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Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity: Comparison of three statistical models

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ABSTRACT

Background: The evaluation of the chemical impact on human health is usually constrained to the analysis of the health effects of exposure to a single chemical or a group of similar chemicals at one time. The effects of chemical mixtures are seldom analyzed. In this study, we applied three statistical models to assess the association between the exposure to a mixture of seven xenobiotics (three phthalate metabolites, two phenols, and two pesticides) and obesity.

Methods: Urinary levels of environmental phenols, pesticides, and phthalate metabolites were measured in adults who participated in the U.S.-based National Health and Nutrition Examination Survey (NHANES) from 2013 to 2014. Body examination was conducted to determine obesity. We fitted multivariable models, using generalized linear (here both logistic and linear) regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) models to estimate the association between chemical exposures and obesity.

Results: Of 1269 individuals included in our final analysis, 38.5% had general obesity and 58.0% had abdominal obesity. In the logistic regression model established for each single chemical, bisphenol S (BPS), mono (carboxyoctyl) phthalate (MCOP), and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP) were associated with both general and abdominal obesity (fourth vs. first quartile). In linear regression, MCOP was associated with BMI and waist circumference. In WQS regression analysis, the WQS index was significantly associated with both general obesity (OR = 1.63, 95% CI: 1.21–2.20) and abdominal obesity (OR = 1.66, 95% CI: 1.18–2.34). MCOP, bisphenol A (BPA), bisphenol S (BPS), and mono ethyl phthalate (MEP) were the most heavily weighing chemicals. In BKMR analysis, the overall effect of mixture was significantly associated with general obesity when all the chemicals were at their 60th percentile or above it, compared to all of them at their 50th percentile. MCOP, BPA, and BPS showed positive trends. By contrast, MECPP showed a flat and modest inverse trend.

Conclusion: When comparing results from these three models, MCOP, BPA, and BPS were identified as the most important factors associated with obesity. We recommend estimating the joint effects of chemical mixtures by applying diverse statistical methods and interpreting their results together, considering their advantages and disadvantages.

1. Introduction

Obesity is one of the most serious global public health issues. In 2016, the World Health Organization (WHO) estimated that 39% of adults were overweight worldwide, of whom 13% were obese (WHO, 2018). Obesity increases the risk of many chronic diseases such as cardiovascular diseases, neurological disorders, diabetes, and even some types of cancer (Gallagher and LeRoith, 2015; O'Brien et al., 2017;

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Abbreviations

BKMR	Bayesian kernel machine regression
BMI	body mass index
BPA	bisphenol A
BPS	bisphenol S
BPF	bisphenol F
CI	confidence interval
DINP	di-isononyl phthalate
DEHP	diethylhexyl phthalate
DEP	diethyl benzene-1,2-dicarboxylate
GPAQ	Global Physical Activity Questionnaire
LOD	lower limit of detection
MEC	mobile examination center
MCOP	mono (carboxyoctyl) phthalate
MECPP	mono (2-ethyl-5-carboxypentyl) phthalate
MEP	mono ethyl phthalate
MET	metabolic equivalent time
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
VIF	variance inflation factor
WQS	weighted quantile sum
2,5-DCP	2,5-dichlorophenol
2,4-DCP	2,4-dichlorophenol

Picon-Ruiz et al., 2017). Annually, at least 2.8 million deaths globally can be attributed to being overweight or obese (WHO, 2018). The control and management of obesity require identification of the potential factors associated with it.

Previous studies have demonstrated that many factors, including genetic predisposition, excessive energy intake, lack of physical activity, etc., can play a role in the development of obesity (Alamuddin et al., 2016; van der Klaauw and Farooqi, 2015). However, these factors cannot completely account for the obesity epidemic. Over recent years, the role of obesogenic endocrine disruptors that promote the development of obesity has been investigated (Muscogiuri et al., 2017; Wang et al., 2016), and environmental phenols, phthalates, and pesticides may play important roles (Dong et al., 2017; Hatch et al., 2008; Liu et al., 2017; Ye et al., 2014). These chemicals have been extensively used in consumer products and detected in consumers (Bradley et al., 2013; Huang et al., 2012; Wei et al., 2014). Humans are exposed to these chemicals through various sources such as from inhalation of dust, ingestion of contaminated foods, and from dermal contact with personal care products (Bui et al., 2016; Vandenberg et al., 2009; Ye et al., 2014). However, to estimate exposures from all the sources and routes accurately is a very difficult task. An alternative method (used here), requiring information of eventual biotransformation pathways, is to assess the combined body exposure from measurement of excreted compounds or their representative metabolites. In this study, urinary phenols, pesticides, and representative metabolites of the phthalates were measured and represent the exposure to multiple sources and routes. Several previous studies have demonstrated correlations between the urinary concentration of these chemicals and obesity. However, most of these focused on the effect of a single chemical at one time (Buser et al., 2014b; Hatch et al., 2008; Li et al., 2015; Twum and Wei, 2011; Ye et al., 2014). In reality, however, the average person is being exposed to various chemicals simultaneously. This can lead to interactions between co-administered chemicals (Czarnota et al., 2015b; Kim et al., 2017; Kim et al., 2013; Kim et al., 2015). Consequently, today, most researchers support the need to study the simultaneous effect of common environmental contaminants (Artacho-Cordon et al., 2016; Chiu et al., 2018; Coker et al., 2018; Coker et al., 2017; Czarnota et al., 2015a; Valeri et al., 2017). The complex exposure pattern, high correlation, and complicated interactions within environmental chemicals require a tailored strategy to assess the mixed effects of multiple pollutants (Billionnet et al., 2012).

We undertook this study to identify urinary chemicals or metabolites that may be associated with obesity based on the U.S. nationwide population data from NHANES participants from 2013 to 2014. We included seven urinary phenols, pesticides, and phthalate metabolites, based on previous studies reporting their association with obesity or their potential obesogenic effects (Liu et al., 2017; Tang-Peronard et al., 2011; Ye et al., 2014). The mixed effects of these chemicals were analyzed using generalized linear regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) models. All three models had advantages and disadvantages. The results of the three methods were interpreted jointly afterward. Our results can offer some advice for longitudinal epidemiological studies and experimental studies to explore the relationship between chemical exposure and obesity further.

2. Materials and methods

2.1. Study population

The NHANES is a cross-sectional, nationwide study aiming to assess the health and nutrition status of children and adults in the USA, carried out periodically since the 1960s. The study population is nationally representative, recruited through a multistage, stratified sampling design. We used publicly available data from participants recruited between 2013 and 2014. Subsample B was the representative sample of the 2013–2014 cycle by first using an algorithm to divide all the samples randomly into 12 groups, and combinations of these groups were predetermined to create the various subsamples (CDC, 2016). Individuals in this subsample had provided urine specimens for measurement of urinary phenol, pesticide, and phthalate metabolites. We included participants aged 20 years and older who had completed measurements of body weight, height, and waist circumference in subsample B. We excluded participants with missing data on covariates, pregnant women, and persons diagnosed with cancer or malignancy (affecting their body weight). We also excluded those with BMI under 18.5 to exclude disturbance from some unknown reasons that induced underweight. Finally, 1269 participants were left for the analysis (Fig. 1). The NHANES survey 2013–2014 was approved by the National Center for Health Statistics Research Ethics Review Board. All participants gave their written consent to participate in the study.

