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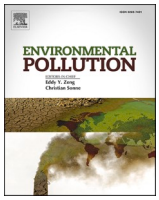

Race-specific associations of urinary phenols and parabens with adipokines in midlife women: The Study of Women's Health Across the Nation (SWAN)☆

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ABSTRACT

Adipokines, cytokines secreted by adipose tissue, may contribute to obesity-related metabolic disease. The role of environmental phenols and parabens in racial difference in metabolic disease burden has been suggested, but there is limited evidence. We examined the cross-sectional associations of urinary phenols and parabens with adipokines and effect modification by race. Urinary concentrations of 6 phenols (bisphenol-A, bisphenol-F, 2,4-diclorophenol, 2,5-diclorophenol, triclosan, benzophenone-3) and 4 parabens (methyl-paraben, ethyl-paraben, propyl-paraben, butyl-paraben) were measured in 2002–2003 among 1200 women (mean age = 52.6) enrolled in the Study of Women's Health Across the Nation Multi-Pollutant Study. Serum adipokines included adiponectin, high molecular weight (HMW)-adiponectin, leptin, soluble leptin receptor (sOB-R). Linear regression models were used to estimate the adjusted percentage change in adipokines per inter-quantile range (IQR) increase in standardized and log-transformed levels of individual urinary phenols and parabens. Bayesian kernel machine regression (BKMR) was used to evaluate the joint effect of urinary phenols and parabens as mixtures. Participants included white (52.5%), black (19.3%), and Asian (28.1%) women. Urinary 2,4-dichlorophenol was associated with 6.02% (95% CI: 1.20%, 10.83%) higher HMW-adiponectin and urinary bisphenol-F was associated with 2.60% (0.48%, 4.71%) higher sOB-R. Urinary methyl-paraben was associated with lower leptin in all women but this association differed by race: 8.58% (−13.99%, −3.18%) lower leptin in white women but 11.68% (3.52%, 19.84%) higher leptin in black women (P interaction = 0.001). No significant associations were observed in Asian women. Additionally, we observed a significant positive overall effect of urinary phenols and parabens mixtures in relation to leptin levels in black, but not in white or Asian women. Urinary bisphenol-F, 2,4-dichlorophenol and methyl-paraben may be associated with favorable profiles of adipokines, but methyl-paraben, widely used in hair and personal care products, was associated with unfavorable leptin levels in black women. Future studies are needed to confirm this racial difference.

1. Introduction

Obesity is a critical public health concern worldwide. The worldwide prevalence of obesity nearly tripled between 1975 and 2016, with over 650 million (about 13%) of the world's adults having obesity in 2016 (Organization, 2020). Obesity increases the risk of cardiovascular disease and type 2 diabetes mellitus through its effects on insulin resistance and endothelial function (Wajchenberg, 2000). Adipokines, cytokine hormones secreted by adipose tissue (Saeedi et al., 2019), may play a role in obesity-linked metabolic syndrome and endothelia dysfunction

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(Lau et al., 2005).

Adiponectin is an anti-inflammatory adipokine that plays an important role in protecting against development of diseases associated with obesity including insulin resistance/diabetes (Achari and Jain, 2017; Yamauchi et al., 2001). High-molecular weight (HMW) adiponectin has been proposed to be the most biologically active form, thus it has been considered to be a better predictor of insulin sensitivity and favorable metabolic parameters than total adiponectin (Hara et al., 2006; Oh et al., 2007). Leptin, a proinflammatory adipokine, is a master regulator of energy balance as well as modulating glucose homeostasis and other biologic functions (Ramos-Lobo and Donato Jr, 2017). Leptin acts by binding to its membrane receptor, which is expressed in many human tissues (Ramos-Lobo and Donato Jr, 2017). Soluble leptin receptor (sOB-R), the product of the proteolytic cleavage of membrane-anchored receptors, is the main binding protein of leptin and increases bioavailability of leptin in plasma (Houseknecht et al., 1996; Schaab and Kratzsch, 2015). The profile of the adipokine levels could be altered by genetic, psychosocial, lifestyle and dietary factors in humans. Recent studies have reported that environmental chemicals may contribute to the adverse profile of adipokines (Ahmed et al., 2020; Hugo et al., 2008; Hugo and Ben-Jonathan, 2016). However, there is still limited evidence in the role of environmental chemicals in adipokine levels.

