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Urinary Triclosan Concentrations Are Inversely Associated with Body Mass Index and Waist Circumference in the US General Population: Experience in NHANES 2003-2010

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Abstract

Background—Humans are extensively exposed to triclosan, an antibacterial and antifungal agent. Triclosan's effects on human health, however, have not been carefully investigated.

Objective—To examine whether triclosan exposure is associated with obesity traits.

Methods—This study included 2,898 children (6-19 years old) and 5,066 adults (20 years or older) who participated in the National Health and Nutrition Examination Surveys (NHANES) 2003-2010 and had a detectable level of urinary triclosan. Multiple linear regression models were used to examine the association between urinary triclosan and both body mass index (BMI) and waist circumference.

Results—Each standard deviation increase in urinary triclosan was associated with a 0.34 (95% confidence interval, CI: 0.05, 0.64) kg/m² lower level of BMI (p=0.02) and 0.92 (95% CI: 0.09, 1.74) cm smaller waist circumference (p=0.03) in boys, and a 0.62 (95% CI: 0.31, 0.94) kg/m² lower level of BMI (p=0.0002) and 1.32 (95% CI: 0.54, 2.09) cm smaller waist circumference in girls (P=0.001); a 0.42 (95% CI: 0.06, 0.77) kg/m² lower level of BMI (P=0.02) and 1.35 (95% CI: 0.48, 2.22) cm smaller waist circumference (P=0.003) in men, and a 0.71 (95% CI: 0.34, 1.07) kg/m² lower level of BMI (P=0.0002) and 1.68 (95% CI: 0.86, 2.50) cm smaller waist circumference (P=0.0001) in women. In both children and adults, there was a consistent trend for

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CONFLICT OF INTEREST

Authors declare that there are no competing financial interests in relation to the work described.

lower levels of BMI and smaller waist circumference with increasing levels of urinary triclosan, from the lowest to the highest quartile of urinary triclosan ($P = 0.001$ in all cases).

Conclusion—Triclosan exposure is inversely associated with BMI and waist circumference. The biological mechanisms linking triclosan exposure to obesity await further investigation.

Keywords

triclosan; obesity; NHANES

INTRODUCTION

Triclosan, or 2,4,4'-trichloro-2'-hydroxydiphenyl ether, originally synthesized in 1972, is a broad-spectrum antimicrobial chemical. It is widely used in household and health care-related products, such as toothpaste, hand/dishwashing soaps, deodorants, and mouthwash, as well as in medical devices, textiles, toys, and construction materials (Bedoux et al., 2012; Dann and Hontela, 2011). Triclosan and its derivatives are present in the environment, particularly in various water bodies and sediments (Bedoux et al., 2012; Perez et al., 2013). As evidence that humans are widely exposed to triclosan, triclosan is detectable in the liver and bile (Geens et al., 2012), fat tissue (Geens et al., 2012), urine (Calafat et al., 2008; Li et al., 2013; Pirard et al., 2012), blood (Allmyr et al., 2006; Allmyr et al., 2008; Wu et al., 2012), nails (Shi et al., 2013), and human milk (Toms et al., 2011).

Due to its widespread use and ubiquitous presence, triclosan has increasingly been a public health concern (Queckenberg et al., 2010; Rodricks et al., 2010). In vitro studies suggest that triclosan reduces global methylation in HepG2 cells (Ma et al., 2013), impairs excitation-contraction coupling and Ca^{2+} dynamics in striated muscle (Cherednichenko et al., 2012), increase estradiol (E2) and progesterone secretion (Gee et al., 2008; Honkisz et al., 2012), and inhibits adipocyte differentiation (Guo et al., 2012) and inflammation (Barros et al., 2010; Kjaerheim et al., 1995; Modeer et al., 1996; Udoji et al., 2010). Triclosan also demonstrates estrogen-like activities (Henry and Fair, 2013) and in humans has been associated with allergy (Bertelsen et al., 2013; Clayton et al., 2011; Savage et al., 2014; Savage et al., 2012), thyroid function (Koeppel et al., 2013), and immune function (Clayton et al., 2011). Lankester and colleagues reported a positive association between urinary triclosan levels and BMI in US adults in National Health and Examination Surveys (NHANES) 2003-2008 (Lankester et al., 2013); so far, very limited data have been published on children. In the current study, we used NHANES 2003-2010 data to examine the relationship between urinary triclosan concentrations and BMI and waist circumference in both children and adults.