2.2. Measurement of chemicals in urine

Spot urine samples were collected at mobile examination centers (MECs). The samples were stored at −20 °C until analysis by the Division of Laboratory Sciences, Organic Analytical Toxicology Branch, at the National Center for Environmental Health (Atlanta, GA). Each of the recruited participants who had all seven urinary phenols, pesticides, and phthalates metabolites analyzed for monoethyl phthalate (MEP) [metabolite of diethyl benzene-1,2-dicarboxylate (DEP)], mono (carboxyoctyl) phthalate (MCOP) [metabolite of di-iso-nonyl phthalate (DINP)], and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP) [metabolites of diethylhexyl phthalate (DEHP)] were selected as the representatives of phthalate metabolites because their primary chemicals claimed over 75% global share (Benjamin et al., 2017), and they were the first three phthalate metabolites of the highest concentration in this population (results not shown). Thus, the finally analyzed chemicals were bisphenol A (BPA), bisphenol S (BPS), and two chlorophenol pesticides [2,4-dichlorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5-DCP)] as well as three representative phthalate metabolites (MEP, MCOP, and MECPP). Urinary concentrations of BPA, BPS, 2,4-DCP, and 2,5-DCP were measured by on-line, solid-phase extraction coupled

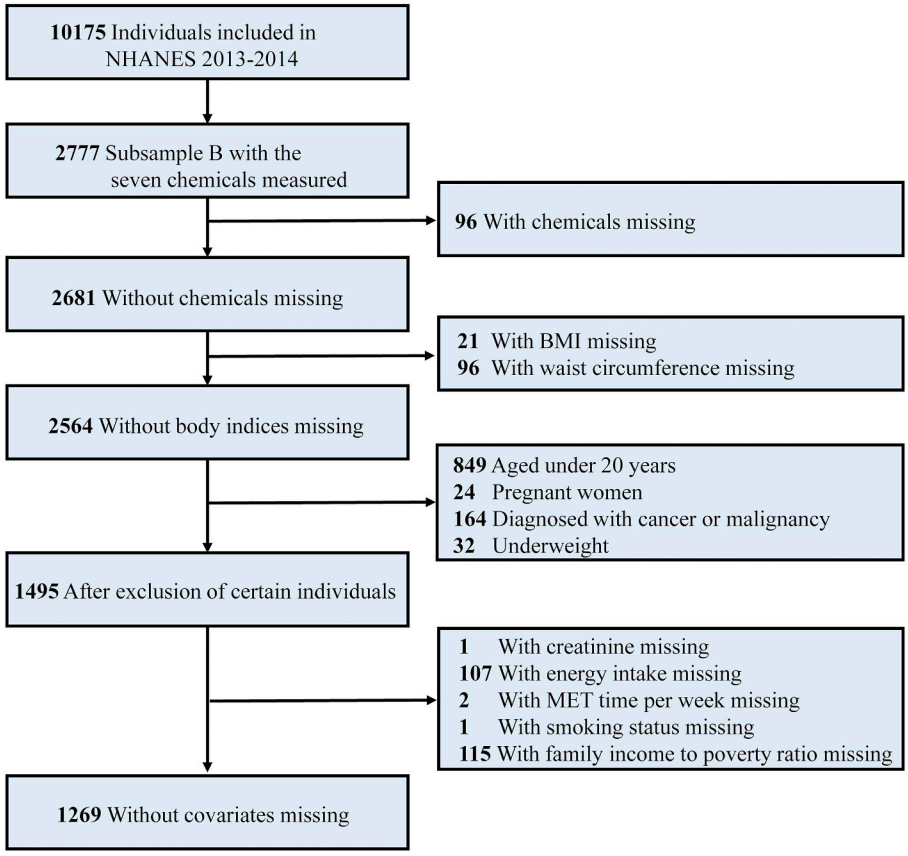

Fig. 1. Flowchart of population included in our final analysis (N = 1269), NHANES, USA, 2013–2014.

to high-performance liquid chromatography and tandem mass spectrometry (on-line SPE-HPLC-isotope dilution-MS/MS). Phthalate metabolites were measured by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS). Detailed information about the chemical measurement methods can be obtained from the NHANES laboratory methods (https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/PHTHTE_H_MET_Phthalates.pdf; https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/EPHPP_H_MET.pdf). The lower limit of detection (LOD) for BPA; BPS; 2,4-DCP; 2,5-DCP; MEP; MCOP; and MECPP were 0.2 μg/L, 0.2 μg/L, 0.1 μg/L, 0.1 μg/L, 1.2 μg/L, 0.3 μg/L, and 0.4 μg/L, respectively. For analytic results below the lower limit of detection, we imputed the lower limit of detection divided by the square root of two. The urinary creatinine concentration in grams per liter was determined with an Enzymatic Roche Cobas 6000 analyzer and used as an internal reference to account for urinary dilution, thus adjusted in the following analysis as a covariate according to the recommendation (Barr et al., 2005).

2.3. Outcomes and covariation assessment

Trained health technicians measured body weight, height, and waist circumference at the MECs. General obesity was defined as BMI of 30 kg/m^2 or higher. Abdominal obesity was classified as absolute waist circumference of 102 cm or above in men and 88 cm or above in women.

Covariates, including age, gender, ethnicity, education levels, family income, physical activity, total energy intake levels, and smoking status were obtained by direct interview. Age and natural ln-transformed creatinine concentration were treated as continuous variables. The categories of other covariates were as follows: gender (female, male), ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and others), education levels (lower than high school, high school, some college or AA degree, college graduation, or above), family income–to-poverty ratio (≤1.30, 1.31–3.50, > 3.50), physical activity (< 600, 600–1199, ≥1200 MET min per week), total energy intake (low: males < 2000 kcal/day, females < 1600 kcal/day; adequate: males 2000–3000 kcal/day, females 1600–2400 kcal/day; high: males > 3000 kcal/day, females > 2400 kcal/day), smoking status (never smoker: < 100 cigarettes in life; former smoker: > 100 cigarettes in life and did not smoke at the time of survey; current smoker: > 100 cigarettes in life and smoked every day or some days at the time of survey). Participants were asked about their physical activity during a typical week, based on the Global Physical Activity Questionnaire (GPAQ). Metabolic equivalent (MET) per week was calculated according to the GPAQ guideline. Total energy intake per day was based on dietary interview data, from which the total energy intake of the first two days was averaged as the participants' energy intake. When data from the second day was absent, the data of the first day represented the typical total energy intake per day.

2.4. Statistical analysis

We compared variations of continuous and categorical variables, using the t and χ^2 tests, respectively. Because concentrations of these seven chemicals were seriously right-skewed, the data were ln-transformed to improve a normal distribution when they were treated as continuous variables. We calculated the Pearson correlation coefficients between ln-transformed concentrations of the seven chemicals.

2.4.1. Statistical model 1: generalized linear regression model

First, we assessed the association between individual chemicals and general obesity or abdominal obesity by comparing the second, third, and fourth quartiles to the first quartile of a chemical's concentration, using multivariate logistic regression. In addition, we fitted a logistic

regression model for each chemical, adjusting for the concentration of other chemicals. Next, we conducted linear regression with ln-transformed concentration of each chemical as continuous variables and BMI or waist circumference as continuous outcome variables. All multivariable analyses were adjusted to gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine concentration.

