Using three statistical methods to analyze the association between exposure to 13 compounds and obesity in children and adolescents: National Health and Nutrition Examination Survey 2005–2010

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Abstract

Background: Various risk factors influence obesity differently, and too much environmental endocrine disruption may increase the occurrence of obesity. However, most of the previous studies have considered only a unitary exposure or a set of similar exposures instead of mixed exposures, which entail complicated interactions. We utilized three statistical models to evaluate the interactions between mixed chemicals to analyze the association between 13 different chemical exposures and obesity in children and adolescents.

Methods: We fitted the generalized linear regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) to analyze the association between the mixed exposures and obesity in the participants aged 6–19 in the National Health and Nutrition Examination Survey (NHANES) 2005–2010.

Results: In the logistic regression model, 2,5-dichlorophenol (2,5-DCP) (P = 0.001), monoethyl phthalate (MEP) (P = 0.005), and mono-isobutyl phthalate (MiBP) (P = 0.023) were found to be positively associated with obesity, while methylparaben (MeP) (P = 0.011) was negatively associated with obesity. In the multivariable linear regression, MEP was the only chemical found to be associated with the body mass index (BMI) z-score (P = 0.003). In the WQS regression model, the WQS index had a significant association (P = 0.001) with the outcome in the obesity model, in which 2,5-DCP (weighted 0.35), 2,4,6-trichlorophenol (2,4,6-TCP) (weighted 0.16), MEP (weighted 0.14), and MiBP (weighted 0.12) all had relatively high weights. In the BKMR model, despite no statistically significant difference in the overall association between the chemical mixtures and the outcome (obesity or BMI z-score), there was nonetheless an increasing trend. 2,5-DCP, MEP, and MiBP were found to be positively associated with obesity, while fixing other chemicals at their median concentrations.

Conclusion: Comparing the three statistical models, we found that

2,5-DCP, MEP, and MiBP may play an important role in the 13 exposures. Considering the advantages and disadvantages of the three statistical models, our study confirms the necessity to combine different statistical models on obesity when dealing with mixed exposures.

Keywords: obesity; adolescent; child; weighted quantile sum (WQS) regression; Bayesian kernel machine regression (BKMR)

Introduction

Obesity is a pandemic disease that cannot be ignored, and the continuous increase in obesity has become an important worldwide health problem in the past 30 years [1]. In 2016, about 18% of children and adolescents aged 5−19 were overweight or obese [2]. Obesity in children increases the risk of health conditions, such as coronary heart disease, diabetes mellitus, hypertension, and heart failure [3-5]. Therefore, it is vital to identify potential risk factors contributing to obesity to reduce the prevalence and mortality rates in obesity-related diseases. Although genetic predisposition, physical activity, and diet play an essential part in the occurrence of obesity, there is still a need for further explanation. More evidence indicates that environmental endocrine-disrupting chemicals might increase the occurrence of obesity [6-9]. Twum et al. demonstrated an underlying relation between exposure to 2,5-dichlorophenol (2,5-DCP) and obesity in children [4]. A significant association was found between bisphenol A (BPA) and general and abdominal obesity [10]. Deierlein showed that phthalates—specifically low-molecular weight phthalates (monoethyl phthalate [MEP], a metabolite of diethyl phthalate (DEP); mono-n-butyl phthalate [MBP], a metabolite of di-n-butyl phthalate (DBP), and mono-isobutyl phthalate [MiBP], a metabolite of di-isobutyl phthalate (DiBP))—had slight associations with girls' anthropometric outcomes [11]. These substances are readily present in our daily lives, since consumer products usually use parabens as preservatives, building and food

packaging materials use phthalates as plasticizers, and the production of pharmaceutical and agricultural products uses 2,5-DCP as a chemical intermediate [12-14]. We can easily contact these environmental endocrine-disrupting chemicals via gastrointestinal intake, dermal contact, and applying products that contain these chemicals [15, 16]. However, most of the previous research studied only a unitary exposure or a set of similar exposures [17-19]. We are exposed to all kinds of chemical exposures simultaneously, which can result in complicated interactions. Therefore, it is necessary to use a suitable statistical model for risk assessment of exposure and obesity [20-22].

We collected data on urinary chemicals or metabolites that had been reported to have an effect on obesity in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2010. We selected three statistical methods, including generalized linear regression, weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) models, to better analyze multi-exposures' co-function on adolescent obesity. All of these three methods have their own advantages and disadvantages, and we expected that this comprehensive analysis would yield insightful and fruitful conclusions.

Methods

Study sample

The NHANES is a cross-sectional nationally representative program, aiming to collect information on adults' and children's health and nutritional condition in the United States, which is reviewed and approved by the National Center for Health Statistics, as one of the departments of Centers for Disease Control and Prevention (CDC). The NHANES program was conducted in the early 1960s and released the data in biennial datasets. In order to get the unbiased national health information on the non-institutionalized population of the United States, the NHANES used a considerate, multi-stage stratification probability sampling design. We collected

publicly accessible data from 2005 and 2010. We selected participants between 6 and 19 years old, with attainable measurements of urinary phenols, parabens, pesticides, and phthalate metabolites simultaneously (n = 2749). Participants whose data on Body mass index (BMI) and covariates were missing were excluded from our analysis (n = 220).