METHODS

Study sample

NHANES is a continuous program that examines a nationally representative sample of about 5,000 persons each year to assess the health and nutritional status of adults and children in the non-institutionalized general population of the United States (<http://www.cdc.gov/nchs/nhanes.htm>). Demographic, socioeconomic, dietary, and health-related data were collected by interviews. Blood and urine samples were collected for laboratory testing. In four surveys

conducted between 2003 and 2010, urinary triclosan concentration was measured in a random sample of survey participants aged 6 years or older. Overall, urinary triclosan concentration was measured in 3,659 children (1,884 boys and 1,775 girls, 6-19 years old) and 6,566 adults (3,251 men and 3,315 women, 20 years or older). Of these, 2,898 children (1,482 boys and 1,416 girls, 6-19 years old) and 5,066 adults (2,509 men and 2,557 women, 20 years or older) had detectable levels of urinary triclosan from the 2003-2010 NHANES database and were included in the current study. The National Centers for Health Statistics Institutional Review Board reviewed and approved the study protocol.

Urine Triclosan Determination

For each study participant, a single spot urine sample per participant was collected during one of three daily examination session periods (i.e., morning, afternoon, evening). The samples were shipped on dry ice to the Centers for Disease Control and Prevention's National Center for Environmental Health and stored at or below -20°C until analyzed. Urinary concentrations of free plus conjugated triclosan were measured by automated solid-phase extraction coupled to isotope dilution-high-performance liquid chromatography-tandem mass spectrometry, as described previously (Calafat et al., 2008). The lower limit of detection was 2.3 ng/ml in all surveys.

Potential Confounders

Race/ethnicity was categorized into Hispanic, non-Hispanic white, non-Hispanic black, and other. Socioeconomic status was indicated by the poverty index ratio and categorized into below 2, 2-5 and 5 or above. Serum cotinine was measured by an isotope dilution-high performance liquid chromatography / atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS); its concentrations were categorized as below 0.015 ng/ml, between 0.015 -12 ng/ml, or 12 ng/ml or above. Urinary Bisphenol A (BPA) concentration was determined by high-performance liquid chromatography and tandem mass spectroscopy, also in spot samples; urinary BPA concentrations below the level of detection were replaced with the value of 0.3 ng/mL by the NHANES. For all variables with missing values, a separate category for missing values was included.

Statistical analyses

The primary outcome variables were BMI and waist circumference. Basic characteristics of the study sample were described by use of means or percentages and their corresponding 95% confidence intervals (CIs) in the following four age and gender groups: boys and girls (6-19 years old) and men and women (20 years or older). To adjust for bias due to dilution of the urine, urinary triclosan concentration was divided by urinary creatinine concentration (Calafat et al., 2008). Creatinine adjusted triclosan concentrations were then standardized to z-scores to facilitate interpretation of the findings. Urinary triclosan concentrations were also categorized into age- and sex-specific quartiles as an ordinal variable. The association of urinary triclosan levels with BMI or waist circumference was examined by using multiple linear regression in each individual group, adjusted for sex, age, race, poverty to income ratio, urinary cotinine levels, and urinary BPA concentrations where appropriate. Sensitivity analyses stratified by race, poverty to income ratio, or urinary

cotinine level were also performed. All data analyses were performed using SAS version 9.3, while taking into account sample weights and design variables.