Environmental phenols and parabens are synthetic chemicals extensively used in personal care and consumer products such as thermal papers, soap, haircare products, and cosmetic products (Bhargava and Leonard, 1996; Chen et al., 2016; Darbre and Harvey, 2008; Gustavsson Gonzalez et al., 2002; Ye et al., 2014). A possible mechanism through which phenols and parabens could operate to alter glucose metabolism is through their ability to bind to peroxisome proliferator-activated receptor-γ (PPARγ), which leads to suppressing adiponectin secretion and elevating leptin secretion (Hiroi et al., 2006; Hu et al., 2013; Hu et al., 2016; Hugo et al., 2008; Taxvig et al., 2012; Wang et al., 2007; Yoon et al., 2000). Despite plausible biological links, information on the association between phenols and parabens and adipokines in human populations is limited. In addition, findings from the few cross-sectional studies that investigated the association between phenols and parabens and adipokines were inconsistent. Urinary or serum bisphenol A (BPA) concentrations were positively associated with serum leptin levels (Lee et al., 2019; Rönn et al., 2014; Zhao et al., 2012) while urinary propyl-paraben and methyl-paraben concentrations were inversely associated with serum leptin in women (Kolatorova et al., 2018; Lee et al., 2019). For adiponectin, some studies found a positive association of serum BPA and urinary ethyl-paraben concentrations with adiponectin levels (Lee et al., 2019; Rönn et al., 2014) while other studies found a negative association with BPA (Hugo et al., 2008; Menale et al., 2017). These studies were conducted using populations of various ages, genders, and races/ethnic groups that may affect the action of environmental disrupting chemicals (EDCs) including phenols and parabens (Beydoun et al., 2014; Hatch et al., 2008; Wei et al., 2006). These inconsistent results may have been caused by population differences.

The burden of obesity has been reported to differ by race/ethnicity, with black women being at higher risk than others (Petersen et al., 2019). Additionally, recent studies have reported that serum adipokine levels differed by race/ethnicity (Azrad et al., 2013; Gandhi et al., 2016; Khan et al., 2012; Morimoto et al., 2014; Smith et al., 2010). EDCs have been suggested as a potential driving factor of disease disparities (James-Todd et al., 2016; Ruiz et al., 2018; Williams et al., 2020). Exposure differences by race/ethnicity have also been reported with black women have higher exposure to phenols/parabens from personal care products (James-Todd et al., 2021). Thus, although the association of phenols/parabens with metabolic outcomes could differ by race/-ethnicity, there is limited empiric evidence of racial/ethnic differences.

Herein, we examined the racial/ethnic-specific associations of urinary concentrations of phenols and parabens with serum levels of adipokines including HMW adiponectin, leptin, and sOB-R in a multi-site, multi-ethnic cohort of middle-aged women in the Study of Women's Health Across the Nation (SWAN). We also examined the individual and overall joint effects of phenols and parabens as mixtures using the Bayesian kernel machine regression (BKMR) approach.

2. Methods

2.1. Study population

We used SWAN which is a multi-site, multi-ethnic longitudinal study conducted to investigate the identify risk factors for age-related women's chronic diseases during the menopausal transition (Sowers et al., 2000). At the baseline (1996–1997), 3302 women aged 42–52 years were recruited from seven study sites (Boston, MA; Chicago, IL; southeastern Michigan; Los Angeles, CA; Oakland, CA; Newark, NJ; and Pittsburgh, PA). Institutional review board approval was obtained at each study site, and all participants provided written informed consent.

The SWAN Multi-Pollutant Study (MPS) was designed to examine to the effect of environmental chemicals, including environmental phenols and parabens, on midlife women's metabolic diseases. A total of 1400 women at the third SWAN follow-up visit (1999–2000) were sampled for the SWAN MPS and all subjects were included in 4 racial/ethnic groups (white, black, Chinese, and Japanese) and 5 study sites (Boston, Pittsburgh, Southeastern Michigan, Los Angeles, Oakland). Women from Chicago and Newark where urine samples were not collected were not included. White women were recruited from all sites; Black women from Boston, Southeastern Michigan, and Pittsburgh; Chinese women from Oakland; and Japanese women from Los Angeles. Urine samples were collected at both MPS baseline (1999–2000) and MPS follow-up visit 3 (2002–2003). Serum adipokine levels were determined at the MPS follow-up visit 3 (2002–2003). For the present study, we excluded women with missing observations in serum adipokine levels, urinary phenols, parabens, and creatinine concentrations at MPS follow-up visit 3, and covariates. This yielded 1200 participants for data analysis (Fig. S1).

2.2. Assessment of urinary phenols and parabens concentrations

All specimens for assessment of phenols and parabens were collected and then stored in the SWAN Repository (http://swanrepository.com/) using a systematic protocol for SWAN. First, we collected urine specimens in 50-mL sterile cups before 9 a.m. The urine specimens were immediately aliquoted into each 0.5 mL vial. They were then stored in freezers at −80 °C until phenol and paraben contents were analyzed. Third, a total of eight phenols (bisphenol-A (BPA), biphenol-S (BPS), bisphenol-F (BPF), 2,4-dichlorophenol, 2,5-dichlorophenol, triclosan, triclocarban, and benzophenone-3) and four parabens (methyl-paraben, ethyl-paraben, propyl-paraben, and butyl-paraben) were analyzed with on-line solid phase extraction coupled to high-performance liquid chromatography–isotope dilution tandem mass spectrometry (MS/MS) by the Applied Research Center of NSF International (Ann Arbor, Michigan), a part of the Michigan Children's Health Exposure Analysis Resource (M-CHEAR) Laboratory Hub. The laboratory procedure manual, published by the Centers for Disease Control and Prevention (CDC) (Method 6301.01), was used for the analysis. The detection rates of urinary phenols and parabens concentrations were from 5.2% to 99.8% at both exposure assessment. BPS and triclocarban had low detection rates (5.2–17.3% for BPS and 9.5–11.4% for triclocarban) and were excluded from this study. Additionally, urinary concentrations of phenols and parabens below LODs were not replaced with constants to avoid potential bias (Nie et al., 2010). To adjust for urine dilution, we applied a covariate-adjusted standardization approach (O'Brien et al., 2016). In summary, we constructed a model for natural log-transformed concentrations of urinary creatinine using the age, race/ethnicity, and body mass index as predictors. Then, we calculated standardized the

concentrations by product of urinary phenols and parabens concentrations and the ratio of observed creatinine levels to fitted creatinine levels. Throughout this study, the urinary phenol and paraben concentrations used applied this covariate-adjusted standardization approach. In the present study, we used urinary concentrations of phenols and parabens analyzed from urine sample at MPS follow-up visit 3 (2002–2003) as a main exposure.