2.4.2. Statistical model 2: weighted quantile sum (WQS) regression model

Second, we used the WQS regression model to evaluate the effects of mixed exposure to seven chemicals, which was a weighted quartile sum approach in conjunction with either linear (continuous outcomes) or logistic (binary outcomes) regression (Carrico et al., 2014; Czarnota et al., 2015a; Czarnota et al., 2015b). This approach took all the measured chemicals into consideration, and chemicals included in this model were constrained to have the same effect direction for the obesity association. By grouping different chemicals into ordinal variables (quartiles), the WQS regression model calculated a weighted linear index, which represented the whole body burden of all seven chemicals. The corresponding weight of each chemical showed how much a particular chemical contributed to the WQS index. The function of the WQS model was as follows.

$$g(\mu) = \beta_0 + \beta_1\left(\sum_{i=0}^{c} \omega_i \mathscr{I}_i\right) + z'\Phi \Big|_b$$

$$\mathrm{WQS} = \sum_{i=1}^{c} \varpi_i \mathscr{I}_i$$

where $\beta_0$was the intercept; z' and Φ represented the matrix of covariates and coefficient of covariates; c was the number of chemicals considered in the analysis (here, seven). The sum of the entire weighted index (ω_i) was equaled to 1, with value of each ranging from 0 to 1 ($\sum_{i=0}^{c} \omega_i \mid_b = 1$, $0 \le \omega_i \le 1$). β_1 was the regression coefficient of the WQS index. $\mathscr{I}_i$ indicated quartiles of the value that a chemical scored ($\mathscr{I}_i = 0$, 1, 2, or 3 represented the 1st, 2nd, 3rd, or 4th quartile, respectively). $g(\mu)$ was a logit link function when the outcomes of interest were binary (general obesity or not, abdominal obesity or not). A linear link was assumed for $g(\mu)$ when outcomes are continuous variables (BMI or waist circumference). The data were randomly split into two data sets (40% as training set and 60% as validation set). In addition, we set β_1 as a non-constrained positive coefficient. By bootstrapping the training set, we obtained the ω_i of each chemical and the estimated $\beta_1$at each time. After bootstrapping 10,000 times, we got 10,000 sets of ω_i and β_1 indices. All the obtained ω_is of each chemical were averaged to get the empirical weights when β_1 was positive and iteration of the same set was successfully converged (with the parameter conv (converge) not equal to 2). The averaged ω_i of each chemical was applied to the function to calculate the statistical significance in the validation data. We also conducted the model with β_1 constrained to be negative to determine whether there was a signal in that direction.

2.4.3. Statistical model 3: Bayesian kernel machine regression (BKMR) model (Bobb et al., 2015)

Third, we used the BKMR model, a non-parametric Bayesian variable selection framework, to evaluate the joint effect of chemicals on obesity and body indices. BKMR combines Bayesian and statistical learning methods to regress an exposure–response function iteratively by a Gaussian kernel function. BKMR can identify nonlinear and non-additive relationships within chemicals. Because the chemicals in our analysis were highly correlated, we conducted a hierarchical variable selection method with 50,000 iterations by a Markov chain Monte Carlo

Table 1
Characteristics of study population (N = 1269), NHANES, USA, 2013–2014.

Characteristics	No obesity	General obesity	*P* value	No abdominal obesity	Abdominal obesity	*P* value
	N = 780	N = 489		N = 533	N = 736	
Age, year	47.16 (17.08)	47.99 (15.92)	0.381	43.79 (16.47)	50.15 (16.26)	< 0.001
Gender			0.001			< 0.001
Male	399 (51.2%)	205 (41.9%)		344 (64.5%)	260 (35.3%)	
Female	381 (48.8%)	284 (58.1%)		189 (35.5%)	476 (64.7%)	
Ethnicity			< 0.001			< 0.001
Hispanic	174 (22.3%)	126 (25.8%)		112 (21.0%)	188 (25.5%)	
Non-Hispanic white	311 (39.9%)	207 (42.3%)		201 (37.7%)	317 (43.1%)	
Non-Hispanic black	147 (18.8%)	129 (26.4%)		100 (18.8%)	176 (23.9%)	
Non-Hispanic Asian	121 (15.5%)	12 (2.5%)		100 (18.8%)	33 (4.5%)	
Other	27 (3.5%)	15 (3.1%)		20 (3.8%)	22 (3.0%)	
Education level			< 0.001			< 0.001
Lower than high school	175 (22.4%)	113 (23.1%)		112 (21.0%)	176 (23.9%)	
High school	158 (20.3%)	127 (26.0%)		105 (19.7%)	180 (24.5%)	
Some college or AA degree	206 (26.4%)	164 (33.5%)		130 (24.4%)	240 (32.6%)	
College graduate or above	241 (30.9%)	85 (17.4%)		186 (34.9%)	140 (19.0%)	
Family income-to-poverty ratio			0.014			0.017
≤1.30	262 (33.6%)	178 (36.4%)		171 (32.1%)	269 (36.5%)	
1.31–3.50	252 (32.3%)	182 (37.2%)		173 (32.5%)	261 (35.5%)	
> 3.5	266 (34.1%)	129 (26.4%)		189 (35.5%)	206 (28.0%)	
Smoking status			0.785			0.393
Never smoker	462 (59.2%)	280 (57.3%)		323 (60.6%)	419 (56.9%)	
Past smoker	159 (20.4%)	105 (21.5%)		103 (19.3%)	161 (21.9%)	
Current smoker	159 (20.4%)	104 (21.3%)		107 (20.1%)	156 (21.2%)	
MET time/week			0.011			< 0.001
< 600	284 (36.4%)	219 (44.8%)		167 (31.3%)	336 (45.7%)	
600–1199	89 (11.4%)	52 (10.6%)		68 (12.8%)	73 (9.9%)	
≥1200	407 (52.2%)	218 (44.6%)		298 (55.9%)	327 (44.4%)	
Total calories, kcal per day			0.917			0.145
Low	320 (41.0%)	195 (39.9%)		201 (37.7%)	314 (42.7%)	
Adequate	324 (41.5%)	208 (42.5%)		229 (43.0%)	303 (41.2%)	
High	136 (17.4%)	86 (17.6%)		103 (19.3%)	119 (16.2%)	

MET time: Metabolic equivalent (MET) per week. Data presented are mean ± SD or n (%). The *t*-test and $\chi 2$ test were between the general obesity and no obesity groups or between the abdominal obesity and no abdominal obesity groups.

algorithm. Based on Pearson correlation coefficient values and their similar exposure sources (Andaluri et al., 2018; Czaplicka, 2004; Wittassek et al., 2011), we grouped MCOP, MEP, MECPP, BPA, and BPS into group 1, and 2,5-DCP and 2,4-DCP into group 2.

$$Y_i = h[Group_1 = (MCOP, MEP, MECPP, BPA, BPS), Group_2 = (2,5-DCP, 2,4-DCP)] + \beta^T Z_i + e_i$$

where $h()$ was the exposure–response function based on nonlinearity and/or interaction among the mixture components, Z_i, and β represented covariates and their coefficients, respectively. Confidence intervals obtained from the BKMR model incorporated the additional uncertainty due to estimation of a high-dimension set of exposures and accounting for multiple-testing penalty. We assumed that the within-group correlation was high and the across-group correlation was low. Using a hierarchical variable selection method, we calculated the group posterior inclusion probability (groupPIP) representing the probability of a mixture group, which was included in the final model after 50,000 iterations. Based on groupPIP, we calculated the conditional posterior inclusion probability (condPIP), which represented the probability that a particular chemical within the group was included in the model. A PIP threshold of 0.5 is usually used (Coker et al., 2018) to determine whether it is important. The BKMR model could analyze the association between mixed exposure and a binary outcome ([1/0] variable; here, whether general/abdominal obesity or not) as well as continuous variables (here, BMI and waist circumference). At the former situation, a probit link function was assumed (Bobb et al., 2018). With probit regression in BKMR, $h()$ could be interpreted as the exposure–response relationship between exposure and a latent continuous outcome (> 0 equal to disease, < 0 equal to control).

