Urinary Bisphenols and Obesity Prevalence Among U.S. Children and Adolescents

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Bisphenol A (BPA) has been recognized as an endocrine disrupting chemical and identified as an obesogen. Although once ubiquitous, human exposure to BPA has been declining owing to its substitution with other bisphenols. Two structurally similar substitutes, bisphenol S (BPS) and bisphenol F (BPF), have raised similar concerns, although fewer studies have been conducted on these newer derivatives. We used data from the US National Health and Nutrition Examination Surveys from 2013 to 2016 to evaluate associations between BPA, BPS, and BPF and body mass outcomes among children and adolescents aged 6 to 19 years. Concentrations of BPA, BPS, and BPF were measured in spot urine samples using HPLC with tandem mass spectrometry. General obesity was defined as ≥95th percentile of the age- and sex-standardized body mass index (BMI) z-scores according to the 2000 US norms. Abdominal obesity was defined as a waist circumference/height ratio of ≥0.5. BPA, BPS, and BPF were detected in 97.5%, 87.8%, and 55.2% of urine samples, respectively. Log-transformed urinary BPS concentrations were associated with an increased prevalence of general obesity (OR, 1.16; 95% CI, 1.02 to 1.32) and abdominal obesity (OR, 1.13; 95% CI, 1.02 to 1.27). BPF detection (vs not detected) was associated with an increased prevalence of abdominal obesity (OR, 1.29; 95% CI, 1.01 to 1.64) and continuous BMI z-score (β = 0.10; 95% CI, 0.01 to 0.20). BPA and total bisphenols were not statistically significantly associated with general obesity, abdominal obesity, or any body mass outcome. These results suggest that BPA substitute chemicals are correlated with obesity in contemporary children.

Freeform/Key Words: bisphenol A, bisphenol S, bisphenol F, bisphenol A replacements, obesity, childhood obesity

Bisphenol A (BPA) is one of the best known synthetic chemical obesogens [1, 2]. It enlarges adipocytes and enhances differentiation from mesenchymal cells to adipocytes [3], inhibits adiponectin function [4], and is a synthetic estrogen and, thereby, can have sex-specific effects on body mass [5]. Although longitudinal cohort studies have not yielded identical results, the totality of laboratory and human evidence has suggested substantial probability of causation [6]. Increasing concern about obesogenic and other adverse effects of BPA have precipitated

Abbreviations: BMI, body mass index; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; LOD, limit of detection; NHANES, US National Health and Nutrition Examination Surveys; PIR, poverty/income ratio.

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the substitution of BPA with 1 of the 40 structurally similar bisphenols currently in use [7]. Although tissue and animal studies of the replacements are lacking, two common analogs, bisphenol S (BPS) and bisphenol F (BPF), have shown estrogenic activity [8, 9]. Furthermore, BPS has been shown to promote preadipocyte differentiation [10], raising the possibility that these BPA replacements can induce the same obesogenic effects in humans.

As a step toward examining this question, we examined the cross-sectional relationships of urinary BPA, BPS, and BPF and body mass outcomes among children in the US National Health and Nutrition Examination Surveys (NHANES) from 2013 to 2016. The present analysis reprises work we performed using the NHANES from 2003 to 2008 [11] and is supported by recent work using NHANES from 2013 to 2014 identifying associations of urinary BPF with obesity in children and adolescents [12].

1. Materials and Methods

A. Study Population

NHANES is a nationally representative survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention that collects and releases data continuously over time in 2-year cycles [13]. The present study combined data from the 2013 to 2014 and 2015 to 2016 cycles to provide more statistically reliable estimates. Data from the questionnaire, laboratory, diet, and physical examination components of the NHANES were used for the present study. The study population was restricted to those aged 6 to 19 years, which resulted in 1831 children and adolescents.

