.05	−0.12 0.21	0.02	−0.12 0.15	0.14	−0.04 0.32	0.04	−0.02 0.09
Leg	Reference	0.33	−0.14 0.79	0.06	−0.49 0.62	0.53	−0.09 1.14	0.12	−0.09 0.34
Trunk	Reference	0.37	−0.16 0.90	0.26	−0.35 0.87	0.49	−0.12 1.09	0.11	−0.12 0.33
Trunk:peripheral fat ratio	Reference	0.045	−0.009 0.099	*0.049*	*0.003* *0.096*	*0.056*	*0.011* *0.102*	0.012	−0.004 0.028
Fat percentage									
Arm	Reference	*2.66*	*0.83* *4.50*	*2.56*	*0.13* *4.99*	1.81	−0.48 4.10	0.67	−0.08 1.43
Leg	Reference	1.54	−0.06 3.14	1.52	−0.54 3.58	1.00	−0.88 2.87	0.43	−0.17 1.04
Trunk	Reference	*2.85*	*0.92* *4.78*	*2.57*	*0.28* *4.85*	*2.79*	*0.44* *5.14*	*0.81*	*0.02* *1.61*
Total body fat percentage	Reference	*2.16*	*0.68* *3.64*	*1.99*	*0.06* *3.92*	1.84	−0.07 3.74	0.60	−0.03 1.23
FMI z-score	Reference	*0.294*	*0.064* *0.524*	*0.295*	*0.022* *0.567*	*0.293*	*0.037* *0.549*	*0.090*	*0.003* *0.177*
LBMI z-score	Reference	0.211	−0.054 0.475	0.136	−0.146 0.419	0.259	−0.051 0.569	0.062	−0.053 0.176

The significance level is $p < 0.05$.
BPA, bisphenol A; CI, confidence interval; FMI, fat mass index; LBMI, lean body mass index.
[a] Survey linear regression models were adjusted for age (months), ethnicity/race, height, caregiver's education, family income:poverty ratio, serum cotinine level, daily calorie intake, television/video watching, computer use, survey year, and urinary creatinine (log-transformed).

changes were observed for the regions of arms, legs, and trunk in boys, while FM changes were observed for the trunk in boys, and for the trunk and arms in girls. Accumulating evidence suggests that adiposity in different parts of the body may have different associations with health outcomes. The Pennington Center Longitudinal Study in 3220 white and African-American adults found that higher trunk adiposity was significantly associated with increased cardiometabolic risks among both men and women, higher arm adiposity was associated with increased cardiometabolic risks among women but not among men, and higher leg adiposity was associated with decreased cardiometabolic risks among both men and women.[48] Similar patterns were observed in children.[48] It is not clear why BPA exposure is associated with a deposition of fat in the trunk and maintenance of fat in the legs, which merits further investigation.

This study has several limitations. First, due to the cross-sectional nature of NHANES, we cannot investigate longitudinal relationships between urinary BPA concentration and changes in body composition. Therefore, we were unable to establish causal relationships based on the present findings. Second, Tanner stage was not assessed for children enrolled in NHANES. Therefore, we were unable to account for the potential impact of puberty on body composition in our analyses. However, urinary BPA concentration did not significantly differ between 8-11 year olds and 12–19 year olds (Table 1) in our study population, and all regression models were adjusted for children's age, which is a significant predictor of onset of puberty. Finally, estimates of FM from DXA have been shown to be different from those calculated using the four-compartment model, which is considered the gold standard for estimating FM.[49] However, given its convenience, reliability and availability, DXA is a more practical approach to evaluate body composition in epidemiological settings.

In conclusion, we found that high urinary BPA concentration may be associated with increased LBM in boys and increased FM in girls. Despite its limitations, our study provided new information on the mechanisms of BPA exposure and obesity. Biomedical experiments and longitudinal studies are warranted to confirm our findings, examine the possible mechanisms, and clarify their temporal relationships. Given the high prevalence of childhood obesity and exposure to BPA in the United States, monitoring and regulating programs on BPA exposure in American children may be a cost-effective approach to reduce the risk of overweight and obesity in this country.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.je.2016.12.001.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220 (in eng).