Measurement of chemical exposures

Urinary samples were collected and stored at -20°C. They were sent to the National Center for Environmental Health, the Organic Analytical Toxicology Branch, for analysis. BPA, benzophenone-3 (BP-3), methylparaben (MeP), ethylparaben (EtP), propyl paraben (PrP), Butyl paraben (BuP), 2,4-DCP, 2,5-DCP, 2,4,5-trichlorophenol (2,4,5-TCP), and 2,4,6-trichlorophenol (2,4,6-TCP) were extracted by on-line solid-phase extraction (SPE). They were measured by high-performance liquid chromatography as well as tandem mass spectrometry (MS/MS). MBzP, MEP, and MiBP were measured by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS). The limit of detection (LOD) for the compounds to be analyzed, including BPA, BP-3, MeP, EtP, PrP, BuP, 2,4-DCP, 2,5-DCP, 2,4,5-TCP, 2,4,6-TCP, MBzP, MEP, and MiBP, were 0.4 μg/L, 0.4 μg/L, 0.2 μg/L, 1.0 μg/L, 1.0 μg/L, 0.2 μg/L, 0.2 μg/L, 0.2 μg/L, 0.1 μg/L, 0.5 μg/L, 0.2 μg/L, 0.5 μg/L, and 0.3 μg/L, respectively. These values below the limit of detection were divided by the square root of 2 to replace the original values. As one study recommended [23], we treated urinary creatinine as a covariate to explain the urinary dilution. Urinary creatinine was measured by a Beckman Synchron CX3 Clinical Analyzer. The NHANES provides detailed information on the measurement method in the section on laboratory methods on its website [24, 25].

Anthropometric variables

Trained health technicians measured the body weight and height according to the standardized protocol. The BMI was calculated using each person’s weight in

kilograms to divide the square of their height in meters. However, because the standard BMI shows differences for the different ages and gender among children, measuring BMI percentiles and the BMI z-score was more appropriate. The BMI z-score was calculated in regards to the children's age, gender, and BMI. An appropriate standard was used, which reflected the number of SDs differing from the mean of the BMI with reference to the same age and gender. The methodology to calculate the BMI z-score specifically for different ages and gender was provided by the CDC [26]. We defined a child to be obese when their BMI was above or equal to the 95th percentile for their age and gender.

Covariates

Covariates, including age, gender, race, education level, family income-to-poverty ratio, caloric intake, serum cotinine, and urinary creatinine, were collected by interview or laboratory detection by NHANES. Race was grouped into Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Race. Education level was categorically grouped into ≤5 grade, 6−8 grade, 9−12 grade, or High School Graduate with No Diploma, High School Graduate and GED or Equivalent, or More than high school. The family income-to-poverty ratio was divided into three groups: ≤1.30, 1.31−3.50, and >3.50. The caloric intake was dichotomously divided into normal intake and excessive intake, according to the Dietary Guidelines for Americans 2010 [27]. Serum cotinine indirectly reflected the exposure to environmental tobacco. Serum cotinine, age, and urinary creatinine were considered to be continuous variables.

Statistical analysis

We used the χ^2 test and the t-test to analyze categorical variables and continuous variables, respectively. We calculated the descriptive statistics on BPA, BP-3, MeP, EtP, PrP, BuP, 2,4-DCP, 2,5-DCP, 2,4,5-TCP, 2,4,6-TCP, MBzP, MEP, and MiBP. Because the distributions of the chemical exposures were skewed, we log-transformed

the concentrations of all chemical exposures. We used the Pearson correlation to calculate the correlation coefficients among all chemical exposures. $p < 0.05$ was considered to be statistically significant.

Generalized linear regression

We conducted multivariate logistic regression to analyze each chemical exposure and the odds ratios (ORs) of obesity in different quartiles. We also fitted a multivariate linear regression model to assess the association between each chemical exposure and the continuous variable of the BMI z-score in different quantiles. In addition, we fitted the models, adjusting for all the chemical exposures. All the regression models were adjusted by age, gender, race, education level, family income-to-poverty ratio, caloric intake, serum cotinine, and urinary creatinine. We used log-transformed urinary creatinine as an independent covariate instead of the creatinine-adjusted concentration [23].

Weighted quantile sum (WQS) regression

The WQS model scored all the chemical exposures into quantiles and estimated the weight index:

$$g(\mu) = \beta_0 + \beta_1 \left(\sum_{i=1}^{c} \omega_i \, q_i \right) + z' \varphi,$$

where $g()$ represents any monotonic link function, μ is the predictable variable, ω is the weight of the *i*th components to be estimated, q_i refers to different quantiles, and $(\sum_{i=1}^{c} \omega_i \, q_i)$ represents the weight quantile sum of the set of *c* components of interest. Furthermore, β_1 denotes the regression coefficient for the weight quantile sum, β_0 is the intercept, z' refers to the covariates, including risk factors and confounders, and φ is the coefficients for the covariates. The weights were estimated between 0 and 1, and added up to 1. In this study, we divided the data into the training set and the validation set, and the seed was set to be 2019. We bootstrapped the training set 1000 times and got the estimated weights, which maximized the likelihood of the

non-linear model. A significant level ($p < 0.05$) was set to test the significance of the weights in each bootstrap. We calculated the $\bar{\omega}_i$ to estimate the weight quantile sum:

$$\mathrm{WQS} = \sum_{i=1}^{c} \bar{\omega}_i q_i$$

$$\bar{\omega}_i = (1/n_B) \sum_{j=1}^{n_B} \omega_{ij,}$$

where n_B represents the number of bootstraps in which β_1 was significant. The estimated WQS was then determined using the validation set. All the chemical exposures were included in the model, and a specific weight was calculated for each component, representing their contribution to the WQS index. The chemical exposures included were constrained to have the same effect with the outcome (all positive or all negative).