B. Measures

B-1. Bisphenol compounds

Concentrations of BPA, BPS, and BPF were measured in spot urine samples using HPLC with tandem mass spectrometry. Further details on the analytical methods have been previously reported [14]. BPA, BPS, and BPF were detected in 97.5%, 87.8%, and 55.2% of samples, respectively (weighted proportions). For BPA and BPS, concentrations less than the limit of detection (LOD) (0.2 and 0.1 ng/mL, respectively) were substituted by the LOD divided by the square root of two. However, because BPF was only detected in just over one half of the samples, substitution was not conducted, and it was analyzed as a dichotomous variable, as less than and greater than the LOD (0.2 ng/mL). The total bisphenol concentrations were calculated by summing the concentrations of BPA, BPS, and BPF. When constructing the total bisphenol concentrations, BPF measures less than the LOD were imputed by the LOD divided by the square root of two.

B-2. Body mass outcomes

Although the primary outcome of interest was obesity, we also examined overweight, severe obesity, and body mass index (BMI) z-scores as a continuous measure and a as measure of abdominal obesity. As a part of the NHANES anthropometry protocol, trained health technicians measured the height, weight, and waist circumference using standardized examination procedures [15]. The BMI was calculated from measured height and weight values as the weight in kilograms divided by the height in meters squared (kg/m^2). Because the BMI changes rapidly in childhood and by age and sex, the BMIs were standardized to age- and sex-adjusted z-scores according to the 2000 US norms [16, 17]. Overweight and obesity (hereafter referred to as general obesity) were defined by the 85th and 95th percentiles of the BMI z-scores, respectively [18]. Severe obesity was defined as >120% of the 95th percentile of the BMI z-scores or a BMI of ≥35 kg/m^2, whichever was lower [19]. The BMI z-score was also examined as a continuous variable. Abdominal obesity was defined as a waist circumference/height ratio ≥0.5 [12, 20].

B-3. Covariates

Data from the two cycles (2013 to 2014 and 2015 to 2016) were combined using the appropriate weighting guidelines [21]. The demographic variables included sex, age, race/ethnicity, education level of the head of household, and the ratio of family income to poverty [or the poverty/income ratio (PIR)]. Behavioral factors were also examined. These included the time spent watching television, caloric intake determined from 24-hour dietary recall interviews, and tobacco smoke exposure. Tobacco smoke exposure was assessed using a composite variable owing to a disparity in the NHANES data availability from the 2013 to 2014 and 2015 to 2016 cycles. In 2013 to 2014, smoke exposure was determined from serum cotinine concentrations (≥2 ng/mL considered as exposure) and in 2015 to 2016, was based on one or more smokers in the child's household or ever having smoked themselves if the child was ≥12 years old.

C. Statistical Analysis

Statistical analyses were based on our previously reported work on BPA and obesity [11]. First, we explored the distribution of bisphenol exposure in the study population by computing the geometric mean values of BPA and BPS for each covariate stratum. For BPF, we examined the study population characteristics across strata of BPF detection (*i.e.,* less than and greater than the LOD). Differences across strata for BPA and BPS were evaluated using Mann-Whitney *U* tests for dichotomous variables and Kruskal-Wallis H tests for variables with two or more categories and for BPF detection using χ^2 tests.

The associations between bisphenol compounds and general obesity were tested by fitting three sets of logistic regression models. First, models were fit, controlling only for urinary creatinine. Second, to assess the potential for heterogeneity in this association, models were stratified by the demographic and behavioral characteristics examined. Finally, fully adjusted models were fit, controlling for the following covariates: urinary creatinine, sex, race/ethnicity, age, head of household education, PIR, serum cotinine exposure and/or smoking, caloric intake, and time spent watching television. Finally, additional multivariable logistic regression models were fit for the overweight, severe obesity, and abdominal obesity outcomes, and a multivariable linear regression model was fit for the BMI z-score outcome, all controlling for these same covariates. In all models, BPA, BPS, and total bisphenols were assessed as natural log-transformed continuous variables. However, because of its lower detection frequency (55.2%), BPF was assessed as dichotomized as less than and greater than the LOD. In subsequent sensitivity analyses, all models were fit again with BPA, BPS, and total bisphenol concentrations, parameterized in quartiles to assess the potential for nonmonotonic associations. All statistical analyses were conducted using Stata, version 14 (StataCorp, College Station, TX). All analyses accounted for the complex survey sampling according to the NHANES analytic guidelines [22] and were appropriately weighted. All statistical tests were two-sided and α of 0.05.