RESULTS

The mean age in years was 12.7 (95% CI: 12.4, 13.0) for boys, 12.6 (95% CI: 12.3, 12.9) for girls, 44.8 (95% CI: 43.9, 45.8) for men, and 46.1 (95% CI: 45.3, 46.8) for women (Table 1). Urinary triclosan concentrations were 18.7 µg/g creatinine (95% CI: 16.8-20.6 µg/g creatinine) in boys, 20.3 µg/g creatinine (95% CI: 17.8-22.9 µg/g creatinine) in girls, 26.2 µg/g creatinine (95% CI: 23.7-28.9 µg/g creatinine) in men, and 29.3 µg/g creatinine (95% CI: 26.6-32.1 µg/g creatinine) in women. Urinary triclosan concentrations seemed to increase progressively with age from 6 years to the mid-twenties in both genders, with no discernable pattern at older ages (data not shown).

Following adjustment for age, race, poverty to income ratio, serum cotinine concentrations, and urinary BPA concentrations, urinary triclosan concentration was significantly associated with BMI in boys ($P=0.02$) and in girls ($P=0.0002$), aged between 6-19 years, with a 0.34 (95% CI: 0.05, 0.64) kg/m² lower level in boys and 0.62 (95% CI: 0.31, 0.94) kg/m² lower level in girls for each standard deviation increase in urinary triclosan levels. Similar trend was also observed for waist circumference in boys ($P=0.03$) and in girls ($P=0.001$), with a 0.92 (95% CI: 0.09, 1.74) cm smaller circumference in boys and 1.32 (95% CI: 0.54, 2.09) cm smaller circumference in girls for each standard deviation increase in urinary triclosan levels. Combining boys and girls together and with additional adjustment for sex, there was a significant association between urinary triclosan concentrations and BMI or waist circumference ($P=9.42\times10^{-6}$ and $P=0.0002$, respectively; Table 2); there was a significant trend for lower levels of BMI and smaller waist circumference from the bottom to the top quartile of urinary triclosan concentrations ($P=0.0001$ and $P=0.001$, respectively; Figure 1).

In the adult groups, significant associations were also found between urinary triclosan concentrations and BMI after adjustment for age, race, poverty to income ratio, serum cotinine concentrations, and urinary BPA concentrations. In men, each standard deviation increase in urinary triclosan concentrations correlated with a decrease of 0.42 (95% CI: 0.06, 0.77) kg/m² in BMI ($P=0.02$). Similarly, BMI in women was seen to decrease by 0.71 (95% CI: 0.34, 1.07) kg/m² for each standard deviation increase in urinary triclosan concentrations ($P=0.0002$). In another analysis, urinary triclosan concentrations were significantly associated with waist circumference in men ($P=0.003$) and in women ($P=0.0001$), with a 1.35 (95% CI: 0.48, 2.22) cm smaller circumference in men and 1.68 (95% CI: 0.86, 2.50) cm smaller circumference in women for each standard deviation increase in urinary triclosan levels. Combining men and women together and with additional adjustment for sex, there was a significant association between urinary triclosan concentrations and BMI or waist circumference ($P=7.87\times10^{-8}$ and $P=1.06\times10^{-8}$, respectively; Table 2); as shown in Figure 2, as urinary triclosan concentrations increased from the lowest to the highest quartile, BMI and waist circumference steadily decreased ($P=0.0001$ and $P=1.17\times10^{-6}$ for BMI and waist circumference, respectively).

When stratified by race, poverty to income ratio, or urinary cotinine level, similar trends were consistently observed (data not shown).

DISCUSSION

In this large representative sample of the US general population, higher levels of urinary triclosan were associated with a lower level of BMI and a smaller waist circumference, two of the most commonly used measures of overweight and obesity. The fact that the inverse association between obesity measures and urinary triclosan concentrations was consistently observed in children and in adults, and in males and in females, with similar trends observed stratified by race, social economic status, and urinary cotinine level, suggests the observed associations between triclosan exposure and obesity indicators are real. However, we cannot establish causality due to the cross-sectional nature of our study.