2. Chan RS, Woo J. Prevention of overweight and obesity: how effective is the current public health approach. *Int J Environ Res Public Health*. 2010;7:765–783 (in eng).
3. Holtcamp W. Obesogens: an environmental link to obesity. *Environ Health Perspect*. 2012;120. a62–8 (in eng).
4. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect*. 2008;116:39–44 (in eng).
5. Grun F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. *Rev Endocr Metab Disord*. 2007;8:161–171 (in eng).
6. Bhandari R, Xiao J, Shankar A. Urinary bisphenol A and obesity in U.S. children. *Am J Epidemiol*. 2013;177:1263–1270 (in eng).
7. Eng DS, Lee JM, Gebremariam A, Meeker JD, Peterson K, Padmanabhan V. Bisphenol A and chronic disease risk factors in US children. *Pediatrics*. 2013;132. e637–45 (in eng).
8. Galloway T, Cipelli R, Guralnik J, et al. Daily bisphenol A excretion and associations with sex hormone concentrations: results from the InCHIANTI adult population study. *Environ Health Perspect*. 2010;118:1603–1608 (in eng).
9. Trasande L, Attina TM, Blustein J. Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. *JAMA*. 2012;308:1113–1121 (in eng).
10. Li DK, Miao M, Zhou Z, et al. Urine bisphenol-A level in relation to obesity and overweight in school-age children. *PLoS One*. 2013;8. e65399 (in eng).
11. Miao M, Yuan W, Zhu G, He X, Li DK. In utero exposure to bisphenol-A and its effect on birth weight of offspring. *Reprod Toxicol*. 2011;32:64–68 (in eng).
12. Wolff MS, Engel SM, Berkowitz GS, et al. Prenatal phenol and phthalate exposures and birth outcomes. *Environ Health Perspect*. 2008;116:1092–1097 (in eng).
13. Ellis KJ, Abrams SA, Wong WW. Monitoring childhood obesity: assessment of the weight/height index. *Am J Epidemiol*. 1999;150:939–946 (in eng).
14. L'Abee C, Visser GH, Liem ET, Kok DE, Sauer PJ, Stolk RP. Comparison of methods to assess body fat in non-obese six to seven-year-old children. *Clin Nutr*. 2010;29:317–322 (in eng).
15. Michels N, Huybrechts I, Bammann K, et al. Caucasian children's fat mass: routine anthropometry v. air-displacement plethysmography. *Br J Nutr*. 2013;109:1528–1537 (in eng).
16. Wang H, Story RE, Venners SA, et al. Patterns and interrelationships of body-fat measures among rural Chinese children aged 6 to 18 years. *Pediatrics*. 2007;120:e94–e101 (in eng).
17. Braun JM, Lanphear BP, Calafat AM, et al. Early-life bisphenol a exposure and child body mass index: a prospective cohort study. *Environ Health Perspect*. 2014;122:1239–1245 (in eng).
18. Carwile JL, Michels KB. Urinary bisphenol A and obesity: NHANES 2003-2006. *Environ Res*. 2011;111:825–830 (in eng).
19. Philippat C, Mortamais M, Chevrier C, et al. Exposure to phthalates and phenols during pregnancy and offspring size at birth. *Environ Health Perspect*. 2012;120:464–470 (in eng).
20. Valvi D, Casas M, Mendez MA, et al. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. *Epidemiology*. 2013;24:791–799 (in eng).
21. Wang HX, Zhou Y, Tang CX, Wu JG, Chen Y, Jiang QW. Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study. *Environ Health*. 2012;11:79 (in eng).
22. Mason C, Craig CL, Katzmarzyk PT. Influence of central and extremity circumferences on all-cause mortality in men and women. *Obes (Silver Spring)*. 2008;16:2690–2695 (in eng).
23. Carey VJ, Walters EE, Colditz GA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am J Epidemiol*. 1997;145:614–619 (in eng).
24. Lee M, Choh AC, Demerath EW, Towne B, Siervogel RM, Czerwinski SA. Associations between trunk, leg and total body adiposity with arterial stiffness. *Am J Hypertens*. 2012;25:1131–1137 (in eng).
25. Fox KA, Despres JP, Richard AJ, et al. Does abdominal obesity have a similar impact on cardiovascular disease and diabetes? A study of 91,246 ambulant patients in 27 European countries. *Eur Heart J*. 2009;30:3055–3063 (in eng).
26. Staiano AE, Gupta AK, Katzmarzyk PT. Cardiometabolic risk factors and fat distribution in children and adolescents. *J Pediatr*. 2014;164:560–565 (in eng).
27. Ronn M, Lind L, Orberg J, et al. Bisphenol A is related to circulating levels of adiponectin, leptin and ghrelin, but not to fat mass or fat distribution in humans. *Chemosphere*. 2014;112:42–48 (in eng).