In the NHANES survey, samples were weighted to reduce the selection bias among subgroups for age, gender, and ethnicity. Therefore, we used unweighted estimation because variables used to count sample weights had already been included in the adjusted model, as recommended previously (Blount et al., 2006; Kim et al., 2017).

All significance levels were set to 0.05 in this study. All analyses were conducted with R (3.5.1). WQS and BKMR were implemented with the R packages “gWQS” (version 1.1.0) and “bkmr” (version 0.2.0), respectively.

3. Results

3.1. Population characteristics

General characteristics of the study population are presented in Table 1. In total, 1269 participants were included in the analysis. The prevalence of general obesity and abdominal obesity were 38.5% and -58.0%, respectively. Gender, ethnicity, education level, family income, and physical activity were significantly different between obese and non-obese participants in both analyzed groups. Age was significantly different between those with abdominal obesity and those without.

3.2. Measurement of urinary phenols and phthalate metabolites and their correlation

All seven chemicals were detectable in ≥90% of the study population. The mean concentration, geometric mean concentration, and distribution of these chemicals are shown in Table 2. BPA and its substitute BPS were detected in 95.0% and 90.0% of participants, respectively, and the concentration of BPA was about two times higher than that of BPS. It was revealed that the concentration of 2,5-DCP was much higher than 2,4-DCP. The urinary concentration of MEP was the highest among the phthalate metabolites, whereas MCOP and MECPP were second and third, successively.

Correlations between the concentrations of these seven chemicals (Fig. 2) were statistically significant (P value < 0.001) (r ranging from 0.16 to 0.77). MECCP was found to be moderately associated with MCOP and BPA (both r = 0.51), and there was a strong correlation between 2,4-DCP and 2,5-DCP (r = 0.77). The other correlations were relatively weak.

3.3. Generalized linear regression model to assess the association between chemical concentration and obesity

We used multivariable logistic regression and linear regression to assess the individual effect of each chemical on obesity. In the multivariable logistic regression analysis, after adjusting for all the covariates, MCOP, MECPP, and BPS showed significant associations with general obesity in the upper two quartiles (Table 3). Meanwhile, there were only significant associations between BPA and both general obesity and abdominal obesity in quartile 3 but not in quartile 4 (Tables 3 and 4). We did not find significant associations between other chemicals and obesity. To adjust for confounding effects of other chemicals, we fitted a separate logistic regression model including all the chemicals. In this analysis, only MCOP was found to be significantly associated with both general (OR: 1.72, 95% CI: 1.14–2.60) and abdominal obesity (OR: 1.57, 95% CI: 1.03–2.39) (Supplementary material Tables S1 and S2).

We assessed the relationship between chemical exposure and body indices, using multivariable linear regression (Table 5). After adjusting for covariates, MCOP was the only chemical found to be associated with BMI and waist circumference in single-chemical analysis. After further adjusting other chemicals simultaneously in one model, MCOP was the only chemical associated with body indices as well (Supplementary material Table S3). All the variance inflation factors (VIFs) in the multivariable linear regression model were fewer than 10 (results not shown), which meant there was little multicollinearity among the chemicals, although some of them were highly correlated.

Table 2
Distribution of exposure biomarkers (N = 1269), NHANES, USA, 2013–2014.

Exposure biomarkers	Detection frequency	GM	Mean	Percentile				
				5th	25th	50th	75th	95th
Phenols (μg/L)								
BPA	95.0%	1.33	3.15	0.14	0.60	1.30	2.70	8.50
BPS	90.0%	0.46	1.34	0.07	0.20	0.40	1.00	3.90
Pesticides (μg/L)								
2,5-DCP	98.2%	3.67	91.89	0.20	0.80	2.50	11.85	278.45
2,4-DCP	94.8%	0.72	3.22	0.07	0.30	0.60	1.40	10.65
Phthalate metabolites (μg/L)								
MEP	99.8%	42.79	189.15	4.50	14.70	36.10	111.50	614.15
MECPP	99.7%	10.26	17.41	1.80	5.50	11.00	18.60	51.05
MCOP	99.8%	19.18	52.55	2.15	7.55	17.80	48.35	221.25

GM: geometric mean.

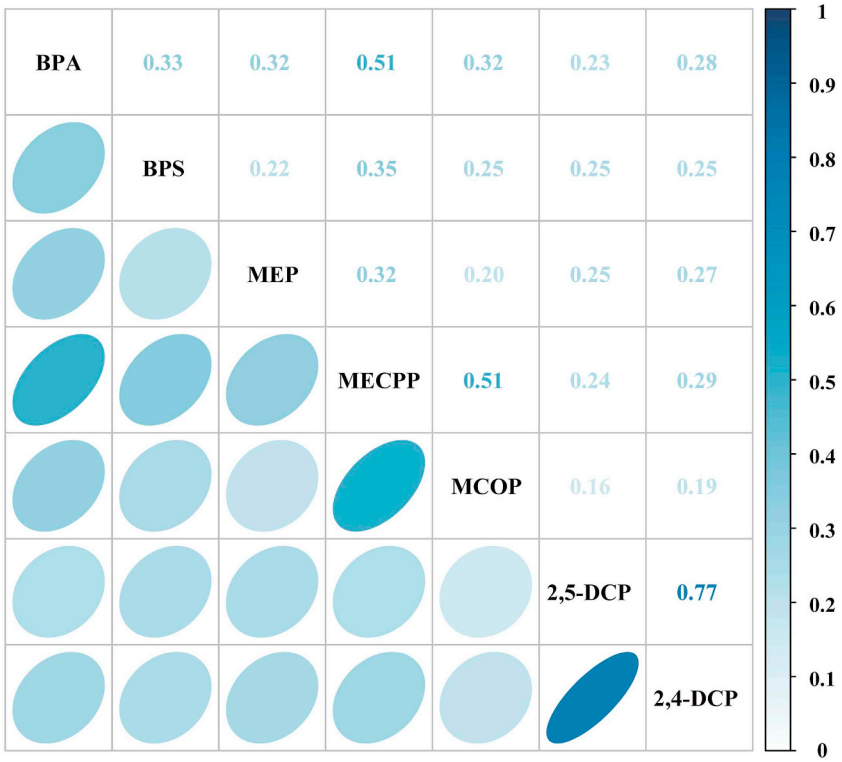

Fig. 2. Pairwise Pearson correlations among urinary concentrations of seven chemicals or metabolites in the population (N = 1269), NHANES, USA, 2013–2014. All the correlations were statistically significant (*P* value < 0.001).

3.4. WQS regression model to assess the association between chemical concentration and obesity

The WQS indices were statistically associated with both general and abdominal obesity. Detailed results of rough and fully adjusted models are presented in Table 6. In the former ones, the WQS index was significantly associated with general obesity (OR: 1.50, 95% CI: 1.13–1.98) and abdominal obesity (OR: 1.49, 95% CI: 1.07–2.07). In the fully adjusted models, a quartile increase in the WQS index was statistically significantly associated with both general (OR = 1.63, 95% CI: 1.21–2.19) and abdominal obesity (OR = 1.66, 95% CI: 1.18–2.33).

The estimated chemical weight for each WQS index is shown in Supplementary material Table S4 and Fig. 3. The highest weighted chemical in both general and abdominal obesity models was MCOP (weighted 0.40 and 0.29, respectively). Following MCOP, MEP, BPA, and BPS were weighted highly in general obesity (weighted 0.21, 0.18, and 0.09, respectively), whereas BPA, MEP, and BPS weighted highly in abdominal obesity (weighted 0.24, 0.17, and 0.13, respectively). MECPP was assigned the lightest weight in both models.