The inverse correlation between obesity measures and urinary triclosan concentrations was consistent across different age and sex groups with the effects of different confounding factors accounted for. In addition, the magnitude of the observed inverse associations was relatively large, with each standard deviation increase in urinary triclosan concentrations associated with 0.34-0.71 units decrease in BMI or 0.92-1.68 cm decrease in waist circumference. Moreover, there was a consistent dose-response relationship between triclosan exposure and BMI and waist circumferences in all age and sex groups. Sensitivity analyses show that the same trend was consistently observed across different races, social economic statuses, or urinary cotinine level strata. Together, these facts strongly suggest that the observed association was less likely to be confounded by known confounding factors.

Few studies have examined the association between obesity measures and triclosan exposure in humans. Lankester and colleagues reported a positive association between urinary triclosan levels and BMI in US adults in NHANES 2003-2008 (Lankester et al., 2013). In their study, they used BMI in those with undetectable triclosan urine samples as the reference; however, in those with detectable urine samples, increased triclosan exposure was associated with decreased BMI, with the difference from the reference group being 1.5, 1.0, and 0.3 kg/m² in the first, second, and top tertile of urinary triclosan levels, respectively (Lankester et al., 2013), which is consistent with our findings. In a very small study (49 obese and 27 non-obese Indian children), Xue and colleagues did not find an association between triclosan exposure and obesity (Xue et al., 2014). Interestingly, Philippat and colleagues reported that prenatal triclosan exposure in late pregnancy was negatively associated with growth parameters and with head circumference at birth (Philippat et al., 2014). Compared to results by Lankester et al, we included children and adolescents in our study, and the decreasing trend in BMI and waist circumference in adults was also observed in children and adolescents, which adds supporting evidence for an inverse association between triclosan exposure and obesity traits.

The underlying mechanisms for a relationship between triclosan exposure and obesity traits are not known. Available data in humans suggest that triclosan exposure is associated with increased serum total triiodothyronine (T3) levels, albeit only in adolescents (aged 12-19 years) (Koeppel et al., 2013). Whether such differences in T3 levels contribute to the inverse

association between triclosan exposure and obesity traits in the current study remains to be studied. In a randomized clinical trial, free thyroxine (T4) levels were higher after four years in the group using triclosan-containing toothpaste compared to the group using placebo, but only because of reduced free T4 levels in the placebo group (Cullinan et al., 2012). At levels observed in human blood, triclosan inhibits adipocyte differentiation of human mesenchymal stem cells (Guo et al., 2012). Previously urinary triclosan concentrations were significantly associated with cigarette smoking in a Korean sample (Kim et al., 2011); however, cigarette smoking was not likely to confound the current findings because we adjusted for serum cotinine levels, and the trend persisted in stratified analyses by serum cotinine level. There is evidence that triclosan in toothpaste may be associated with improved oral health (Grossman et al., 2002; Riley and Lamont, 2013), and oral health is known to be associated with reduced obesity measures (Ostberg et al., 2012; Zeigler et al., 2012). It is not clear whether inhibition of inflammation is a potential mechanism for reduced obesity measures associated with triclosan exposure. Taken together, the underlying mechanisms for the observed inverse association between urinary triclosan concentrations and obesity measures are yet to be fully elucidated.

Our study has several strengths. The sample size in the current study was relatively large. Data were collected from national surveys with rigorous quality assurance/control measures. We also performed sensitivity analyses in which similar trends were consistently observed. Despite its strengths, our study was cross-sectional in nature; consequently, a causal relationship cannot be established. In the current study, spot urine samples were used, which may have caused some bias because triclosan is usually rapidly metabolized and excreted (Sandborgh-Englund et al., 2006). However, such bias, if present, was more likely to be nondifferential. Further, previous studies have suggested that urinary concentrations in samples collected 6 weeks apart show high correlation ($r=0.61$) in pregnant women (Bertelsen et al., 2014), which suggests that urinary triclosan concentrations may represent habitual exposure rather than random exposure.

In conclusion, higher triclosan exposure was associated with more desirable measures of overweight and obesity in the US general population with detectable triclosan exposure, and the relationship was consistent across different age and sex groups. Prospective studies are needed to confirm the findings from this cross-sectional study. Given triclosan's ubiquitous presence in the environment and its potential public health implications, more interdisciplinary studies are needed to systematically document the health consequences of triclosan exposure and to dissect the underlying mechanisms.