28. National Center for Health Statistics, Centers for Disease Control and Prevention. *Analytic and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES)*; 2006. Hyattsville, MD, USA. Available https://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf.
29. Lee SY, Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care*. 2008;11:566–572 (in eng).
30. Bitar A, Vernet J, Coudert J, Vermorel M. Longitudinal changes in body composition, physical capacities and energy expenditure in boys and girls during the onset of puberty. *Eur J Nutr*. 2000;39:157–163 (in eng).
31. Centers for Disease Control and Prevention. *Laboratory Procedure Manual: The National Health and Nutrition Examination Survey (NHANES) 2003-2004*; 2005. Available https://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l24eph_c_met_phenols.pdf.
32. Centers for Disease Control and Prevention. *Laboratory Procedure Manual: The National Health and Nutrition Examination Survey (NHANES) 2005-2006*; 2009. Available https://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/eph_d_met_phenols_parabens.pdf.
33. Centers for Disease Control and Prevention. *The National Health and Nutrition Examination Survey (NHANES) 2003-2004 Data Documentation, Codebook, and Frequencies: Dual-energy X-Ray Absorptiometry*; 2008. Available https://wwwn.cdc.gov/Nchs/Data/Nhanes/Dxa/dxx_c.pdf.
34. Schoeller DA, Tylavsky FA, Baer DJ, et al. QDR 4500A dual-energy X-ray absorptiometer underestimates fat mass in comparison with criterion methods in adults. *Am J Clin Nutr*. 2005;81:1018–1025 (in eng).
35. National Center for Health Statistics, Centers for Disease Control and Prevention. *The National Health and Nutrition Examination Survey (NHANES): Technical Documentation for the 1999-2004 Dual Energy X-Ray Absorptiometry (DXA) Multiple Imputation Data Files*; 2008. Available https://wwwn.cdc.gov/Nchs/Data/Nhanes/Dxa/dxa_techdoc.pdf.
36. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399 (in eng).
37. Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *Am J Clin Nutr*. 2013;98:49–56 (in eng).
38. Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb*. 2007;14:245–252 (in eng).
39. Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect*. 2001;109:675–680 (in eng).
40. Kandaraki E, Chatzigeorgiou A, Livadas S, et al. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. *J Clin Endocrinol Metab*. 2011;96:E480–E484 (in eng).
41. Wang B, Wang H, Zhou W, et al. Exposure to bisphenol A among school children in eastern China: a multicenter cross-sectional study. *J Expo Sci Environ Epidemiol*. 2014;24:657–664 (in eng).
42. Ode JJ, Pivarnik JM, Reeves MJ, Knous JL. Body mass index as a predictor of percent fat in college athletes and nonathletes. *Med Sci Sports Exerc*. 2007;39:403–409 (in eng).
43. Arslanian S, Suprasongsin C. Testosterone treatment in adolescents with delayed puberty: changes in body composition, protein, fat, and glucose metabolism. *J Clin Endocrinol Metab*. 1997;82:3213–3220 (in eng).
44. Durmaz E, Asci A, Erkekoglu P, Akcurin S, Gumusel BK, Bircan I. Urinary bisphenol a levels in girls with idiopathic central precocious puberty. *J Clin Res Pediatr Endocrinol*. 2014;6:16–21 (in eng).
45. Ben-Jonathan N, Hugo ER, Brandebourg TD. Effects of bisphenol A on adipokine release from human adipose tissue: implications for the metabolic syndrome. *Mol Cell Endocrinol*. 2009;304:49–54 (in eng).
46. Hugo ER, Brandebourg TD, Woo JG, Loftus J, Alexander JW, Ben-Jonathan N. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. *Environ Health Perspect*. 2008;116:1642–1647 (in eng).
47. Acconcia F, Pallottini V, Marino M. Molecular mechanisms of action of BPA. *Dose Response*. 2015;13, 155932581561058 2. (in eng).
48. Hu G, Bouchard C, Bray GA, et al. Trunk versus extremity adiposity and cardiometabolic risk factors in white and African American adults. *Diabetes Care*. 2011;34:1415–1418 (in eng).
49. Van Der Ploeg GE, Withers RT, Laforgia J. Percent body fat via DEXA: comparison with a four-compartment model. *J Appl Physiol*. 1985;2003(94):499–506 (in eng).