Bayesian kernel machine regression (BKMR)

The BKMR model utilizes a non-parametric approach to flexibly model the association between chemical exposures and healthy outcomes, including the nonlinear and/or interactions in the exposure-outcome association. A high-dimension exposure-response relationship induced by multiple variables incorporated in the model would make it difficult to ascertain the basis function. Thus, we used a kernel machine regression:

$$Y_i = h(z_i) + x_i\beta + \epsilon_i,$$

where Y_i is the health outcome, *i* refers to the individual ($i = 1, 2, 3 \ldots n$), z_i is the chemical exposures, x_i is the potential confounders, and β represents the effect of the covariates. ϵ_i is the residual that obeys the normal distribution N (0, σ^2). $h()$ is the function that fits the exposure and the outcome considering nonlinear and interactions between the exposures. We grouped the chemical exposures into three groups, according to their resource and correlation with each other. A hierarchical

variable selection approach was used to estimate the posterior inclusion probability of highly correlated variables, which was based on our prior knowledge. The model was fit with 1000 iterations using a Markov chain Monte Carlo (MCMC) method.

We also analyzed the association between the quantiles of the chemical exposures and binary healthy outcome (obesity and non-obesity) using a probit BKMR model:

$$\Phi^{-1}(\mu_i) = h(z_i) + x_i\beta,$$

where Φ^{-1} is the link function and μ_i is the probability of the binary outcome.

All of the statistical analysis were conducted using R software (version 3.6.0).

Results

Participant characteristics

There were 2529 children and adolescents included in our study. The general characteristics of the participants are presented in Table 1. The prevalence of obesity was 22.50%. It showed that the mean age of obesity and non-obesity is close: approximately 12-and-a-half years old. About half (45%) of the participants were $\leq$5 grade, and 53% had a normal caloric intake. The mean (SD) BMI and waist circumferences were 30.36 (6.96) and 94.79 (21.02) cm in the obesity group and 19.70 (3.66) and 69.36 (12.62) cm in the non-obesity group, respectively. The mean (SD) BMI z-scores were 2.13 (0.33) in the obesity group and 0.18 (0.94) in the non-obesity group. There were significant differences between the obesity and non-obesity participants in terms of race, family income, caloric intake, serum cotinine, BMI, BMI z-score, and waist circumference.

Measurement of chemical exposures and their metabolites

The LOD and the detection frequency of the chemicals above the LOD are shown in Table 2. The detection frequency of MEP (99.9%) and of 2,4,6-TCP (29.7%) had the highest and lowest detection frequency of chemical exposures. Table 2 also shows

the geometric concentration, the mean, and the distribution of the chemical exposures. The highest and the lowest geometric means of the chemical exposures were related to the 2,5-DCP (455.6) μg / L and 2,4,5-TCP (0.10) μg / L.

Correlation between chemical exposures

We found significant correlations ($P < 0.05$) among 13 chemicals (Fig. 1), in addition to the correlation between BP-3 and 2,4-DCP (0.57). There was a positive correlation between other compounds, except for a negative correlation of BP-3 with 2,5-DCP ($r = -0.06$). 2,5-DCP was found to be strongly associated with 2,4-DCP ($r = 0.87$). Additionally, a moderate correlation between MeP and PrP ($r = 0.81$) was found.

Generalized linear regression

The results from the multivariable logistic and linear regression models adjusted for the covariates for children and adolescents are shown in Tables 3 and 4, respectively. The adjusted multivariable logistic regression analysis revealed a statistically significant association between obesity and MeP ($P = 0.011$), 2,5-DCP ($P = 0.001$), MEP ($P = 0.005$), and MiBP ($P = 0.023$), with MeP showing a negative association with dichotomous variable obesity (OR [95%CI]: 0.66 (0.48-0.91), fourth vs. first quartile). When comparing the 2nd, 3rd, and 4th 2,5-DCP quartiles with the reference quartile, 2,5-DCP had a higher odds ratio (OR [95% CI]: 1.30 (0.96-1.78); 1.59 (1.17-2.17), and 1.74 (1.27-2.39), respectively) (Table 3). When comparing the second, third, and fourth quartiles of MEP with the reference quartile, MEP had a higher odds ratio (OR [95% CI]: 1.08 (0.79−1.47); 1.32 (1.10−1.83), and 1.47 (1.04−2.07), respectively; Table 3). We used adjusted multivariable linear regression to evaluate the relation between 13 chemical exposures and the BMI z-score (Table 4). We only found MEP to be positively associated with the BMI z-score ($p = 0.003$).