To analyze mixture exposure–induced body index changes further, we recoded BMI and waist circumference in continuous outcomes and fitted a WQS model to assess the effects of exposure to seven environmental chemicals on body indices. The results showed that the WQS index was not significantly associated with BMI in a rough model (Table 7) but was statistically significant when further adjusted for other covariates (β = 1.08, 95% CI: 0.17–2.00). A quartile increase of the WQS index was associated with waist circumference increase by 3.02 cm (96% CI: 0.89–5.15) after adjusting for all covariates. The weight of each chemical is reported in Supplementary material Table S5 and Fig. 4, and MCOP, BPA, BPS, and MEP were the most weighted chemicals in both models. MECPP was weighted lightest in both models.

Table 3
Association between single urinary chemical/metabolite concentration and general obesity (N = 1269), NHANES, USA, 2013–2014.

Exposure biomarkers	Quartile 1	Quartile 2		Quartile 3		Quartile 4	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Phenols							
BPA	Ref	1.35 (0.93, 1.97)	0.116	1.90 (1.28, 2.80)	0.001	1.53 (0.99, 2.35)	0.055
BPS	Ref	1.05 (0.73, 1.52)	0.782	1.52 (1.07, 2.16)	0.019	1.44 (1.01, 2.07)	0.045
Pesticides							
2,5-DCP	Ref	1.11 (0.78, 1.57)	0.571	1.20 (0.83, 1.72)	0.327	0.98 (0.68, 1.43)	0.935
2,4-DCP	Ref	0.99 (0.69, 1.41)	0.945	0.89 (0.62, 1.28)	0.528	1.10 (0.77, 1.57)	0.603
Phthalate metabolites							
MCOP	Ref	1.20 (0.83, 1.72)	0.337	1.74 (1.20, 2.51)	0.003	1.80 (1.22, 2.65)	0.003
MECPP	Ref	1.61 (1.10, 2.36)	0.014	1.57 (1.04, 2.38)	0.033	1.62 (1.04, 2.51)	0.032
MEP	Ref	0.92 (0.64, 1.32)	0.658	1.05 (0.72, 1.52)	0.814	1.28 (0.87, 1.88)	0.213

OR: odds ratio; CI: confidence interval. Estimated odds ratios (ORs) were compared with the first exposure quartile; quartile cut points were based on all the participants in this study (N = 1269). Models were adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

Table 4
Association between single urinary chemical/metabolite concentration and abdominal obesity (N = 1269), NHANES, USA, 2013–2014.

Exposure biomarkers	Quartile 1	Quartile 2		Quartile 3		Quartile 4	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Phenols							
BPA	Ref	1.19 (0.81, 1.75)	0.368	1.59 (1.05, 2.39)	0.028	1.36 (0.87, 2.13)	0.175
BPS	Ref	1.14 (0.78, 1.65)	0.495	1.26 (0.88, 1.82)	0.211	1.47 (1.01, 2.16)	0.045
Pesticides							
2,5-DCP	Ref	1.14 (0.79, 1.64)	0.484	1.18 (0.81, 1.74)	0.383	1.00 (0.68, 1.47)	0.989
2,4-DCP	Ref	0.73 (0.50, 1.06)	0.099	0.83 (0.57, 1.21)	0.335	0.84 (0.58, 1.23)	0.367
Phthalate metabolites							
MCOP	Ref	1.25 (0.87, 1.81)	0.230	1.48 (1.01, 2.16)	0.044	1.70 (1.14, 2.54)	0.009
MECPP	Ref	1.45 (0.98, 2.13)	0.061	1.44 (0.94, 2.19)	0.093	1.59 (1.01, 2.51)	0.044
MEP	Ref	1.07 (0.74, 1.54)	0.722	1.04 (0.71, 1.52)	0.855	1.30 (0.87, 1.95)	0.201

OR: odds ratio; CI: confidence interval. Estimated odds ratios (ORs) were compared with the first exposure quartile; quartile cut points were based on all the participants in this study (N = 1269). Models were adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

We also analyzed whether there was a negative association with the chemical mixture and obesity as well as body indices. No significant negative association was found (results not shown).

3.5. BKMR model to assess the association between chemical concentration and obesity

We treated the ln-transformed concentration of each chemical as continuous variables and first fitted the BKMR model to assess the joint effect of chemical exposures on binary outcomes (general and abdominal obesity). The probabilities of inclusion derived from the BKMR model for the two groups (groupPIP) and each chemical (condPIP) are summarized in Table 8. In general obesity, the groupPIP of the phthalate metabolites and bisphenol group was higher than 0.5. In addition, the condPIP of MCOP was extremely high at 0.96 within this group, whereas the condPIPs of others in this group were low. The groupPIPs in the abdominal analysis were both < 0.5. The overall associations between the chemical mixture and the latent continuous outcomes are shown in Fig. 5. Although confidence intervals were wide, the latent continuous outcome of general obesity showed significant increase when all the chemicals were at their 60th percentile or above, compared to their 50th percentile, indicating a significant, positive association with general obesity. Although no statistically significant difference was found in the abdominal obesity model, there was an increasing trend. The trends of exposure–response functions of the seven chemicals are shown in Fig. 6. When all the other chemicals were at their median levels, MCOP showed increasing associations with general and abdominal obesity with a little decrease in general obesity in the highest concentration. MEP, BPA, and BPS showed a positive relationship with obesity, whereas MECPP showed a flat or inverse relationship. We further investigated the interactions between chemicals. We fixed other chemicals at their median levels and determined the exposure–response function of a single chemical for the second chemical fixed at its 10th, 50th, and 90th percentages, respectively. The results are shown in Supplementary material Fig. S1. There was a potential interaction between 2,4-DCP and 2,5-DCP. The other slopes of the exposure–response function of a certain chemical were similar at different quantiles of another chemical, with others fixed at their middle levels, which indicated no interactions.

To analyze mixture exposure–induced body index changes in the BKMR model, we treated BMI and waist circumference as continuous outcomes. The probabilities of inclusion derived from the BKMR model

Table 6
Association between WQS regression index and general and abdominal obesity (N = 1269), NHANES, USA, 2013–2014.

Outcomes	OR	95% CI of OR	*P* value
General obesity			
Model 1	1.50	(1.13, 1.98)	0.005
Model 2	1.63	(1.21, 2.−20)	0.001
Abdominal obesity			
Model 1	1.49	(1.07, 2.08)	0.019
Model 2	1.66	(1.18, 2.34)	0.004

OR: odds ratio; CI: confidence interval; OR estimates represent the odds ratios of general or abdominal obesity when the WQS index was increased by one quartile. Model 1: Adjusted for gender, ethnicity, age, and ln-transformed creatinine. Model 2: Adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

Table 5
Association between single urinary chemical/metabolite concentration and BMI or waist circumference (N = 1269), NHANES, USA, 2013–2014.