2. Results

The median concentrations of BPA, BPS, and BPF were 1.3 ng/mL (25th percentile, 0.7 ng/mL; 75th percentile, 2.3 ng/mL), 0.4 ng/mL (25th percentile, 0.2 ng/mL; 75th percentile, 0.8 ng/mL), and 0.2 ng/mL (25th percentile, LOD or less; 75th percentile, 0.7 ng/mL), respectively. Age and sex were not significantly associated with BPA or BPS; however, those with detectable BPF concentrations were more likely to be adolescents (age, 12 to 19 years; 59.5%) vs children (age, 6 to 11 years) compared with those without detectable BPF concentrations (51.6%; $P = 0.02$; Table 1). The BPA and BPS concentrations were inversely associated with PIR, such that those with a low PIR (*i.e.,* lower income) tended to have greater BPA and BPS concentrations compared with those with a greater PIR. This trend was similar for head of household education and BPS. Finally, BPA, BPS, and BPF exposure

Table 1. Study Population Characteristics in Total Sample Stratified by BPA and BPS Concentrations and BPF Detection, NHANES from 2013 to 2016

Characteristic	Total[a] (n = 1831), n (%)	BPA (ng/mL)			BPS (ng/mL)			BPF Detection, % (SE)				
		GM	GSE	*P* Value[b]	GM	GSE	*P* Value[b]	Yes (n = 948)		No (n = 883)		*P* Value[c]
Sex												
Male	937 (50.76)	1.29	0.06		0.36	0.02		50.94	1.97	50.93	2.21	
Female	894 (49.24)	1.23	0.06	0.13	0.39	0.02	0.94	49.06	1.97	49.07	2.21	1.00
Age group, y												
6–11	965 (44.36)	1.28	0.05		0.36	0.02		40.54	2.37	48.40	1.81	
12–19	866 (55.64)	1.24	0.06	0.70	0.39	0.02	0.30	59.46	2.37	51.60	1.81	0.02
Smoke exposure[d]												
Yes	364 (21.72)	1.32	0.07		0.39	0.03		20.12	2.37	23.64	1.62	
No	1330 (78.28)	1.23	0.05	0.89	0.37	0.02	0.29	79.88	2.37	76.36	1.62	0.20
Missing	137 (6.84)	1.32	0.17	0.56	0.37	0.04	0.48	7.40	1.31	6.41	1.73	0.61
PIR quartile												
First (<0.8)	415 (16.89)	1.40	0.09		0.47	0.03		16.04	1.96	17.96	2.17	
Second (≥0.8 to <1.47)	416 (19.19)	1.30	0.07		0.37	0.04		17.87	1.64	20.87	2.48	
Third (≥1.47 to <2.92)	423 (27.81)	1.23	0.07		0.35	0.03		27.53	1.98	28.15	2.44	
Fourth (≥2.92)	418 (36.11)	1.22	0.08	0.02	0.33	0.02	0.00	38.56	3.26	33.01	3.94	0.31
Income information missing	159 (8.47)	1.11	0.13	0.43	0.58	0.07	0.00	5.65	1.10	8.30	1.15	0.10
Head of household education level												
<9th Grade	207 (7.80)	1.21	0.14		0.46	0.04		7.24	1.20	8.59	1.78	
≥9th Grade but less than high school	255 (11.19)	1.33	0.11		0.36	0.04		10.13	1.30	12.68	1.89	
High school graduation	393 (21.39)	1.33	0.08		0.39	0.04		24.12	1.99	17.58	1.46	
Some college or associate's degree	557 (33.87)	1.28	0.08		0.36	0.03		32.75	2.82	35.21	1.96	
College or more	358 (25.75)	1.15	0.10	0.10	0.36	0.03	0.05	25.75	2.84	24.99	2.95	0.09
Education information missing	61 (2.97)	1.28	0.21	0.94	0.47	0.07	0.63	2.16	0.75	3.82	0.83	0.18
Race/ethnicity												
Mexican American Hispanic	428 (15.78)	1.24	0.06		0.45	0.03		14.51	2.22	17.45	3.19	
Other Hispanic	206 (7.53)	1.21	0.07		0.54	0.05		5.72	0.73	9.78	1.44	
Non-Hispanic white	487 (53.15)	1.21	0.06		0.31	0.02		56.62	3.67	48.68	5.39	
Non-Hispanic black	440 (14.23)	1.66	0.12		0.50	0.03		15.52	2.31	12.91	2.47	
Other/multiple	270 (9.31)	1.07	0.10	0.00	0.37	0.03	0.00	7.63	1.05	11.17	1.71	0.01
Time spent watching television, h												
<2	675 (40.42)	1.30	0.08		0.36	0.02		40.72	2.76	39.52	2.25	
≥2	1133 (59.58)	1.25	0.04	0.74	0.39	0.02	0.13	59.28	2.76	60.48	2.25	0.75
Television watching information missing	23 (1.51)	0.62	0.18	0.08	0.33	0.12	0.38	1.69	0.60	1.12	0.32	0.37