The second, third, and fourth MEP quartiles had a higher BMI z-score (β [95% CI]: 0.03 (-0.11, 0.16); 0.12 (-0.02, 0.26), and 0.16 (0.01, 0.31), respectively) compared with the lowest reference quartile (Table 4).

In the multivariate logistic and linear regression models, including all the chemical exposures, adjusting for the confounding effects of other chemicals, 2,5-DCP, 2,4-DCP, and MEP were found to have a significant association with both the dichotomous variable obesity (OR [95% CI]: 1.74 (1.36−2.33), 0.55(0.38−0.78), and 1.43 (1.15−1.77), respectively) and continuous variate BMI z-score (β [95% CI]: 0.15 (0.05−0.25), -0.23 (-0.38 − -0.08), and 0.17 (-0.07−0.20), respectively) (see Additional File 1, Tables S1 and S2). We calculated the variance inflation factors (VIFs) (see Additional File 1, Tables S3), and none of them was higher than 10.

Table 5 Association between the WQS index and obesity in NHANES 2005–2010 (N = 2529)

Outcomes	OR/β	95% CI of OR	P value
Obesity			
Model 1	1.61	(1.25, 2.07)	<0.001
Model 2	1.53	(1.18, 2.00)	0.001
BMI z-score			
Model 1	0.12	(0.002, 0.24)	0.047
Model 2	0.11	(-0.03, 0.25)	0.117

CI: confidence interval. The weighted quantile sum (WQS) regression was fitted for the obesity and BMI z-score, which scored all the chemical exposures into quantiles and estimated the weight index. OR estimates represent the odds ratios of obesity as 1 quartile increased in the WQS index. β estimates represent the mean differences in the BMI z-score as 1 quartile increased in the WQS index. Model 1: Adjusted for age, gender, ethnicity, and ln-transformed creatinine. Model 2: Adjusted

for age, gender, ethnicity, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and ln-transformed creatinine.

WQS regression

We fitted the WQS regression model to the data to evaluate the relationship between the chemical exposures and the outcome in the roughly and fully adjusted models, respectively (Table 5). The WQS index had a significant association with obesity in Model 1 (OR [95% CI]: 1.61 (1.25∼2.07)). In Model 2, the WQS index had a significantly positive association with obesity after being adjusted for all covariates (OR [95% CI]: 1.53 (1.18−2.00)). We also calculated the estimated chemical weights of the dichotomous variable obesity, which are presented in Fig. 2a. The highest weighted chemical in the fully adjusted obesity model was 2,5-DCP (weighted 0.35), followed by 2,4,6-TCP, MEP, and MiBP (weighted 0.16, 0.14, and 0.12, respectively). We also treated the BMI z-score as a continuous variable and fitted the WQS model (Table 5). However, we did not find any significant association between the exposures and the BMI z-score (β [95% CI]: 0.11 (-0.03−0.25)). The estimated chemical weights of BMI z-score are presented in Fig. 2b. The highest weighted chemical in the BMI z-score model was 2,5-DCP (weighted 0.29). Next to this were EtP, MEP, and 2,4,6-TCP, weighted 0.19, 0.18, and 0.12, respectively.

Table 6 Group posterior inclusion probabilities (PIPs) and conditional posterior inclusion probabilities in the Bayesian kernel machine regression (BKMR) model in National Health and Nutrition Examination Survey (NHANES) 2005–2010 (N = 2529)

Chemicals	Group	Obesity		BMI z-score	
		groupPIP	condPIP	groupPIP	condPIP
Phenols					
BPA	1	0.756	0.056	0.612	0.314
BP-3	1	0.756	0.093	0.612	0.150

Paraben					
BuP	1	0.756	0.058	0.612	0.059
EtP	1	0.756	0.066	0.612	0.163
MeP	1	0.756	0.437	0.612	0.203
PrP	1	0.756	0.291	0.612	0.111
Pesticides					
2,5-DCP	2	0.926	0.782	0.616	0.201
2,4-DCP	2	0.926	0.065	0.616	0.247
2,4,5-TCP	2	0.926	0.069	0.616	0.380
2,4,6-TCP	2	0.926	0.084	0.616	0.172
Phthalate metabolites					
MBzP	3	0.750	0.312	0.648	0.151
MEP	3	0.750	0.403	0.648	0.630
MiBP	3	0.750	0.285	0.648	0.219

Models were adjusted for age, gender, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and ln-transformed creatinine.

BKMR

We grouped 13 chemical exposures into three groups, according to their resource and correlation with each other, and fitted the BKMR model to analyze the simultaneous exposure with obesity and BMI z-score. In the obesity model, the group posterior inclusion probabilities (PIP) of the pesticides group was 0.926, while the group PIP of phenol and phthalates metabolites was higher than 0.5 (Table 6). In the pesticides group, 2,5-DCP seemed to drive the effect of the whole group (CondPIP = 0.782; Table 6). In the phthalate metabolites group, MEP drove the main effect of the whole group (CondPIP: 0.403), while MeP drove the main effect in the phenols group (CondPIP = 0.437) (Table 6). The overall association between the chemical mixtures and the binominal outcome is shown in Fig. 3a. We found a positive tendency