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Figure 1.

BMI and waist circumference by quartile of urinary triclosan concentrations in US children (6-19 years old), NHANES 2003-2010. P values were adjusted for age, sex, race, poverty to income ratio, urinary Bisphenol A concentrations, and serum cotinine levels.

Figure 2. BMI and waist circumference by quartile of urinary triclosan concentrations in US adults (20-85 years old), NHANES 2003-2010. P values were adjusted for age, sex, race, poverty to income ratio, urinary Bisphenol A concentrations, and serum cotinine levels.

Table 1

Characteristics of the study sample, NHANES 2003-2010

	Male			Female		
	Point estimate	95% CI: Lower	95% CI: Upper	Point estimate	95% CI: Lower	95% CI: Upper
Children and adolescents	n=1,482			n=1,416		
Age (years)	12.7	12.4	13.0	12.6	12.3	12.9
BMI (kg/m ²)	21.5	21.1	21.9	21.5	21.1	21.9
Waist (cm)	75.2	74.0	76.2	74.2	73.2	75.2
Race						
Hispanic	17.0	13.9	20.7	17.3	14.0	21.2
Non-Hispanic White	61.0	55.9	65.8	60.2	55.2	65.0
Non-Hispanic Black	15.3	12.6	18.4	15.0	12.7	17.6
Other	6.7	5.1	8.9	7.5	5.6	10.0
Cotinine (%)						
<0.015 ng/ml	13.4	10.6	16.7	18.4	15.3	21.9
<12 ng/ml	64.6	61.1	68.0	62.6	58.2	66.7
12 ng/ml	10.2	8.4	12.4	6.8	5.1	9.0
Missing	11.8	10.0	13.9	12.2	10.2	14.7
Poverty index ratio (%)						
<2	41.5	37.8	45.3	41.7	36.9	46.6
2-	40.0	36.2	44.0	36.9	33.1	41.0
5	14.3	12.1	16.8	15.8	12.6	19.6
Missing	4.2	2.9	6.0	5.6	4.2	7.5
Triclosan (µg/L) *	23.6	21.3	26.0	21.7	18.9	24.5
Triclosan (µg/g) *	18.7	16.8	20.6	20.3	17.8	22.9
Bisphenol A (µg/L) *	2.90	2.70	3.09	2.65	2.44	2.87
Bisphenol A (µg/g) *	2.29	2.13	2.46	2.49	2.32	2.66
Adults	n=2,509			n=2,557		
Age (years)	44.8	43.9	45.8	46.1	45.3	46.8
BMI (kg/m ²)	28.8	28.5	29.1	28.6	28.2	29.0
Waist (cm)	101.2	100.3	102.1	94.7	93.9	95.5
Race (%)						
Hispanic	13.2	10.8	16.2	12.3	10.1	14.9
Non-Hispanic White	69.6	65.7	73.3	69.2	65.3	72.7
Non-Hispanic Black	10.7	9.0	12.8	12.6	10.5	15.2
Other	6.4	4.9	8.3	5.9	4.6	7.4
Cotinine (%)						
<0.015 ng/ml	14.2	12.2	16.5	24.3	21.5	27.3
<12 ng/ml	52.1	49.3	54.9	51.6	48.1	55.0
12 ng/ml	29.8	27.0	32.7	20.1	18.0	22.5

	Male			Female		
	Point estimate	95% CI: Lower	95% CI: Upper	Point estimate	95% CI: Lower	95% CI: Upper
Missing	3.9	3.1	4.8	4.0	3.1	5.3
Poverty index ratio (%)						
<2	28.0	25.8	30.4	32.5	30.3	34.9
2-	39.4	36.8	42.0	38.8	36.5	41.1
5	26.4	23.8	29.2	22.3	20.3	24.4
Missing	6.2	5.2	7.5	6.4	5.4	7.6
Triclosan (µg/L) *	33.8	30.7	36.9	26.3	24.0	28.6
Triclosan (µg/g) *	26.2	23.7	28.9	29.3	26.6	32.1
Bisphenol A (µg/L) *	2.28	2.16	2.40	2.00	1.88	2.12
Bisphenol A (µg/g) *	1.77	1.69	1.84	2.23	2.13	2.32

CI: confidence interval

* Geometric mean and 95% confidence interval.