2.3. Assessment of serum adipokine levels

Serum HMW adiponectin, leptin, and sOB-R were determined at the University of Michigan, in duplicate, using commercially available colorimetric enzyme immunoassay kits based on the manufacturer's instruction (HMW adiponectin and leptin, Millipore, St. Charles, MO; and sOB-R, R&D Systems, Minneapolis, MN). The mean coefficients of variation (CV) for duplicate samples and LODs were 8.1% and 0.5 ng/mL for HMW adiponectin; 4% and 0.5 ng/mL for leptin; and 3.7% and 0.3 ng/mL for sOB-R.

2.4. Covariates

Information on age, five study site (Los Angeles, Oakland, Pittsburgh, Michigan, and Boston), four race/ethnicity (White, Black, Japanese, and Chinese), educational level (high school diploma or less, some college, a four-year college, and graduate school or higher), smoking status (never, former, and current), physical activity score, and menopausal status (pre-, peri-, post-menopause, and current hormone use) were assessed from self-administered questionnaire at MPS follow-up visit 3 (2002–2003). The total physical activity score is the sum of the physical activity scores in sports/exercise, household/caregiving, and daily routine domain, and it ranged from 3 to 15 with 15 representing the highest level of physical activity. Obesity status (Non-obese and obese) was classified based on the body mass index (BMI) at MPS follow-up visit 3; obese was defined as a BMI $\geq$ 30 kg/m^2 for black and white and BMI $\geq$ 27.5 kg/m^2 for Asian (Jih et al., 2014). Total caloric intake per day was collected one year before MPS follow-up visit 3 (2001–2002) using a detailed semi-quantitative food frequency questionnaire (FFQ).

2.5. Statistical analysis

We used multivariable linear regression to examine the association between urinary phenol and paraben concentrations and serum adipokine levels. Urinary phenol and paraben concentrations were log-transformed and then were standardized to better compare the association of urinary phenol and paraben concentrations with different distributions. All models were adjusted for age, study site and race, education level, total physical activity score, menopausal status, smoking status, total caloric intake, and obesity status. Percent changes of serum adipokine levels and 95% confidence intervals (CIs) were calculated for an inter-quartile range (IQR) increase in standardized and log-transformed urinary phenol and paraben concentrations. To evaluate effect modification by race (white, black, Asian), we repeated the same linear regression models in each race group.

We conducted sensitivity analyses to evaluate robustness of the associations. First, we additionally adjusted for urinary monoethyl phthalate (MEP), a metabolite of diethyl phthalate which is used in personal care products (Parlett et al., 2013). Second, we conducted stratified analyses by obesity as an alternative approach for evaluating the role of obesity, an important determinant of adipokines. Third, we used the average concentrations of two exposure measurements, at MPS baseline (1999/2000) and at the MPS follow-up visit 3 (2002/2003).

To evaluate the overall effect as mixtures, we used a BKMR method (Bobb et al., 2015) which was proposed for estimating the health effects of environmental mixtures. A strength of BKMR is that it can capture non-linearity between chemicals and health outcome as well as interaction effect among chemicals. Individual effect of each phenol or paraben was estimated as changes in average level of serum adipokine when one chemical concentration was increased from its 25th percentile to its 75th percentile value while the concentrations of the other chemicals and covariates were fixed at their median. The overall effect of urinary phenols and parabens was estimated as changes in average level of serum adipokines when all chemical concentration were increased from their 25th percentile to their 75th percentile value while all covariates were fixed. The same confounders listed above were included in the base model.

All analyses were conducted using SAS, version 9.3 (SAS Institute Inc.) and R, version 3.6.1 (R Core Team). For the BKMR analysis, we utilized the R package 'bkmr' version 0.2.0. Two-sided $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

The characteristics of the study population overall and stratified by race are presented in Table 1. Participants included white (52.5%), black (19.3%), and Asian (Chinese and Japanese, 28.1%) women. The average age was 52.6 years (standard deviation (SD) = 2.6). Study site, total physical activity score, and obesity status differed significantly by race ($P < 0.01$). Generally, white women were more likely to be more highly educated, never smokers, and non-obese while black women were more likely to be physically inactive and to consume more calories per day.