between chemical exposures and the outcome, in spite of no statistically significant difference. Fig. 4 a illustrates the positive associations of 2,5-DCP, MEP, and MiBP with obesity in the BKMR models, while controlling all other chemical exposures at their median level. EtP, MeP, PrP, 2,4-DCP, and MBzP demonstrated negative association with obesity, while no other chemical exposures showed a noteworthy change in slope. We also investigated the relationship between the outcome and a unitary predictor in exposures while fixing another predictor in exposures at the 10th, 50th, and 90th quantiles (and holding the remnant predictors to their median level), and the results are shown in Fig. 5 a. Since the slopes were similar at different percentages of other chemicals, no obvious interaction was found in the obesity model. In the BMI z-score model, the values of the group PIP of all groups were higher than 0.5 (Table 6). BPA, 2,4,5-TCP, and MEP drove the main effect of their group (CondPIP: 0.314, 0.380, and 0.630, respectively). The overall risk of the chemical mixtures on the outcome are presented in Fig. 3b. They revealed a positive association of the mixed exposures with the BMI z-score, when we compared all the predictors fixed at different levels with their 50th percentiles. 2,5-DCP, MEP, MiBP, and BP-3 had a trend of a positive association with the BMI z-score, while BPA, MeP, PrP, and 2,4-DCP had a negative association (Fig. 4 b). No obvious interaction was found in the BMI z-score model (Fig. 5 b).

Discussion

Due to the interactions between chemicals, it would be inaccurate to fit only the generalized linear regression model. Therefore, we further used the WQS and BKMR models, which can deal with the interaction between chemicals. However, we still need to comprehensively consider the results of these three methods.

The generalized linear regression showed a positive association between 2,5-DCP, MEP, and MiBP and obesity; however, MeP was negative with the outcome. MEP was significantly associated with the BMI z-score. In the WQS model, 2,5-DCP, 2,4,6-TCP, MEP, and MiBP were found to have relatively high weights in the obesity

model, while MiBP weighted slightly in the BMI z-score model. In the BKMR model, although no significant association was found between the overall risk of the mixed chemicals and obesity (either obesity or the BMI z-score), there was an upward trend. 2,5-DCP, MEP, and MiBP were found to have a positive association in the obesity model, when fixing others at their median concentration, while in the BMI z-score model, 2,5-DCP, MEP, MiBP, and BP-3 were positively correlated with the BMI z-score. These results point out the necessity for combining three different models, considering their various advantages and disadvantages.

The generalized linear model, which is used frequently to deal with the exposure-response model, has a fast modeling speed and allowed us to obtain an understandable interpretation of the coefficients. Usually, in the analysis to evaluate the association between exposures and outcome, a unitary exposure or a set of similar exposures is included [12, 28, 29]. Our study included 13 chemical exposures of different sorts. It should be noted that the generalized linear model could not analyze the interactions between exposures. The results may be confusing due to the co-linear or interactions between the exposures.

WQS and BKMR were used to analyze the association between health outcomes and chemical mixtures, including a range of highly correlated predictors. They are able to resolve the non-linear and complicated interactions between chemical exposures. The WQS mode can include mixed chemicals exposures, with possible high correlations and interactions that are common in real life. In our analysis, 2,5-DCP, 2,4,6-TCP, MEP, and MiBP were weighted highly in the WQS model. Among these, it is worth noting that 2,4,6-TCP was found to weigh highly in the WQS model, yet was found to have a negligible relationship with obesity in the other two models, which may be due to the limitation of the WQS model. The WQS model may lose the full exposure information of the chemical exposures using the quantiles to score the exposures. MeP weighed slightly in the WQS model, which differed from the results in the generalized linear regression model. This may result from its negative correlation with the outcome. In addition, the WQS model may result in a

slight weight if a large number of exposures were included, or if there were complex interactions within mixed exposures. Two likely important exposures would have smaller weights if 1 of them was highly correlated with another one that was assigned a slight weight [30]. Another limitation of WQS is that all chemical exposures included in the model must have the same effective trend with the outcome, otherwise they will be distributed to a negligible weight in the WQS model [31]. However, when it comes to the interactions between chemical exposures, the WQS model still has a high specificity and sensitivity when dealing with mixed predictors, considering the correlated high-dimensional mixtures.

The BKMR model is a new approach to deal with the complexity of mixed exposures. Unlike the WQS model, the BKMR model analyzes not only the exposure-response function of the overall risk of mixed chemical exposures but also the interaction between two chemical exposures. In our study, 2,5-DCP, MEP, and MiBP have a positive association with the continuous variable BMI z-score, which was consistent with the results of our findings in the other two models. However, with the non-linear exposure-response function, other exposures were slightly or negatively associated with the outcomes, which showed consistency with its slight weight in the WQS model. Among the three groups, the parabens were found to have an inverse association with obesity, which is consistent with a previous study [12]. Previous studies could not reach consensus concerning phthalate and BPA, [32-34], and further studies are needed. It is worth noting that BP-3 had a positive relationship with the continuous variable but had no relationship with the dichotomous variable of obesity. This may be due to the misleading information when we artificially classified the continuous variable into a dichotomous variable. Furthermore, the flat relationship of 2,4,5-TCP and 2,4,6-TCP may be due to the low limit of detection, which needs further investigation. The BKMR model also has some limitations. An inconspicuous overall risk association may be observed when exposures which were positive with the outcome or were negative with the outcome both exist [22]. Additionally, when

the exposure-response is linear and interactions are slight, it is more suitable to use the WQS model [35].