(*Continued*)

Table 1. Study Population Characteristics in Total Sample Stratified by BPA and BPS Concentrations and BPF Detection, NHANES from 2013 to 2016 (Continued)

Characteristic	Total[a] (n = 1831), n (%)	BPA (ng/mL)			BPS (ng/mL)			BPF Detection, % (SE)				
		GM	GSE	*P* Value[b]	GM	GSE	*P* Value[b]	Yes (n = 948)		No (n = 883)		*P* Value[c]
Caloric intake[e]												
USDA cutpoint or less	1179 (75.86)	1.26	0.05		0.37	0.02		76.52	1.55	74.95	2.10	
Greater than USDA cutpoint	413 (24.14)	1.23	0.09	0.51	0.38	0.04	0.24	23.48	1.55	25.05	2.10	0.59
Caloric intake information missing	239 (11.33)	1.36	0.12	0.89	0.38	0.04	0.29	11.00	1.55	11.50	1.47	0.83
Obesity[f]												
Yes	381 (19.55)	1.34	0.08		0.47	0.04		20.77	1.89	18.13	1.95	
No	1439 (80.45)	1.23	0.05	0.17	0.35	0.02	0.00	79.23	1.89	81.87	1.95	0.20
Missing	11 (0.50)	2.60	1.27	0.63	0.79	0.27	0.21	0.65	0.31	0.25	0.14	0.20
Severe obesity[g]												
Yes	253 (12.68)	1.33	0.09		0.49	0.05		13.04	1.51	12.39	1.68	
No	1567 (87.32)	1.24	0.05	0.26	0.36	0.02	0.00	86.96	1.51	87.61	1.68	0.74
Missing	11 (0.50)	2.60	1.27	0.63	0.79	0.27	0.21	0.65	0.31	0.25	0.14	0.20
Abdominal obesity[h]												
Yes	669 (36.22)	1.26	0.05		0.42	0.03		38.22	2.53	33.75	2.74	
No	1108 (63.78)	1.26	0.05	0.94	0.35	0.02	0.00	61.78	2.53	66.25	2.74	0.11
Missing	54 (2.86)	1.10	0.27	0.55	0.48	0.12	0.08	3.25	0.58	1.18	0.31	0.00
Overweight or higher[i]												
Yes	712 (38.22)	1.29	0.06		0.42	0.02		40.64	2.30	35.25	2.21	
No	1108 (61.78)	1.23	0.05	0.19	0.35	0.02	0.00	59.36	2.30	64.75	2.21	0.02
Missing	11 (0.50)	2.60	1.27	0.63	0.79	0.27	0.21	0.65	0.31	0.25	0.14	0.20
BPA quartile												
First	440 (24.63)	0.37	0.01		0.21	0.01		19.17	1.70	31.35	2.07	
Second	460 (24.62)	0.91	0.01		0.35	0.03		22.65	1.83	27.06	2.18	
Third	454 (24.96)	1.60	0.01		0.45	0.03		26.82	1.89	22.65	1.84	
Fourth	477 (25.79)	4.41	0.10	0.00	0.59	0.04	0.00	31.36	1.76	18.94	1.70	0.00