3.1.1. Urinary concentrations of phenols and parabens

The least square geometric means (LSGMs) of creatinine-adjusted urinary phenol and paraben concentrations are presented in Table 2. In general, black women had higher concentrations of dichlorophenols, methyl-paraben, ethyl-paraben and propyl-paraben compared with white and Asian women. Asian women had higher concentrations of triclosan and butyl-paraben than the other racial groups. Urinary concentrations of benzophenone-3 were higher in white and Asian women than in black women. This racial difference needs to be interpreted with caution, because benzophenone-3 is an ultraviolet filter included in sunscreen (Gustavsson Gonzalez et al., 2002) and Asian and white women who were recruited from west coast (Los Angeles, Oakland) may have been more likely to have used sunscreen products containing benzophenone-3. Spearman correlation matrix of creatinine-adjusted phenol and paraben concentrations is presented in Fig. S2. Parabens and benzophenone-3 were modestly and positively correlated with each other but bisphenols were weakly correlated with other chemicals.

3.1.2. Serum levels of adipokines

The geometric mean levels of HMW-adiponectin, leptin, and sOB-R were 5.26 μg/mL (geometric standard deviation (GSD) = 2.40), 17.80 ng/mL (GSD = 2.45), and 30.13 ng/mL (GSD = 1.38) (Table 1). Higher levels of HMW-adiponectin were observed in white women, whereas higher levels of leptin and lower levels of sOB-R were observed in black women (Table 1). The LSGMs of serum HMW adiponectin, leptin, and sOB-R stratified by race are presented in Table S1. The geometric mean of HMW-adiponectin in white women (6.39 ng/mL, 95% CIs: 5.76, 7.09) was higher than in black women (3.70 ng/mL, 95% CIs: 3.22, 4.25). The geometric mean of leptin was higher in black women (25.06 ng/mL, 95% CI: 22.33, 28.12) than in white women (21.98 ng/mL 95% CI: 20.17, 23.95) whereas the geometric mean of sOB-R was lower in black women (27.78 ng/mL, 95% CI: 26.37, 29.27) than in white women (30.02 ng/mL, 95% CI: 28.87, 31.21).

3.1.3. Associations of urinary phenol and paraben concentrations with serum adipokine levels

The associations between the concentrations of urinary phenol and paraben and serum adipokine levels in the entire population are presented in Table 3. IQRs of urinary phenol and paraben concentrations

Table 1
Characteristics of study population stratified by race.

	All subjects (N = 1200)	White (N = 630)	Black (N = 232)	Asian (N = 338)	*P*
Age (years)	52.57 ± 2.63	52.56 ± 2.75	52.23 ± 2.51	52.81 ± 2.47	0.035
Site					<0.001
Los Angeles	342 (28.5)	152 (24.13)	–	190 (56.21)	
Oakland	267 (22.25)	119 (18.89)	–	148 (43.79)	
Pittsburgh	203 (16.91)	142 (22.54)	61 (26.29)	–	
Michigan	193 (16.08)	84 (13.33)	109 (46.98)	–	
Boston	195 (16.25)	133 (21.11)	62 (26.72)	–	
Education levels					<0.001
High schools or less	204 (17.0)	72 (11.43)	63 (27.16)	69 (20.41)	
Some college	379 (31.58)	188 (29.84)	97 (41.81)	94 (27.81)	
College	309 (25.75)	161 (25.56)	38 (16.38)	110 (32.54)	
Post-college	308 (25.66)	209 (33.17)	34 (14.66)	65 (19.23)	
Menopause status					0.011
Pre-menopause	41 (3.41)	19 (3.02)	10 (4.31)	12 (3.55)	
Peri-menopause	453 (37.75)	222 (35.24)	100 (43.1)	131 (38.76)	
Post-menopause	553 (46.08)	288 (45.71)	106 (45.69)	159 (47.04)	
Hormone therapy	153 (12.75)	101 (16.03)	16 (6.9)	36 (10.65)	
Physical activity score	7.66 ± 1.75	7.47 ± 1.59	7.23 ± 1.75	7.92 ± 1.79	<0.001
Smoking status					<0.001
Never	711 (59.25)	369 (58.57)	86 (37.07)	256 (75.74)	
Former	290 (24.16)	171 (27.14)	62 (26.72)	57 (16.86)	
Current	199 (16.58)	90 (14.29)	84 (36.21)	25 (7.4)	
Total caloric intake (kcal/day)	1750.16 ± 697.9	1742.3 ± 624.99	1794.02 ± 857.94	1734.7 ± 705.44	0.822
Obesity status	451 (37.58)	212 (33.65)	139 (59.91)	100 (29.59)	<0.001
HMW-adiponectin, μg/mL	5.26 ± 2.40	6.70 ± 2.20	3.20 ± 2.21	4.71 ± 2.50	<0.001
Leptin, ng/mL	17.80 ± 2.45	19.15 ± 2.39	30.61 ± 1.94	10.71 ± 2.28	<0.001
Soluble Leptin Receptor, ng/mL	30.13 ± 1.38	31.16 ± 1.37	26.62 ± 1.35	30.84 ± 1.40	<0.001

Note: Data are expressed as mean ± standard deviation (SD) or n (%).

are presented in Table S2. Adjusted percent change (95% CIs) for HMW-adiponectin per IQR increase in urinary 2,4 dichlorophenol was 6.02% (95% CI: 1.20%, 10.83%). Urinary BPF and 2,5-dichlorophenol were not significantly associated with higher HMW-adiponectin [7.84% (95% CI: 0.29%, 15.97%) for BPF and 5.04% (95% CI: 0.67%, 10.76%) for 2,5-dichlorophenol]. Urinary methyl-paraben was associated with lower leptin levels [percent change = −5.29% (95% CI: 10.33%, −0.24%)] and higher sOB-R [percent change = 2.29% (95% CI: 0.01%, 4.58%)]. Also, urinary BPF and ethyl-paraben were associated with higher sOB-R [2.60% (95% CI: 0.48%, 4.71%) for BPF and 2.67% (0.11%, 5.23%) for ethyl-paraben].