Exposure biomarkers	BMI			Waist circumference		
	β	95% CI	*P* value	β	95% CI	*P* value
Phenols						
BPA	0.16	(−0.26, 0.57)	0.459	0.32	(−0.66, 1.30)	0.525
BPS	0.24	(−0.08, 0.56)	0.145	0.61	(−0.15, 1.37)	0.117
Pesticides						
2,5-DCP	0.09	(−0.10, 0.27)	0.366	0.20	(−0.24, 0.64)	0.376
2,4-DCP	0.23	(−0.06, 0.53)	0.118	0.46	(−0.23, 1.15)	0.192
Phthalate metabolites						
MCOP	0.36	(0.06, 0.66)	0.019	0.98	(0.28, 1.69)	0.006
MECPP	0.16	(−0.32, 0.63)	0.511	0.68	(−0.44, 1.80)	0.236
MEP	0.12	(−0.15, 0.39)	0.385	0.17	(−0.47, 0.80)	0.612

CI: confidence interval; all urinary chemical/metabolite concentrations were in micrograms per liter and were naturally ln-transformed. Models were adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

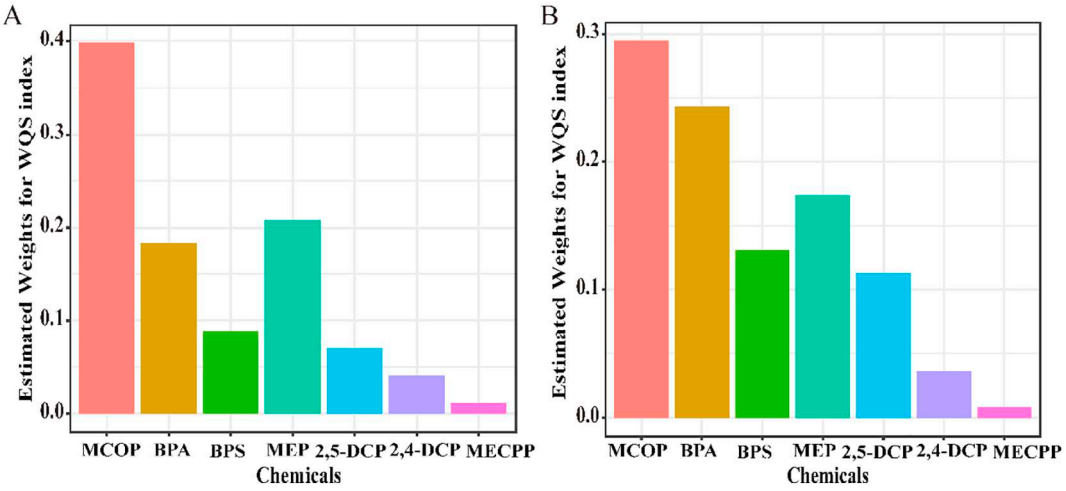

Fig. 3. WQS model regression index weights for general (A) and abdominal obesity (B). Models were adjusted for gender, ethnicity, educational levels, age, family income-to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

Table 7
Association between weighted quantile sum regression index and body indices by WQS (N = 1269), NHANES, USA, 2013–2014.

Outcomes	β	95% CI	*P* value
BMI			
Model 1	0.91	(−0.01, 1.82)	0.052
Model 2	1.08	(0.17, 2.00)	0.020
Waist circumference			
Model 1	2.50	(0.36, 4.64)	0.022
Model 2	3.02	(0.89, 5.15)	0.006

CI: confidence interval; β estimates represent mean differences in BMI or waist circumference when the WQS index was increased by one quartile. Model 1: Adjusted for gender, ethnicity, age, and ln-transformed creatinine. Model 2: Adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

are summarized in Table 9. The groupPIPs in both the models were relatively small. We analyzed the overall effect of the chemical mixture on body indices, and the waist circumference and BMI showed increasing trends when all the chemicals were at their 60th percentile or above, compared to their 50th percentile (Fig. 7).

Table 8
Posterior inclusion probabilities (PIPs) for group inclusion and conditional inclusion into obesity models, using Bayesian kernel machine regression (BKMR) model (N = 1269), NHANES, USA, 2013–2014.

Chemicals	Group	General obesity		Abdominal obesity	
		groupPIP	condPIP	groupPIP	condPIP
MCOP	1	0.96	0.96	0.44	0.63
MECPP	1	0.96	0.01	0.44	0.09
MEP	1	0.96	0.01	0.44	0.02
BPA	1	0.96	0.01	0.44	0.06
BPS	1	0.96	0.02	0.44	0.19
2,5-DCP	2	0.06	0.20	0.38	0.27
2,4-DCP	2	0.06	0.80	0.38	0.73

Models were adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

4. Discussion

In this study, we considered the results of diverse statistical methods to examine the effects of seven correlated environmental chemicals on obesity in the general population of the United States. On one hand, the generalized linear regression pointed out the association between

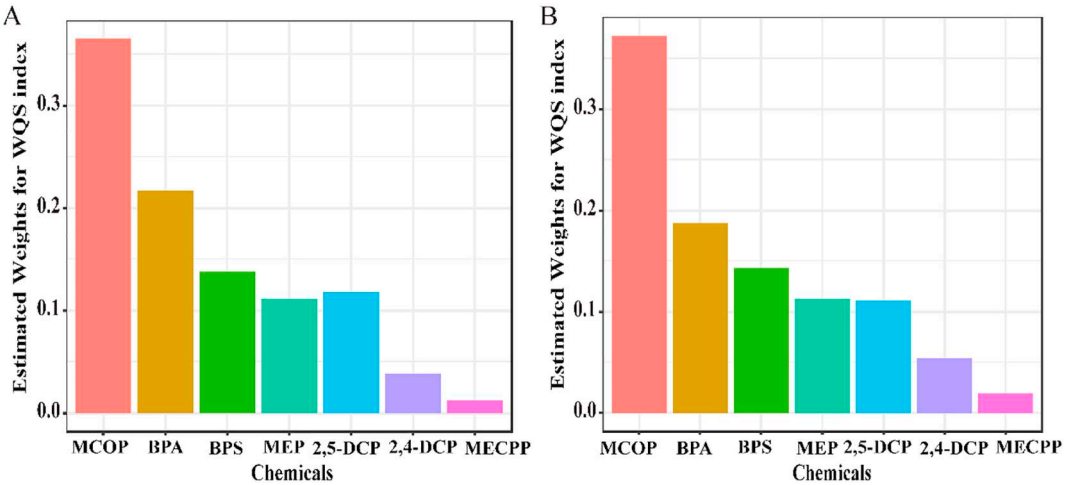

Fig. 4. WQS model regression index weights for BMI (A) and waist circumference (B). Models were adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

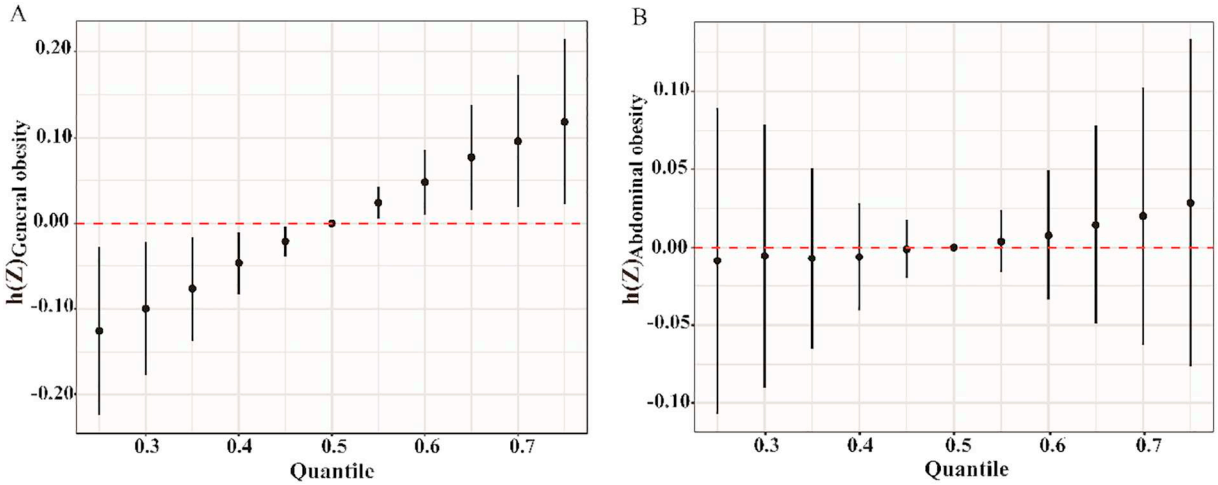

Fig. 5. Joint effect (95% CI) of the mixture on general obesity (A) and abdominal obesity (B) by BKMR model when all the chemicals at particular percentiles were compared to all the chemicals at their 50th percentile. h(Z) can be interpreted as the relationship between chemicals and a latent continuous outcome (continuous marker of the binary obesity outcomes). The results were adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