Abbreviations: GM, geometric mean; GSE, geometric standard error; USDA, US Department of Agriculture.
[a]All cell counts provided are unweighted, with percentages weighted to NHANES environmental subsample.
[b]*P* values generated from Mann-Whitney *U* tests for dichotomous variables and Kruskal-Wallis H tests for variables with two or more categories.
[c]*P* values generated from χ^2 tests.
[d]Composite variable consisting of serum cotinine concentrations ≥2 ng/mL for 2013 to 2014 and questionnaire proxies for 2015 to 2016.
[e]USDA cut point for children with high physical activity.
[f]Obesity defined as ≥95th percentile of age- and sex-standardized BMI z-scores.
[g]Severe obesity defined as ≥120% of the 95th percentile of age- and sex-standardized BMI z-scores or a BMI of ≥35 kg/m^{2}greater, whichever was lower.
[h]Defined as waist circumference (cm)/height (cm) ≥0.5.
[i]Overweight defined as ≥85th percentile of age- and sex-standardized body mass index (BMI) z-scores.

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Table 2. Associations of Natural Log-Transformed Urinary BPS and BPA and Total Bisphenols and Obesity[a] Adjusted for Urinary Creatinine Concentrations in Strata Defined by Sample Characteristics

	Prevalence of Obesity[a]			ln (BPS Concentration)		ln (BPA Concentration)		ln (Total Bisphenols)	
Characteristic	**Obese/Total (Unweighted)**	**Obese in Stratum, %**	**SE**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Entire sample	381/1820	19.55	1.58	1.19	1.04–1.37	1.04	0.88–1.22	1.06	0.94–1.21
Sex									
Male	205/935	19.56	2.19	1.18	0.99–1.42	1.09	0.93–1.28	1.12	0.95–1.31
Female	176/885	19.53	1.76	1.22	1.01–1.48	0.98	0.72–1.34	1.00	0.79–1.26
Age group, y									
6–11	193/962	17.59	1.61	1.25	1.03–1.51	1.00	0.80–1.26	1.04	0.82–1.33
12–19	188/858	21.11	2.28	1.18	0.98–1.42	1.10	0.89–1.35	1.08	0.93–1.27
Smoke exposure[b]									
Yes	80/361	22.40	3.89	1.15	0.79–1.66	0.95	0.70–1.29	1.17	0.91–1.51
No	280/1323	19.46	1.61	1.20	1.03–1.39	1.06	0.88–1.28	1.03	0.88–1.21
PIR									
Less than median (1.47)	201/827	23.80	1.73	1.06	0.92–1.23	0.92	0.73–1.16	1.02	0.86–1.20
Median or greater	146/837	16.97	2.02	1.27	1.03–1.58	1.08	0.86–1.36	1.07	0.87–1.31
Head of household education level									
High school or less	215/848	25.25	2.15	1.07	0.89–1.29	0.96	0.83–1.12	1.05	0.86–1.27
Some college or more	160/913	15.97	1.66	1.28	1.07–1.54	1.01	0.78–1.31	1.02	0.82–1.25
Race/ethnicity									
Hispanic	166/629	26.90	1.52	1.21	1.06–1.38	1.18	0.99–1.41	1.22	1.02–1.46
Non-Hispanic white	78/486	15.84	2.40	1.15	0.91–1.47	1.01	0.76–1.34	0.93	0.76–1.13
Non-Hispanic black	96/439	22.68	2.84	1.05	0.83–1.33	0.71	0.44–1.15	0.93	0.67–1.27
Other/multiple	41/266	17.62	3.09	1.14	0.70–1.84	1.30	0.83–2.03	1.73	1.10–2.72
Time spent watching television, h									
<2	115/693	15.57	1.98	1.27	1.05–1.53	1.12	0.84–1.50	0.99	0.78–1.26
≥2	266/1127	22.35	1.92	1.14	0.96–1.36	1.00	0.83–1.20	1.11	0.92–1.34
Caloric intake[c]									
USDA cutpoint or less	293/1408	19.13	1.65	1.23	1.06–1.43	1.04	0.83–1.29	1.10	0.96–1.26
Greater than USDA cutpoint	88/412	21.08	3.34	1.05	0.78–1.42	1.03	0.75–1.41	0.93	0.66–1.31

Abbreviation: USDA, US Department of Agriculture.

[a]Obesity defined as ≥95th percentile of age- and sex-standardized BMI z-scores.