The race-specific associations between urinary phenol and paraben concentrations and serum adipokine levels are presented in Fig. 1. Adjusted percent changes in serum HMW-adiponectin per IQR increase in urinary phenols and parabens were 6.48% (95% CI: 0.46%, 12.50%) for BPF and 9.32% (95% CI:2.27%, 16.36%) for 2,4-dichlorophenol among white women. For leptin, we found that the associations for methyl-paraben were opposite between white and black women [percent change = −8.58% (95% CI: 13.99%, −3.18%) in white women and 11.68% (95% CI: 3.52%, 19.84%) in black women; P_interaction = 0.001] (Table S3). No significant association was observed in Asian

Table 3
Percent change (95% confidence interval) in serum adipokine levels for an inter-quartile range increase in standardized log-transformed urinary concentrations of phenols and parabens.

Phenols and parabens[a]	HMW-Adiponectin[b]	Leptin[b]	sOB-R[b]
BPA	0.86 (−4.17,5.9)	0.34 (−3.83,4.52)	0.87 (−1.02,2.75)
BPF	7.84 (−0.29,15.97)	−2.52 (−7.20,2.16)	**2.60 (0.48,4.71)**
2,4-dichlorophenol	**6.02 (1.20,10.83)**	−1.72 (−5.72,2.28)	1.33 (−0.47,3.14)
2,5-dichlorophenol	5.04 (−0.67,10.76)	−0.23 (−4.97,4.51)	0.71 (−1.43,2.86)
Triclosan	1.19 (−4.71,7.08)	2.41 (−2.48,7.3)	2.01 (−0.20,4.22)
Methyl paraben	1.24 (−4.86,7.33)	**−5.29 (-10.33,-0.24)**	**2.29 (0.01,4.58)**
Ethyl paraben	4.7 (−2.12,11.53)	−4.42 (−10.08,1.23)	**2.67 (0.11,5.23)**
Propyl paraben	3.67 (−3.06,10.4)	−4.04 (−9.61,1.54)	2.24 (−0.28,4.76)
Butyl paraben	3.34 (−3.45,10.14)	−2.32 (−7.96,3.31)	0.86 (−1.69,3.41)
Benzophenone-3	1.03 (−6.23,8.29)	−4.76 (−10.77,1.25)	1.46 (−1.26,4.19)

Abbreviation: HMW, High molecular weight; sOB-R, soluble leptin receptor.
[a] All urinary phenols and parabens concentrations were log-transformed and standardized.
[b] All models were adjusted for age, race, site, education level, smoking status, menopausal status, physical activity score, total caloric intake (per day), and obesity status.

Table 2
Least square geometric mean with 95% confidence intervals of creatinine-adjusted urinary phenols and parabens concentrations stratified by race.

	Detection rate (%)	White (N = 630)	Black (N = 232)	Asian (N = 338)
BPA	82.98	1.43 (1.25,1.63)	1.51 (1.27,1.80)	1.14 (0.96,1.35)
BPF	73.32	0.98 (0.86,1.12)	1.06 (0.89,1.26)	0.7 (0.59,0.83)
2,4-dichlorophenol	98.50	1.33 (1.13,1.55)	2.75 (2.23,3.39)	2.21 (1.8,2.71)
2,5-dichlorophenol	99.79	4.79 (3.91,5.86)	16.12 (12.28,21.15)	12.71 (9.72,16.63)
Triclosan	80.83	10.99 (8.79,13.73)	12.31 (9.13,16.59)	16.96 (12.63,22.78)
Methyl paraben	99.71	66.25 (54.76,80.16)	239.55 (185.48,309.39)	68.41 (53.14,88.07)
Ethyl paraben	58.94	2.53 (2.01,3.18)	3.67 (2.70,4.98)	2.65 (1.96,3.59)
Propyl paraben	97.71	10.51 (8.22,13.42)	29.06 (20.92,40.38)	8.16 (5.90,11.3)
Butyl paraben	52.79	0.49 (0.38,0.63)	0.62 (0.44,0.87)	0.65 (0.47,0.91)
Benzophenone-3	97.42	23.65 (17.94,31.17)	15.23 (10.51,22.06)	21.06 (14.6,30.37)

All models were adjusted for age, site, education level, smoking status, menopausal status, physical activity score, total caloric intake (per day), and obesity status.