MCOP, MECPP, and BPS and obesity. On the other hand, the WQS model identified the roles of MCOP, BPA, MEP, and BPS in the development of obesity, whereas MECPP had a marginal role. In the BKMR model, we found that overall mixed exposure was significantly associated with general obesity. Although no significant association between overall mixed exposure and other outcomes (abdominal obesity and body indices) appeared, there were increasing trends. The univariate exposure–response function showed a positive relationship between MCOP, BPA, BPS, and MEP to obesity, but not for MECPP. This study highlighted the importance of assessing the joint effects of chemicals on health outcomes by using different statistical methods and comparing their results, with consideration of the advantages and disadvantages of particular methods.

The generalized linear regression model, including multivariable logistic and linear regression, is most commonly used to assess the health effects of chemicals (Bhandari et al., 2013; Kim et al., 2017; Scinicariello and Buser, 2016; Wei et al., 2014; Ye et al., 2014). The results are straightforward and easily interpreted. Previous studies with multivariable logistic and linear regression analyses found associations between obesity and many environmental chemicals such as high molecular weight–phthalate metabolites (including MECPP, MEHHP, MEOHP, MEHP, MBZP, MCNP, and MCOP) and MEP and BPA in adults

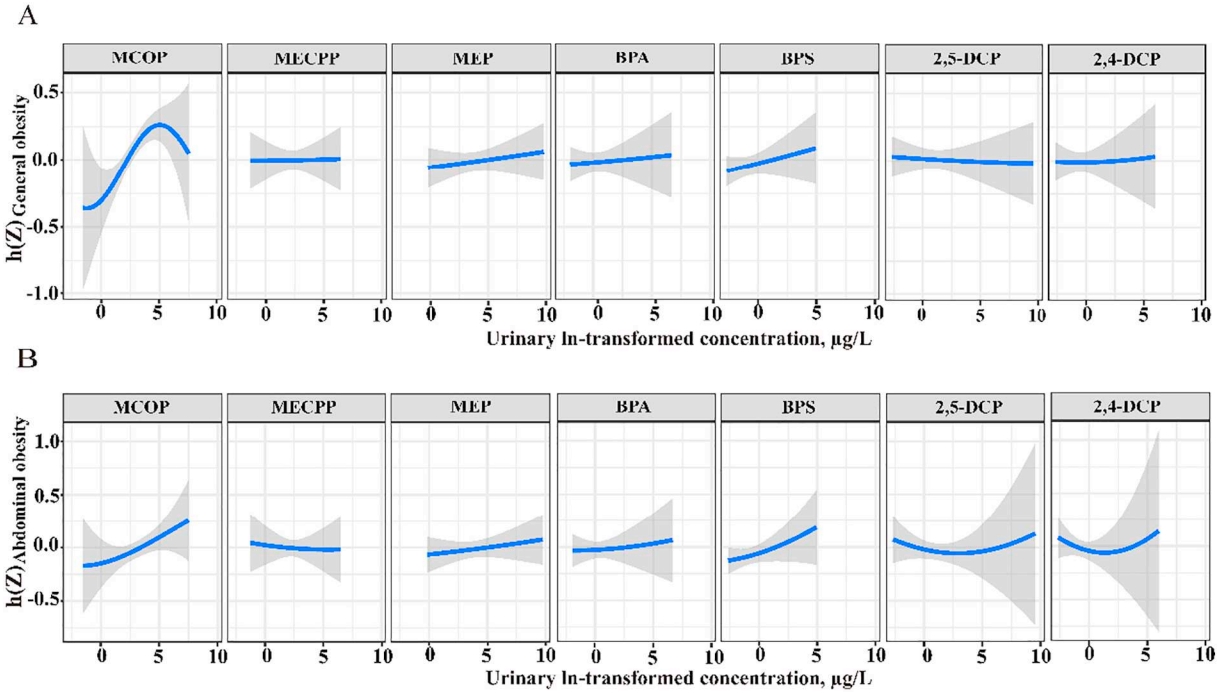

Fig. 6. Univariate exposure–response function (95% CI) between selected chemical concentrations and general obesity (A) and abdominal obesity (B) while fixing the concentrations of other chemicals at median values. h(Z) can be interpreted as the relationship between chemicals and a latent continuous outcome (continuous marker of the binary obesity outcomes). The results were assessed by the BKMR model adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

Table 9
Posterior inclusion probabilities (PIPs) for group inclusion and conditional inclusion into body index models, using the Bayesian kernel machine regression (BKMR) model (N = 1269), NHANES, USA, 2013–2014.

Chemicals	Group	BMI		Waist circumstance	
		groupPIP	condPIP	groupPIP	condPIP
MCOP	1	0.14	0.70	0.25	0.94
MECPP	1	0.14	0.08	0.25	0.03
MEP	1	0.14	0.07	0.25	0.01
BPA	1	0.14	0.06	0.25	0.01
BPS	1	0.14	0.10	0.25	0.01
2,5-DCP	2	0.03	0.06	< 0.01	0.10
2,4-DCP	2	0.03	0.94	< 0.01	0.90

(Buser et al., 2014a; Hatch et al., 2008; Liu et al., 2017; Stahlhut et al., 2007). Usually a single chemical or a group of similar chemicals were included in these analyses, making their results easy to understand. However, to study causality, we need to take into account mixed environmental exposures and their complex, nonlinear interactions (Kim et al., 2017; Valeri et al., 2017). Ignoring the joint effects of other chemicals could contribute to false positive or false negative results (Czarnota et al., 2015a). In our analysis, MCOP and MECPP exposures were highly correlated. The positive relationship of either MCOP or MECPP with obesity in single-chemical analysis might be due to the confounding effect of the other chemical. Including all the chemicals of interest in one generalized linear regression model is not correct, because high correlation between chemicals might lead to result distortion (Marill, 2004). In addition, chemical interaction cannot be found in a simple model.

WQS and BKMR are two models recently developed to analyze the effects of chemical mixtures on health. A series of chemicals with high correlations can be taken into account. However, they both have advantages and disadvantages. The WQS regression model examined the whole-body burden of chemical exposures based on the weights empirically determined by bootstrap sampling. This approach better encompasses the real-life complex exposures. In our analysis, MCOP, BPA, MEP, and BPS were weighted highly; of these, MEP did not show significant association with obesity in the generalized linear regression model. MECPP was weighted lightly in WQS analysis, which was inconsistent with our results in generalized linear regression analysis. This suggested that the positive relationship between MECPP and obesity observed when estimating the effect of individual chemicals might be due to the interaction with its highly correlated MCOP. Our results support previous findings indicating that the WQS regression model is more sensitive than single-chemical analyses in identifying important factors (Artacho-Cordon et al., 2016; Nieves et al., 2016). One important limitation of WQS is that the joint effects of chemicals with diverse effect directions cannot be assessed simultaneously. If chemicals with inverse associations with obesity were misclassified in the WQS model, they would be assigned negligible weights in the WQS index, positively associated with obesity (Czarnota et al., 2015a; Czarnota et al., 2015b).