[b]Composite variable consisting of serum cotinine concentrations ≥2 ng/mL for 2013 to 2014 and questionnaire proxies for 2015 to 2016.

[c]USDA cutpoint for children with high physical activity.

varied with race/ethnicity but in different patterns. For example, compared with all other race/ethnicities, non-Hispanic blacks had the greatest concentrations of BPA, and non-Hispanic blacks and Hispanics had the greatest concentrations of BPS. Finally, those with detectable BPF were more likely to be non-Hispanic whites and blacks compared with those without detectable BPF.

The overall prevalence of general obesity among those aged 6 to 19 years between 2013 and 2016 was 19.6% and of severe obesity was 12.7%. Abdominal obesity was more common (36.2%). In bivariate analyses, the BPS levels were greater among those who were obese (0.47 vs 0.35 ng/mL among nonobese; $P < 0.01$), severely obese (0.49 vs 0.36 ng/mL; $P < 0.01$), or abdominally obese (0.42 vs 0.35 among nonabdominally obese; $P < 0.01$). For BPA, although the estimates appeared in this same direction for obese vs not obese, the difference was not statistically significant (1.34 vs 1.23; $P = 0.17$). BPF detection was not significantly associated with any obesity measure, but it was associated with being overweight or higher ($P = 0.02$). BPA correlated positively with both BPS (Spearman $\rho = 0.35$) and BPF (Spearman $\rho = 0.24$; $P < 0.01$).

Table 3. Associations of BPF Detection and Obesity[a] Adjusted for Urinary Creatinine Concentrations in Strata Defined by Sample Characteristics

	BPF Detection					
	Less Than LOD (Reference)		Greater Than LOD			
Variable	Obese,[a] %	SE	OR	95% CI	Obese,[a]	SE
Entire sample	18.13	1.95	1.13	0.87–1.48	20.77	1.89
Sex						
Male	16.34	2.55	1.37	0.94–1.98	22.43	2.60
Female	19.98	2.32	0.93	0.62–1.40	19.02	2.41
Age group, y						
6–11	17.04	2.22	1.00	0.63–1.60	17.85	2.42
12–19	19.14	2.51	1.23	0.85–1.76	22.78	2.79
Smoke exposure[b]						
Yes	19.27	4.78	1.49	0.81–2.74	25.15	4.28
No	17.99	1.96	1.12	0.83–1.52	20.82	2.15
PIR						
Less than median (1.47)	21.04	2.43	1.28	0.92–1.77	26.31	2.02
Median or more	14.99	2.54	1.23	0.81–1.88	18.42	2.33
Head of household education level						
High school or less	24.50	2.69	1.07	0.71–1.61	25.86	3.01
Some college or more	14.13	2.25	1.18	0.78–1.79	17.48	2.04
Race/ethnicity						
Hispanic	27.56	2.33	0.82	0.56–1.22	25.61	2.42
Non-Hispanic white	13.98	3.25	1.26	0.74–2.14	17.17	2.67
Non-Hispanic black	18.90	3.21	1.36	0.82–2.27	25.53	3.69
Other/multiple	12.39	2.64	2.44	1.24–4.79	25.07	5.53
Time spent watching television, h						
<2	16.21	2.59	0.89	0.52–1.52	15.11	2.69
≥2	19.48	2.25	1.29	0.91–1.82	24.63	2.51
Caloric intake[c]						
USDA cutpoint or less	17.78	2.09	1.12	0.81–1.54	20.28	2.03
Greater than USDA cutpoint	19.34	3.59	1.18	0.68–2.05	22.61	4.41

Abbreviation: USDA, US Department of Agriculture.

[a]Obesity defined as ≥95th percentile of age- and sex-standardized BMI z-scores.

[b]Composite variable consisting of serum cotinine concentrations ≥2 ng/mL for 2013 to 2014 and questionnaire proxies for 2015 to 2016.

[c]USDA cutpoint for children with high physical activity.