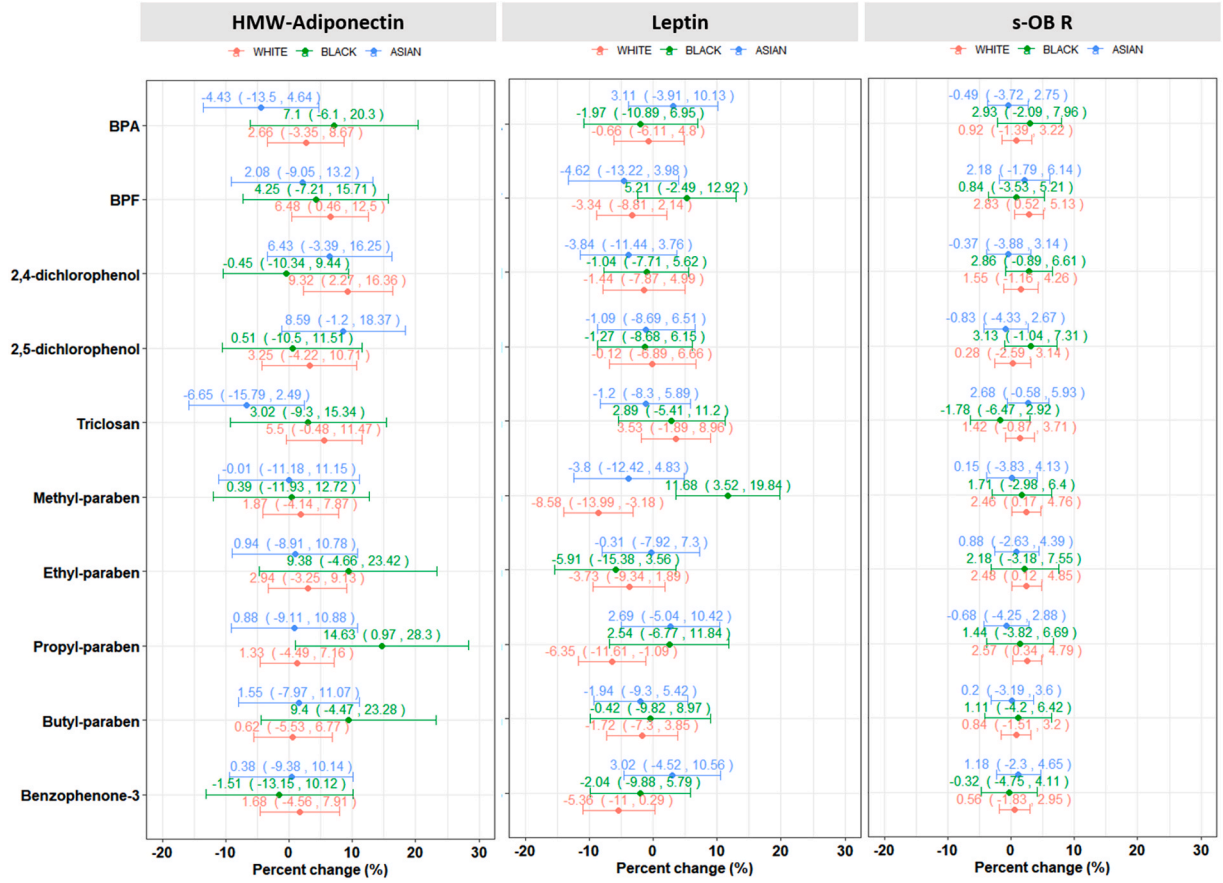

Fig. 1. Percent change (95% confidence interval) in serum adipokine levels for an inter-quartile range increase in standardized log-transformed urinary concentrations of phenols and parabens by race (White (N = 630), Black (N = 232), Asian (N = 338)). All models were adjusted for age, site, education level, smoking status, menopausal status, physical activity score, total caloric intake (per day), and obesity status. Abbreviation: HMW, High molecular weight; sOB-R, soluble leptin receptor.

women [percent change = −3.80% (95% CI: 12.42%, 4.83%)]. For sOB-R, significant positive associations were observed with BPF, methyl-paraben, ethyl-paraben, and propyl-paraben among only white women [percent change = 2.83% (95% CI: 0.52%, 5.13%) for BPF, 2.46% (0.17%, 4.76%) for methyl-paraben, 2.48% (0.12%, 4.85%) for ethyl-paraben, and 2.57% (0.34%, 4.79%) for propyl paraben]. No statistically significant associations were found for other chemicals.

Additional adjustment for urinary concentrations of MEP did not change the results (Table S4). In stratified analyses, the associations between BPF, 2,4-dichlorophenol and 2,5-dichlorophenol and HMW-adiponectin and between ethyl paraben and sOB-R were significant only among non-obese women but the differences in effect by obesity were not statistically significant (Table S5). In addition, similar associations were found when the average concentrations of two measurements at MPS baseline and at the MPS follow-up visit 3 were used (Fig. S3).