There were several limitations to our study. First, because of the design of the cross-sectional survey project, which collected all of the data at a single time point, there was a limit to the inference of the causation between the chemical exposures and obesity. Second, we used the education level of the individuals themselves instead of their parents' education level, which can be a factor, since parental education can change their intention to alter the obesity risk factor [36]. Third, chemical concentrations below the limit of detection were simply replaced by the value of the limit of detection divided by the square root of 2, which may cause inaccurate results. Fourth, obesity is the result of a combination of the long-term effects of various factors. We determined that the concentration of various exposures in urine does not justify a full inference about the mixed chemical exposures on individuals. Further prospective studies are required to investigate the long-term exposure.

Conclusion

Our study uses three statistical models to analyze the mixed chemical exposures with obesity. 2,5-DCP, MEP, and MiBP were found to have a significant association with the outcome in all models; these results may lead to a false conclusion if only one model is considered. Since all of the models have their own advantages and disadvantages, our study confirms the necessity of combining different statistical models when dealing with the effects of mixed exposures on obesity.

Additional Files

Additional File1: Table S1. Association between chemical exposures and obesity with all the chemicals included in NHANES 2005−2010 (N = 2529). **Table S2.** Association between chemical exposures and BMI z-score with all of the chemicals

included in NHANES 2005−2010 (N = 2529). **Table S3.** Variance inflation factors (VIFs) in the multivariate logistic and linear regression models, including all the chemical exposures, adjusting for the confounding effects of other chemicals in NHANES 2005−2010 (N = 2529). **Additional File 2:** Datasets generated and analyzed during the current study.

Abbreviation

2,4-DCP: 2,4-Dichlorophenol; 2,5-DCP: 2,5-Dichlorophenol; 2,4,5-TCP: 2,4,5-trichlorophenol; 2,4,6-TCP: 2,4,6-Trichlorophenol; BP-3: Benzophenone-3; BKMR: Bayesian kernel machine regression; BMI: Body Mass Index; BPA: bisphenol A; BuP: Butyl paraben; CDC: Centers for Disease Control and Prevention; CI: confidence interval; DBP: di-n-butyl phthalate; DF: Detection frequency; DiBP: di-isobutyl phthalate; EtP: Ethyl paraben; GM: geometric mean; HPLC-ESI-MS/MS: high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry; LOD: limit of detection; MBP: mono-n-butyl phthalate; MCMC: Markov chain Monte Carlo; MeP: Methyl paraben; MEP: monoethyl phthalate; MiBP: mono-isobutyl phthalate; MS: mass spectrometry; NHANES: National Health and Nutrition Examination Survey; ORs: odds ratios; PIP: posterior inclusion probabilities; PrP: Propyl paraben; SD: Standard Deviation; SPE: solid phase extraction; VIFs: variance inflation factors; WQS: weighted quantile sum.

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Author's contributions

B.S. Wu participated in the study design, collected and organized data, carried out the statistical analysis, and prepared the first draft of the manuscript. Y. Jiang participated in the study design, in the coordination and the execution of data collection, statistical analysis and in writing the manuscript. X.Q. Jin participated in the study design, and gave critical appraisal of the manuscript. L. He coordinated the study design, and gave critical appraisal of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available in the Additional File2.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Table 1 Demographic characteristics of the National Health and Nutrition Examination Survey 2005–2010 participants (N = 2529), aged 6−19 years

Characteristics	Obesity	No obesity	P value
	569	1959	
Age (y), mean (SE)	12.54 (3.82)	12.52 (4.01)	0.926
Gender			0.651
Male	276 (10.91%)	1038 (41.04%)	
Female	250 (9.89%)	964 (38.12%)	
Race			<0.001
Mexican American	163 (6.45%)	550 (21.75%)	
Other Hispanic	56 (2.21%)	175 (6.92%)	
Non-Hispanic White	114 (4.51%)	637 (25.19%)	
Non-Hispanic Black	170 (6.72%)	520 (20.56%)	
Other Race	23 (0.91%)	120 (4.74%)	
Education level			0.172
≤5 grade	235 (9.29%)	902 (35.67%)	
6-8 grade	125 (4.94%)	435 (17.20%)	
9-12 grade, No Diploma	127 (5.02%)	485 (19.18%)	
High School Graduate	26 (1.03%)	85 (3.36%)	
GED or Equivalent, More than high school	13 (0.51%)	95 (3.76%)	
Family income-to-poverty ratio			0.010
≤1.30	269 (10.64%)	884 (34.95%)	
1.31,3.50	181 (7.16%)	711 (28.11%)	
>3.50	76 (3.01%)	407 (16.09%)	
Caloric intake			0.001
Normal intake	306 (12.10%)	1033 (40.85%)	
Excessive intake	220 (8.70%)	969 (38.32%)	

Serum cotinine (ng/mL), mean (SE)	6.03 (33.39)	10.24 (46.32)	0.042
Urinary creatine (mg/dL), GM (SE)	117.63 (77.82)	17.20 (82.12)	0.016
BMI, mean (SE)	30.36 (6.96)	19.70 (3.66)	<0.001
BMI z-score, mean (SE)	2.13 (0.33)	0.18 (0.94)	<0.001
Waist Circumference (cm), mean (SE)	94.79 (21.02)	69.36 (12.62)	<0.001

BMI: body mass index. Data are presented as mean $\pm$ SD or Geometric mean $\pm$ SD or n (%). The t-test and χ^2 test were between the general obesity and no obesity groups.