The BKMR analysis can identify nonlinear effects and between chemical interactions (Bobb et al., 2015). Compared to the WQS regression model, BKMR analysis could capture the exposure–response relationship, with other chemicals fixed at certain levels. In addition, the interaction between each two of these chemicals can be detected. In our analysis, MCOP showed a positive association with the latent continuous outcome of general obesity, whereas there was a negative trend in the highest concentration with wide confidence interval. MEP, BPA, and BPS showed a positive association with obesity. However, MECPP, the metabolite of DEHP, showed a flat or negative association, which was, to some extent, consistent with its light weight in WQS regression analysis. Previous studies about secondary metabolites of DEHP and obesity could not draw a solid conclusion (Dong et al., 2017; Hatch et al., 2008; Stahlhut et al., 2007; Yaghjyan et al., 2015). These conflicting results were probably due to lack of accounting for other highly correlated chemicals in the same models. One limitation of the BKMR model results from its kernel algorithm. Fixing other chemicals at certain levels to extrapolate the exposure–response function does not allow estimation of the effects of co-exposure patterns with both high and low levels of chemicals. Our analysis with the BKMR permitted the evaluation of the whole-body effect of chemicals with different effect directions as well as interactions among them. Positive associations were found between chemical mixture and obesity as well as between the chemical mixture and body indices. However, significant positive association was found only between overall exposure and general obesity in the BKMR model. This might due to the negative exposure–response relationship of MECPP, which to some extent neutralized the positive association. To date, the WQS and BKMR models have not been directly compared. Using both of them simultaneously allowed consideration of their strengths and weaknesses, to disentangle the interactions between chemical mixtures.

A descriptive summary of results and comparison of these three statistical models appears in Table 10. In environmental epidemiology

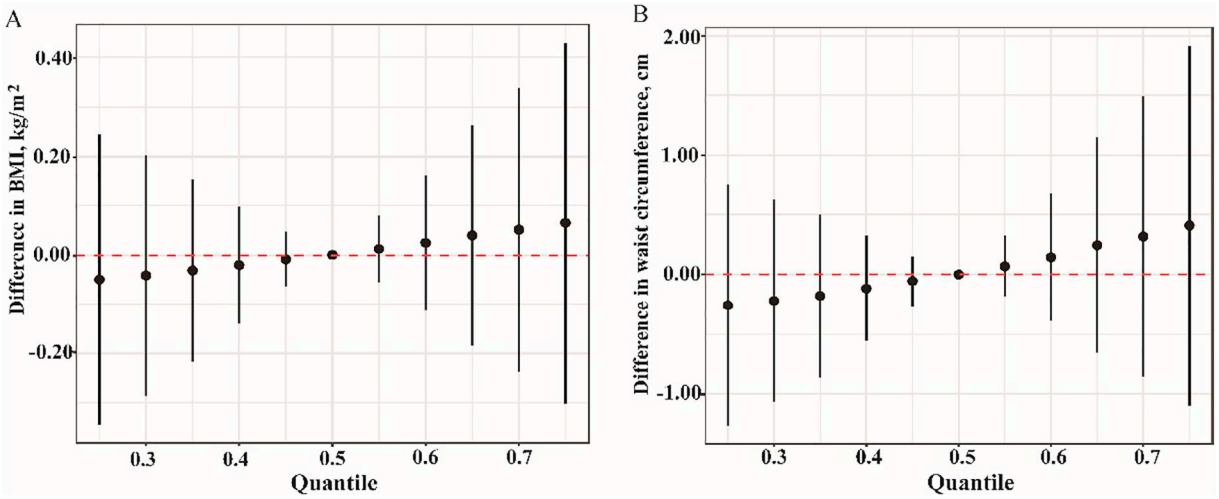

Fig. 7. Joint effect (95% CI) of the mixture on BMI (A) or waist circumference (B) when all the chemicals at particular percentiles were compared to all the chemicals at their 50th percentile. The results were assessed by the BKMR model, adjusted for gender, ethnicity, educational levels, age, family income–to-poverty ratio, smoking status, energy intake levels, physical activity, and ln-transformed creatinine.

Table 10
A comparison of the statistical tools to assess the association between selected chemical contaminants and obesity, NHANES, USA, 2013–2014.

Methods	Outcomes focused	Chemicals associated with outcomes	Advantages	Limitations
Generalized linear regression model	Obesity	With obesity: MCOP, MECPP, BPS, BPA	Straightforward and easily interpreted	Limited to mixed environment exposures and nonlinear interactions
	Body indices	With body indices: MCOP		Potential distortion caused by high correlation and multicollinearity
WQS	Obesity	Highest weights: MCOP, BPA, MEP, and BPS	Examining the whole-body burden of chemical mixture exposures	Limited in assessing joint effects of chemicals with diverse effect directions
	Body indices	Lightest weight: MECPP		
BKMR	Obesity	Positive trend: MCOP, BPA, and BPS Negative trend: MECPP	Identifying interactions between chemicals Extrapolating nonlinear exposure–response functions	Limited in estimating the effects of co-exposure patterns with both high and low levels of chemicals

Body indices: Including BMI and waist circumference in this study.

studies, generalized linear regression can provide a simple relationship between single chemicals and outcomes. The WQS model can explore the effect that a mixed exposure burden has on the outcomes in one direction per occasion. The BKMR model can explore the exposure–response function of each chemical while controlling other chemicals at certain levels and, in addition, explore interactions between any two of the chemicals. Thus, these three models evaluate different aspects, and a joint interpretation afterward will reveal their strengths, limitations, and eventual complementation.

Our analyses have some limitations. We used unweighted data and assumed that the study population was representative of the U.S. adult population. Previously, authors have argued that when covariates used to calculate sample weights are already included in the regression model, the unweighted estimation is preferred to the weighted one (Blount et al., 2006; Graubard and Korn, 1999). However, whether this rule also applies to WQS and BKMR models is not clear. Because the aim of our analysis was to compare different methods and find an analysis strategy to solve the problem of mixture exposure, the unweighted data analysis was not the purpose of our study. Another limitation of our study was in simply substituting the values below the lower limit of detection with a fixed value. Although a previous study found that inserting a single value is unbiased when the percentage of measurements below detection limits is small (5–10%) (Lubin et al., 2004), using multiple imputations is a better approach to ensure unbiased estimates of effects. In addition, we used data from a cross-sectional survey. Chemicals measured in this study could only reflect recent exposures, but obesity is a disorder developed over a long time. It might introduce confounding by neglecting the long-term influence of chemicals. Finally, our analysis could not draw a causal inference of mixed chemical exposure on obesity. Large prospective cohort studies and experimental studies are needed to provide more evidence.

5. Conclusions

We applied generalized linear regression, WQS regression, and BKMR regression models to assess the association between obesity and seven potential obesogens. When considering the results of these three models, we concluded that the whole-body burden of seven chemicals was significantly associated with both general and abdominal obesity. MCOP, BPA, and BPS were the most significantly associated with obesity. Our study demonstrated the importance of applying different methods to evaluate health effects of chemical mixtures. We recommend using different methods and interpreting their results together to yield a more reliable conclusion.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.11.076.

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