3.2. Overall joint effects of urinary phenol and paraben as mixtures

Differences in predicted serum leptin levels when the standardized and log-transformed urinary concentrations of each phenol and paraben were increased from their 25th to 75th percentile are presented in Table 4. We observed that the difference in predicted serum leptin by changes in urinary concentrations of all phenols and parabens were 7.04 (95% credible interval: 0.02, 14.06) in black women, whereas no overall joint effects were observed in white or Asian women. In black women, the individual effect of methyl-paraben with simultaneous adjustment for the other chemicals was statistically significant and much higher

Table 4
Difference (95% credible interval) in predicted serum leptin levels when the standardized concentrations of log-transformed urinary phenols and parabens were increased from their 25th to 75th percentile via Bayesian kernel machine regression (BKMR).

	White[a] (N = 630)	Black[a] (N = 232)	Asian[a] (N = 338)
BPA	−0.60 (−6.49,3.02)	0.35 (−3.43,4.13)	0.79 (−1.62,3.20)
BPF	−7.85 (−30.47,11.6)	3.64 (−0.18,7.46)	−0.32 (−1.83,1.18)
2,4-dichlorophenol	−0.75 (−10.8,5.15)	1.03 (−3.30,5.36)	−0.33 (−1.74,1.07)
2,5-dichlorophenol	−0.29 (−10.3,5.13)	0.04 (−4.42,4.51)	−0.17 (−1.77,1.42)
Triclosan	2.28 (−9.23,5.90)	1.76 (−1.56,5.08)	−0.22 (−1.83,1.40)
Methyl paraben	−3.44 (−24.7,10.9)	**5.85 (0.51,11.19)**	−0.75 (−2.56,1.07)
Ethyl paraben	1.35 (−18.15,10.0)	−3.69 (−8.19,0.81)	−0.15 (−2.12,1.81)
Propyl paraben	−1.91 (−21.18,9.88)	−2.12 (−6.53,2.29)	−0.16 (−1.99,1.66)
Butyl paraben	−0.74 (−7.33,3.38)	1.00 (−3.04,5.04)	−0.41 (−3.02,2.20)
Benzophenone-3	−1.12 (−12.53,5.85)	0.59 (−2.67,3.85)	0.20 (−1.61,2.00)
Overall	−1.70 (−22.16,10.49)	7.04 (0.02,14.06)	−1.36 (−5.02,2.30)

[a] All models were adjusted for age, site, education level, smoking status, menopausal status, physical activity score, total caloric intake (per day), and obesity status.

than those of the other phenols and parabens [difference = 5.85 (95% credible interval: 0.51, 11.19)]. We did not find any significant associations for HMW-adiponectin and sOB-R (Table S5).

4. Discussion

This study examined the cross-sectional associations between urinary concentrations of six phenols and four parabens with serum adipokine levels in a multi-racial/ethnic, community-based cohort of midlife women in the United States. Overall, we observed that urinary concentrations of phenols and parabens, especially BPF, 2,4-dichlorophenol, and methyl-paraben, were associated with favorable profiles of adipokines (higher adiponectin, higher sOB-R, and lower leptin) in the entire population. However, race-specific analyses suggest these associations may differ by race. In black women, the concentration of methyl-paraben, was approximately four times higher compared to white and Asian women and was significantly associated with higher leptin levels. A significant inverse association between methyl-paraben and leptin was observed in white women and no significant association was observed in Asian women. The overall joint effect of urinary phenols and parabens on serum leptin levels was positive and statistically significant only in black women. Methyl-paraben was identified as the most prominent contributor within phenol and paraben mixtures among black women. These findings suggest that exposure to phenols and parabens may not promote unfavorable changes in adipokines in midlife women, but high exposure to methyl-paraben in black women may play a role in leptin resistance and related metabolic disorders.

Methyl-paraben is the most commonly used paraben. It has a short linear alkyl chain. The adipogenic potency of parabens increases with increasing length of the linear alkyl chain (Hu et al., 2013; Hu et al., 2017; Kodani et al., 2016). However, a recent study found that methyl-paraben exposure by daily oral gavage (100 mg/kg/day) was associated with increasing serum leptin levels in female mice. Butyl-paraben exposure with the same daily oral gavage did not have the same effect (Hu et al., 2016). Parabens with longer alkyl chains are more efficiently hydrolyzed than parabens with short alkyl chains in liver microsomes and plasma (Ozaki et al., 2013). Higher unmetabolized methyl-paraben accumulation in plasma or tissue compartments may thus result in more pronounced in vivo effects (Hu et al., 2017). Methyl-paraben was the only paraben detected in human adipose tissue (Artacho-Cordón et al., 2017). Paraben exposure has been shown to induce changes in gene expression related to adipocyte differentiation and promote lipid accumulation in murine 3T3-L1 cells (Hu et al., 2013) and adipose tissues in female mice (Hu et al., 2016), suggesting that parabens may potentially play a role in unfavorable adipokine profiles. However, parabens have also been shown to suppress leptin mRNA in human primary adipocytes (Hu et al., 2013), contrary to the results found in murine 3T3-L1 cells. In addition, a study with rat experimental models conducted by another research group found that butyl-paraben, a weak ligand of PPAR receptors, caused reduced plasma levels of leptin (Boberg et al., 2008). It is unclear that these opposite adipogenic effects of parabens are attributed to cell-dependency or differences between *in vitro* and in vivo settings or species, and therefore, cannot explain our discrepant findings between white and black women.