In models controlling for creatinine only, BPS was associated with an increased odds of general obesity (OR, 1.19; 95% CI, 1.04 to 1.37; Table 2). Although the point estimates for BPA, total bisphenols, and BPF detection were greater than one, they were not statistically significant (Tables 2 and 3). These associations did not materially vary across most demographic or behavioral variable strata. However, the estimates tended to be greater for boys than for girls for BPA, BPF detection, and total bisphenol concentrations (Tables 2 and 3). In addition, the estimates among those of other or multiple races were elevated compared with those of all other race/ethnicities for BPA, BPF detection, and total bisphenol concentrations.

In the adjusted models, log-transformed continuous BPS concentrations were associated with increased odds of general obesity, severe obesity, and abdominal obesity (Table 4). For each log-unit increase in BPS, the odds of general obesity increased by 16% (OR, 1.16; 95% CI, 1.02 to 1.32), severe obesity by 18% (OR, 1.18; 95% CI, 1.03 to 1.35), and abdominal obesity by 13% (OR, 1.13; 95% CI, 1.02 to 1.27). The association between log-transformed BPS and the continuous BMI z-score was nearly statistically significant (β = 0.06; 95% CI, −0.01 to 0.12). However, the BPS quartiles were not significantly associated statistically with any outcome, although the estimates were greater than one and had increased in magnitude as the quartiles increased. In addition, although BPF detection (vs less than the LOD) was not significantly associated statistically with general or severe obesity, it was with an increased odds of overweight (OR, 1.27; 95% CI, 1.06 to 1.51) and abdominal obesity (OR, 1.29; 95% CI, 1.01 to 1.64) and an increase in the BMI z-score (β = 0.10; 95% CI, 0.01 to 0.20).

Neither BPA nor total bisphenols, when expressed as log-transformed continuous variables or as quartiles, were significantly associated statistically with any body mass outcomes, although the estimates were generally greater than one.

3. Discussion

The present study has documented a modest positive association between BPS and increases in standardized body mass index measures (*i.e.,* obesity and severe obesity) in a representative US sample of children and adolescents. The association was most apparent when BPS was considered as a log-transformed continuous variable vs as quartiles. The BPS concentrations and BPF detection were also associated with abdominal obesity. Finally, BPF was positively associated with overweight and an increase in BMI z-scores overall. However, BPA was not significantly associated with any body mass outcome.

Just as with the previous studies of this topic [11, 12], our results should be interpreted with caution. The cross-sectional design precluded our ability to infer whether exposure to bisphenols might influence weight gain or obesity or whether obese children might have greater exposure to, or excretion of, bisphenol compounds. The methodologic issues involved in the study of this relationship have been well described [23]. One key issue is that BPS and BPF are metabolized rapidly by the human body [24, 25]; thus, spot urine samples are limited in their ability to reflect long-term exposure levels [26, 27]. This is problematic when assessing these chemicals in relation to obesity, which occurs incrementally over time and has a multifactorial etiology [28]. Finally, the situation is further complicated because food and beverage packaging, in particular, the lining of aluminum cans, contains bisphenols. Therefore, those who consume more of these products are more likely to have higher exposure levels [29, 30] and, perhaps, are more likely to be obese [31–34]. However, one method we used to account for this was to adjust for caloric intake, which did not substantially alter the estimates (data not shown). Nonetheless, taken together, these issues make it difficult to infer a causative relationship between bisphenol chemicals and obesity. However, owing to the repeated observations of this association in both cross-sectional [11, 12, 35–40] and longitudinal [41, 42] studies and the biologic plausibility and evidence from toxicological studies [10, 43, 44], the potentially obesogenic influences of bisphenol chemicals merits further attention and examination.

Although the associations between BPA, total bisphenol, and BPF detection and general obesity were not statistically significant, we noted potential heterogeneity in the measures of

Table 4. Associations of Urinary BPS, BPF, BPA, and Total Bisphenol Concentrations and Body Mass Outcomes From Multivariable Models[a]