Table 2 Distribution of the chemical exposures in National Health and Nutrition Examination Survey (NHANES) 2005−2010 (N =2529)

Chemical exposures	LOD (ng/mL)	DF (%)	GM	Mean	Min	P5	P25	P50	P75	P95	Max
Phenols (ng/mL)											
BPA	0.4	92.8%	4.79	4.23	0.28	0.40	1.20	2.30	4.30	13.10	241.00
BP-3	0.4	97.1%	490.00	262.00	0.28	1.40	4.80	12.30	39.63	537.65	94100.00
Paraben (ng/mL)											
BuP	0.2	43.3%	6.98	3.82	0.14	0.14	0.14	0.14	0.53	13.50	1240.00
EtP	1.0	45.1%	24.91	13.80	0.71	0.71	0.71	0.71	2.10	11.93	1760.00
MeP	1.0	99.4%	417.70	271.80	0.71	4.44	6.90	57.90	224.00	1100.00	14900.00
PrP	0.2	93.8%	96.65	58.27	0.14	0.20	1.30	6.50	37.15	282.00	4150.00
Pesticides (μ g/L)											
2,5-DCP	0.2	98.6%	455.60	250.80	0.14	0.70	3.40	11.70	54.40	955.65	19400.00

2,4-DCP	0.2	90.3%	11.47	6.88	0.14	0.14	0.50	1.10	2.80	25.66	1230.00
2,4,5-TCP	0.1	30.5%	0.10	0.13	0.07	0.07	0.07	0.07	0.10	0.30	25.70
2,4,6-TCP	0.5	29.7%	0.45	0.61	0.35	0.35	0.35	0.35	0.60	1.50	19.00
Phthalate metabolites (ng/mL)											
MBzP	0.2	98.9%	36.93	29.86	0.15	1.49	6.48	14.68	31.20	90.74	3806.57
MEP	0.5	99.9%	357.90	250.80	0.37	11.09	33.47	76.93	209.82	1022.46	11810.04
MiBP	0.3	98.7%	25.27	20.80	0.21	1.50	5.23	10.90	20.52	52.07	6286.00

LOD: limit of detection; DF: detection frequency; GM: geometric mean.

Table 3 Association between a single chemical exposure and obesity in the National Health and Nutrition Examination Survey (NHANES) 2005–2010 (N = 2529)

Chemical exposures	Quartile 1	Quartile 2		Quartile 3		Quartile 4		Total	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Phenols									
BPA	Ref	0.94 (0.69,1.28)	0.689	1.02 (0.75,1.40)	0.888	1.04 (0.76,1.46)	0.802	1.04 (0.80, 1.36)	0.771
BP-3	Ref	0.94 (0.71,1.25)	0.682	1.10 (0.83,1.46)	0.517	0.95 (0.70,1.29)	0.735	0.98 (0.86, 1.13)	0.826
Paraben									
BuP	Ref		Ref	0.88 (0.67,1.15)	0.37	1.05 (0.81,1.35)	0.716	0.99 (0.84, 1.15)	0.877
EtP	Ref		Ref	0.73 (0.51,1.02)	0.073	0.91 (0.71,1.15)	0.422	0.90 (0.75, 1.07)	0.232

MeP	Ref	0.71	0.020	0.69	0.015	0.66	0.012	0.81	0.011
		(0.53,0.95)		(0.52,0.93)		(0.48,0.91)		(0.70, 0.95)	
PrP	Ref	1.13	0.392	0.87	0.366	0.74	0.078	0.91	0.168
		(0.85,1.50)		(0.64,1.18)		(0.53,1.03)		(0.80, 1.04)	
Pesticides									
2,5-DCP	Ref	1.30	0.092	1.59	0.003	1.74	0.001	1.21	0.001
		(0.96,1.78)		(1.17,2.17)		(1.27,2.39)		(1.08, 1.35)	
2,4-DCP	Ref	0.97	0.822	1.00	0.991	1.02	0.902	1.11	0.236
		(0.71,1.32)		(0.73,1.38)		(0.74,1.42)		(0.94, 1.30)	
2,4,5-TCP	Ref		Ref	1.29	0.093	0.90	0.445	0.87	0.517
				(0.95,1.72)		(0.68,1.18)		(0.56, 1.32)	
2,4,6-DCP	Ref		Ref	1.11	0.520	0.95	0.666	0.93	0.734
				(0.80,1.54)		(0.74,1.21)		(0.60, 1.42)	
Phthalate metabolites									
MBzP	Ref	1.05	0.758	1.05	0.757	0.90	0.556	0.97	0.774
		(0.78,1.41)		(0.77,1.44)		(0.64,1.27)		(0.77, 1.22)	

MEP	Ref	1.08	0.628	1.32	0.086	1.47	0.028	1.33	0.005
		(0.79,1.47)		(1.10,1.83)		(1.04,2.07)		(1.09, 1.63)	
MiBP	Ref	1.31	0.085	1.38	0.055	1.46	0.039	1.37	0.023
		(0.96,1.79)		(0.99,1.92)		(1.02,2.10)		(1.04, 1.80)	

OR: odds ratio; CI: confidence interval. Multivariable logistic regression was conducted, and odds ratios (ORs) were calculated while comparing the second, third, and fourth quartiles of each chemical with reference to the first exposure quartile (N = 2529). Models were adjusted for age, gender, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine and ln-transformed creatinine.