Disparities in exposure to EDCs is another possible explanation. In the present study, urinary concentrations of methyl-paraben were much higher in black women than the other racial groups (240 ng/mL in black vs. 66 ng/mL in white, and 68 ng/mL in Asian women, Table 2). Racial/ethnic differences in urinary concentrations of personal care and consumer product chemicals have been reported in the National Health and Nutrition Examination Survey (NHANES) (Calafat et al., 2010; Nguyen et al., 2020). Black women generally use more hair care products, such as hair oils, lotions, chemical relaxers, and leave-in conditioners which typically contain parabens as preservatives and other EDCs such as phthalates (Helm et al., 2018; James-Todd et al., 2012; James-Todd et al., 2021). Although it is unclear that higher exposure to EDCs in black women contributes to racial/ethnic disparities in obesity and other metabolic diseases, a recent study showed that EDC exposure, associated disease burden, and medical costs were higher in non-Hispanic black Americans compared with their proportion of the total population (16.5% vs. 12.6%) (Attina et al., 2019). The observed racial difference in the association between methyl-paraben and leptin should not be interpreted as an example of hormesis, i.e., low-level exposures to toxicants can be beneficial (Thayer et al., 2005), given the overlap of methyl-paraben exposure levels between white and black women (Fig. S4).

To date, only a few studies have investigated the association between paraben and adipokine levels in human populations. One study with 459 Korean women aged 20–48 years found positive associations of urinary ethyl-paraben and propyl-paraben with serum adiponectin levels [Adjusted regression coefficient (β) = 0.569 (95% CI: 0.233,0.906] for ethyl-paraben, β = 0.343 (95% CI: 0.003,0.682) for propyl-paraben]. They also found an inverse association of urinary propyl-paraben with serum leptin levels [β = -1.717 (95% CI: 3.176, −0.258)] (Lee et al., 2019). A cross-sectional study of 27 healthy women with regular menstrual cycles conducted in the Czech Republic found an inverse association between plasma methyl-paraben and plasma leptin [Adjusted regression coefficient (β) = −0.771 (95% CI: 1.424, −0.118)] (Kolatorova et al., 2018). Both findings are in line with our findings in white women. A recent study of 73 Mexican midlife women found that urinary concentrations of methyl- and propyl-parabens were associated with increased odds of metabolic syndrome, although these associations were not statistically significant due to the small sample size (Zamora et al., 2021).

Additionally, we found a positive association between BPF and sOB-R. A decrease in sOB-R and a concurrent increase in leptin levels indicates a state of leptin resistance (Shimizu et al., 2002). Contrary to our findings, an *in vitro* study reported that BPF increased release of leptin from the adipocytes (Ramskov Tetzlaff et al., 2020). However, the association between BPF and obesity may differ by sex; a positive association was observed in males whereas an inverse association was observed in females (Liu et al., 2019), which is in line with our findings. It is biologically plausible that sex differences in estrogenic activity of BPF may lead to different susceptibilities to obesity (Rochester and Bolden, 2015; Yang et al., 2017). Thus, further investigations are warranted to clarify the association between BPF and leptin and sOB-R levels in women.

Our study also found a positive association between 2,4-dichlorophenol and HMW-adiponectin. No biological or epidemiologic studies of dichlorophenols and serum adipokines have been reported, and therefore, it is difficult to interpret our finding. Further studies are needed to confirm our finding in other populations and to understand underlying biological mechanisms.

To the best of our knowledge, this is the first study to examine race-specific associations of urinary phenols and parabens with serum adipokine levels using a multi-racial/ethnic cohort of women who were transitioning to menopause. Our findings can be generalizable to other racially/ethnically diverse populations of midlife women. Furthermore, we identified independent associations for individual urinary phenols and parabens after controlling for confounding due to co-pollutants using the BKMR approach, which allowed us to handle non-linear associations and interaction effects between chemicals.

Our study also has several limitations. First, phenols and parabens are chemicals with short half-lives and therefore, urinary concentrations are subject to exposure measurement errors. Although our urinary concentrations of phenols and parabens were assessed at two time-points to account for within person variability, some chemicals, such as bisphenols and 2,4-dichlorophenol, had low intra class correlations (ICCs) (Fig. S5). However, methyl-paraben had a moderate ICC (ICC = 0.53) between urinary concentrations measured at two-time points (Fig. S5) and the average concentrations over two times showed consistent results, suggesting that our findings were robust and the

impact of exposure measurement error was small. Second, although we adjusted for many potential confounders including phthalates, residual confounding cannot be ruled out. Third, the cross-sectional observations limit the validity of causal inference. Future studies with longitudinal measurements of both adipokines and phenols and parabens are needed to verify our findings.

5. Conclusions

This study demonstrated that urinary concentrations of phenols and parabens, especially BPF, 2,4-dichlorophenol, and methyl-paraben, were associated with favorable profiles of adipokines. However, methyl-paraben, widely used in hair and personal care products, was associated with higher and unfavorable levels of serum leptin in black women whose urine concentrations were approximately four times higher compared with white and Asian women. Further studies of potential causal links between methyl-paraben exposure from the use of hair and personal care products and leptin and the underlying biological mechanisms are warranted. Future epidemiologic studies are needed to confirm this racial/ethnic difference.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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