	Obesity[b]		Severe Obesity[c]		Abdominal Obesity[d]		Overweight[e]		BMI Z-Score	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	***β***	**95% CI**
ln(BPS)[f]	1.16	1.02–1.32	1.18	1.03–1.35	1.13	1.02–1.27	1.09	0.99–1.19	0.06	−0.01 to 0.12
BPS quartile										
Second vs first	0.96	0.65–1.41	1.25	0.84–1.87	0.99	0.72–1.37	1.02	0.71–1.48	0.08	−0.09 to 0.24
Third vs first	1.17	0.73–1.89	1.49	0.83–2.66	1.14	0.72–1.80	1.17	0.82–1.68	0.10	−0.13 to 0.34
Fourth vs first	1.43	0.89–2.32	1.62	0.95–2.75	1.33	0.91–1.96	1.16	0.81–1.65	0.14	−0.10 to 0.37
BPF detected (vs less than LOD)	1.18	0.92–1.52	1.03	0.72–1.48	1.29	1.01–1.64	1.27	1.06–1.51	0.10	0.01 to 0.20
ln(BPA)[f]	1.04	0.88–1.22	0.99	0.82–1.18	1.00	0.88–1.15	1.01	0.88–1.17	−0.03	−0.13 to 0.06
BPA quartile										
Second vs first	1.29	0.88–1.87	1.57	0.96–2.57	0.99	0.72–1.37	1.1	0.8–1.51	0.08	−0.08 to 0.24
Third vs first	1.09	0.67–1.77	1.04	0.62–1.76	1.15	0.81–1.63	1.38	0.91–2.1	0.16	−0.03 to 0.36
Fourth vs first	1.30	0.83–2.02	1.14	0.61–2.15	1.24	0.87–1.78	1.24	0.84–1.85	−0.01	−0.25 to 0.23
ln(total bisphenol)[f]	1.06	0.93–1.21	1.02	0.85–1.23	1.05	0.95–1.15	1.03	0.94–1.14	−0.01	−0.09 to 0.08
Total bisphenol quartile										
Second vs first	1.14	0.78–1.68	1.34	0.83–2.15	0.99	0.77–1.27	1.05	0.76–1.45	0.16	−0.01 to 0.32
Third vs first	0.97	0.67–1.39	0.90	0.54–1.5	1.19	0.83–1.71	1.07	0.74–1.53	0.07	−0.12 to 0.26
Fourth vs first	1.32	0.87–2.00	1.24	0.71–2.18	1.19	0.84–1.67	1.16	0.83–1.61	0.04	−0.19 to 0.28

[a]Models controlled for urinary creatinine, sex, age, race/ethnicity, smoke exposure, PIR, head of household education level, time spent watching television, and caloric intake.
[b]Obesity defined as ≥95th percentile of age- and sex-standardized BMI z-scores.
[c]Severe obesity defined as ≥120% of the 95th percentile of age- and sex-standardized BMI z-scores or a BMI of ≥35 kg/m^2, whichever was lower.
[d]Abdominal obesity defined as ratio between waist circumference and height ≥0.5.
[e]Overweight defined as ≥85th percentile of age- and sex-standardized BMI z-scores.
[f]Change in the respective outcome associated with a log-unit increase in each corresponding bisphenol concentration.

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association across the strata of race/ethnicity. For example, boys and those of other or multiple races tended to have slightly stronger associations between bisphenols and general obesity compared with those of the other subgroups (*i.e.,* girls and those of all other race/ethnicities). In contrast, our previous work showed that the associations between BPA and obesity were concentrated among non-Hispanic whites [11]. Differences across racial and/or ethnic groups could be explained, in part, by the different exposure patterns [45] or potential interactions with unmeasured behavioral [46], genetic, or epigenetic [47] differences. However, these associations and differences by race/ethnicity found in the present study were not statistically significant; thus, these potential explanations are solely hypothesis generating.

As BPA levels have declined, the use of BPS and its detection in human samples has increased in recent years [48]. Therefore, as the associations between BPA and obesity have attenuated as BPA levels have declined, it is possible that the associations between BPS and body mass could change as the levels increase. In our previous work on BPA and obesity among children in NHANES 2003 to 2008 [11], the median urinary BPA concentration was 2.8 ng/mL (interquartile range, 1.5 to 5.6), an order of magnitude greater than the current BPS levels in the present study. Thus, the potential health effects of BPS and other BPA replacement compounds should continue to be monitored, given that human exposure to these compounds is likely to continue to increase in the future.

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Additonal Information

Disclosure Summary: The authors have nothing to disclose.

Data Availability: All data generated or analyzed during this study are included in the present report or in the data repositories listed in the references.

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