Table 4 Association between single chemical exposure and BMI z-score in National Health and Nutrition Examination Survey (NHANES) 2005–2010 (N = 2529)

Chemical exposures	Quartile 1	Quartile 2		Quartile 3		Quartile 4		Total	
		(95%CI)	P value	(95%CI)	P value	(95%CI)	P value	(95%CI)	P value
Phenols									
BPA	Ref	0.02	0.774	0.07	0.329	-0.01	0.891	-0.06	0.331
		(-0.12, 0.16)		(-0.07, 0.21)		(-0.16, 0.14)		(-0.18, 0.06)	
BP-3	Ref	0.06	0.338	0.05	0.396	0.07	0.319	0.02	0.533
		(-0.07, 0.19)		(-0.08, 0.19)		(-0.07, 0.21)		(-0.04, 0.08)	
Paraben									
BuP	Ref	Ref		-0.01	0.817	-0.01	0.969	-0.01	0.812
				(-0.14, 0.11)		(-0.12, 0.12)		(-0.08, 0.06)	
EtP	Ref	Ref		-0.02	0.746	0.01	0.940	-0.01	0.953
				(-0.18, 0.13)		(-0.11, 0.12)		(-0.08, 0.07)	
MeP	Ref	-0.13	0.059	-0.12	0.081	-0.14	0.071	-0.05	0.144

		(-0.23, 0.01)		(-0.26, 0.02)		(-0.29, 0.01)		(-0.12, 0.02)	
PrP	Ref	0.02	0.824	-0.05	0.497	-0.09	0.262	-0.02	0.368
		(-0.12, 0.15)		(-0.18, 0.09)		(-0.24, 0.06)		(-0.08, 0.03)	
Pesticides									
2,5-DCP	Ref	0.04	0.538	0.14	0.050	0.07	0.358	0.02	0.457
		(-0.09, 0.17)		(0, 0.27)		(-0.08, 0.21)		(-0.03, 0.07)	
2,4-DCP	Ref	-0.08	0.276	0.03	0.710	-0.09	0.241	-0.03	0.377
		(-0.21, 0.06)		(-0.12, 0.17)		(-0.24, 0.06)		(-0.11, 0.04)	
2,4,5-TCP	Ref	Ref		0.07	0.369	-0.03	0.613	0.01	0.960
				(-0.08, 0.21)		(-0.16, 0.09)		(-0.19, 0.19)	
2,4,6-TCP	Ref	Ref		-0.04	0.656	0.01	0.942	0.02	0.876
				(-0.19, 0.12)		(-0.11, 0.12)		(-0.18, 0.21)	
Phthalate metabolites									
MBzP	Ref	0.02	0.830	-0.04	0.577	-0.04	0.594	0	0.988
		(-0.12, 0.15)		(-0.18, 0.10)		(-0.20, 0.11)		(-0.10, 0.11)	
MEP	Ref	0.03	0.705	0.12	0.097	0.16	0.044	0.13	0.003

		(-0.11, 0.16)		(-0.02, 0.26)		(0.01, 0.31)		(0.04, 0.23)	
MiBP	Ref	0.11	0.118	0.07	0.381	0.08	0.307	0.06	0.337
		(-0.03, 0.24)		(-0.08, 0.21)		(-0.08, 0.25)		(-0.06, 0.19)	

CI: confidence interval; Multivariable linear regression was conducted and regression coefficients (β) were calculated while comparing the second, third and fourth quartiles of each chemical with reference to the first exposure quartile (N = 2529). Models were adjusted for age, gender, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and ln-transformed creatinine.

Figure legends

Figure 1. Pearson's correlations among the urinary concentrations of 13 chemical exposures or metabolites (N = 2529), NHANES, USA, 2005-2010. All the correlations were statistically significant ($P < 0.05$), except those of BP-3 and 2,4-DCP ($P = 0.57$).

Figure 2. WQS model regression index weights for the obesity (A) and BMI z-score (B). Models were adjusted for age, gender, race, education levels, family income-to-poverty ratio, caloric intake, serum cotinine, and In-transformed creatinine.

Figure 3. Overall risk (95% CI) of chemical exposures on obesity (A) and BMI z-score (B) when comparing all the chemicals at different percentiles with their median level. Models were adjusted for age, gender, race, educational levels, family income-to poverty ratio, caloric intake, serum cotinine, and In-transformed creatinine.

Figure 4. Association and 95% credible intervals for each chemical exposure with obesity (A) and BMI z-score (B) while fixing other chemical exposures at their median level. The model was adjusted for age, gender, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and In-transformed creatinine.

Figure 5. Association between exposure 1 with obesity (A) and BMI z-score (B), while fixing exposure 2 at the 10th, 50th, and 90th quantiles (and holding the remnant predictors to their median level). The models were adjusted for age, gender, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and In-transformed creatinine.

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