Table 2

Regression analyses of BMI and waist circumferences with urinary triclosan concentrations, NHANES 2003-2010

Independent variable	BMI		Waist Circumference	
	Beta (95% CI)	P	Beta (95% CI)	P
Children and adolescents				
Age (years)	0.73 (0.67-0.79)	2.74×10^{-137}	2.33 (2.20-2.46)	1.58×10^{-253}
Female sex	0.11 (-0.29-0.51)	0.57	-0.66 (-1.77-0.44)	0.23
Race (other as reference)				
Hispanic	1.80 (0.89-2.71)	0.0002	5.35 (2.72-7.97)	0.0001
Non-Hispanic White	1.07 (0.24-1.90)	0.012	3.94 (1.40-6.49)	0.003
Non-Hispanic Black	2.31 (1.49-3.13)	1.80×10^{-8}	3.44 (1.01-5.87)	0.006
Poverty to income ratio (5 as reference)				
Missing	0.61 (-0.32-1.54)	0.20	1.08 (-1.48-3.64)	0.40
<2	0.99 (0.32-1.67)	0.005	2.71 (0.71-4.71)	0.009
2-5	0.69 (-0.00-1.39)	0.05	1.48 (-0.38-3.35)	0.12
Cotinine (12 ng/ml as reference)				
Missing	0.28 (-0.84-1.40)	0.61	0.74 (-2.33-3.81)	0.63
<0.015 ng/ml	-0.04 (-1.15-1.08)	0.95	1.09 (-2.04-4.21)	0.49
<12 ng/ml	0.96 (-0.05-1.98)	0.06	3.01 (0.26-5.75)	0.03
Bisphenol A z-score	0.07 (-0.17-0.31)	0.55	0.28 (-0.35-0.91)	0.37
Triclosan z-score	-0.47 (-0.69 - -0.26)	9.42×10^{-6}	-1.09 (-1.64 - -0.54)	0.0002
Adults				
Age (years)	0.02 (0.01-0.04)	0.0001	0.20 (0.17-0.23)	6.33×10^{-44}
Female sex	-0.30 (-0.87-0.27)	0.29	-6.81 (-8.08 - -5.54)	8.20×10^{-27}
Race (other as reference)				
Hispanic	2.50 (1.43-3.56)	2.60×10^{-6}	5.40 (2.72-8.08)	0.0002
Non-Hispanic White	1.75 (0.85-2.66)	0.0003	5.22 (2.79-7.64)	0.0001
Non-Hispanic Black	3.86 (2.83-4.90)	9.33×10^{-14}	6.76 (4.32-9.20)	3.02×10^{-8}
Poverty to income ratio (5 as reference)				
Missing	-1.03 (-1.86 - -0.19)	0.017	-2.47 (-4.57 - -0.36)	0.022
<2	0.56 (-0.09-1.21)	0.09	1.75 (0.21-3.28)	0.03
2-5	0.75 (0.13-1.37)	0.02	2.23 (0.75-3.71)	0.004
Cotinine (12 ng/ml as reference)				
Missing	0.20 (-0.99 - 1.39)	0.74	-0.61 (-3.45-2.24)	0.67
<0.015 ng/ml	0.60 (-0.13-1.32)	0.11	0.28 (-1.53-2.09)	0.75
<12 ng/ml	1.49 (0.95-2.03)	4.25×10^{-8}	2.11 (0.84-3.38)	0.002
Bisphenol A z-score	0.05 (-0.18-0.27)	0.67	0.01 (-0.53-0.53)	0.98
Triclosan z-score	-0.58 (-0.79 - -0.36)	7.87×10^{-8}	-1.54 (-2.08 - -1.00)	1.06×10^{-8}