Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

The Impact of High-Resolution LC-MS/MS Detected Environmental Exposures on Obesity: A Study of Cumulative Effects Through Statistical Modeling

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Background: Obesity is a major and escalating public health challenge worldwide. Growing evidence implicates environmental chemicals, especially organophosphate flame retardants (OFRs) and per- and polyfluoroalkyl substances (PFAS), as potential obesogens due to their ability to disrupt endocrine function and lipid metabolism. However, data on the association between these chemical mixtures and overweight in Chinese populations—particularly in industrialized regions—are scarce, representing a critical knowledge gap.

Methods: We conducted a matched case–control study of 214 adults from northern China, including 107 overweight individuals (body mass index [BMI] ≥ 24 kg/m^2) and 107 normal-weight controls (BMI < 24 kg/m^2), pair-matched by age and sex. Using high-resolution liquid chromatography–tandem mass spectrometry (LC-MS/MS), we quantified serum concentrations of 202 environmental exposures. Multivariable logistic regression, Weighted Quantile Sum (WQS) regression, and Bayesian Kernel Machine Regression (BKMR) models were employed to assess individual and cumulative associations with overweight, adjusting for key metabolic covariates (eg, blood pressure, lipids, and fasting glucose).

Results: Thirteen chemicals showed significant differences between groups ($|\log_2$ fold change$| \geq 1$). Ten were elevated in the overweight group, most notably tris(2-butoxyethyl) phosphate (TBOEP; adjusted odds ratio [OR] = 2.40, 95% confidence interval [CI]: 1.79–3.33), 1,3,5-triazine-2,4,6-trione tris(2,3-dibromopropyl) ester (TBC), perfluorooctanoic acid (PFOA), and perfluorobutane sulfonic acid (PFBS). The WQS index reflecting the combined effect of these 13 chemicals was strongly associated with higher odds of overweight (OR = 2.33, 95% CI: 1.77–3.07). BKMR analysis further revealed a non-linear cumulative exposure–response relationship, with maximal risk observed at moderate exposure levels.

Conclusion: This study provides robust epidemiological evidence that circulating levels of specific environmental pollutants—particularly TBOEP, PFOA, PFBS, and TBC—are significantly associated with increased likelihood of overweight in a northern Chinese adult population. Our findings highlight the potential contribution of complex chemical mixtures to obesity etiology in rapidly industrializing settings and underscore the need for targeted environmental health interventions.

Keywords: obesity, environmental exposures, overweight

Introduction

Obesity is a pressing global public health issue that has risen dramatically over the past 40 years. Between 1975 and 2014, adult obesity rates surged, with men increasing from 3.2% to 10.8% and women from 6.4% to 14.9%.[1] By 2014, severe obesity prevalence (body mass index, BMI > 40 kg/m^2) reached 0.64% in men and 1.6% in women.[2] The latest data from the World Health Organization (WHO) indicates that the global obesity rate among adults aged 18 and older

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has more than doubled from 6% in 1990 to 16% in 2022.[3] Obesity significantly elevates the risk of various health conditions, including type 2 diabetes,[4] cardiovascular diseases,[5] musculoskeletal disorders,[6] Alzheimer's disease,[7] rheumatoid arthritis,[8] depression,[9] and several cancers.[10] This increased risk can shorten life expectancy by 5 to 20 years,[11] highlighting the critical need for effective obesity control and prevention strategies.

There are numerous causes of obesity, with overeating,[12] low energy expenditure, and lack of physical activity being the three main contributors. However, as industrialization continues to advance, an increasing number of researchers have begun to focus on the correlation between environmental pollution and obesity.[13] Studies have found that air pollution has become one of the major threats to global health and is a significant risk factor for non-communicable diseases.[14] A growing body of epidemiological research further confirms that air pollutants such as particulate matter (PM), nitrogen oxides (NOx), ozone (O_3), and polycyclic aromatic hydrocarbons (PAHs) are closely associated with overweight and obesity.[15] Once obesity develops, it can further trigger chronic inflammation and type 2 diabetes, thereby exacerbating the adverse health effects of environmental pollution.[16] In addition, endocrine disrupting chemicals (EDCs) and persistent organic pollutants (POPs) are also considered significant threats to human health. A systematic review analyzed 75 epidemiological studies published between 2014 and 2024 on the relationship between endocrine-disrupting chemicals (EDCs) and obesity.[17] The review found that early-life exposure to obesogens may increase later obesity risk via epigenetic and transgenerational effects. Lipophilic POPs promote obesity through pathways including lipogenesis, lipid accumulation, insulin resistance, inflammation, and gut microbiota dysbiosis.[18]

However, not all studies support the link between EDCs/POPs and obesity, for example, one study found a negative correlation between perfluorooctanoate (PFOA) and girls' BMI and waist-to-hip ratio.[19] Additionally, a study of 1245 women aged 45–56 found no clear association between per- and polyfluoroalkyl substances (PFAS) and BMI.[20] The inconsistency in research findings indicates that the relationship between EDCs, POPs, and obesity remains unclear. Moreover, the influence of multiple covariate factors contributes to the heterogeneity observed in many studies. In light of this, we collected data from the population in northern China, used liquid chromatography-tandem mass spectrometry (LC-MS/MS) technology to detect the expression of EDCs and POPs in the blood, and analyzed the correlation between blood EDCs and POP levels and overweight in the Chinese population, aiming to provide a reference for clarifying the hazards of EDCs and POPs.

Methods

Selection of Study Subjects

A total of 236 patients from northern China who underwent physical examinations at Xuzhou Central Hospital between June and December 2024 were included in the study. All patients received comprehensive physical assessments, which included tests for blood lipids, fasting blood glucose, and blood pressure. The inclusion criteria were as follows: 1) Participants aged 18 years or older; 2) Provision of a signed informed consent form. The exclusion criteria included: 1) Patients diagnosed with hypertension or diabetes; 2) Obese patients with a body mass index (BMI) of 30 or higher; 3) Patients with severe heart, liver, lung, or kidney failure; 4) Patients with psychiatric disorders that impair effective communication. This study received approval from the Ethics Committee of Xuzhou Central Hospital.

This study was approved by the Ethics Committee of Xuzhou Central Hospital, and all participants provided written informed consent prior to their enrollment. All procedures involving human subjects in this study were conducted in accordance with the ethical standards of Xuzhou Central Hospital, as well as the 1964 Helsinki Declaration and its subsequent amendments.

Collection of Clinical Characteristics

General clinical data of enrolled participants were collected, including sex and age. Physical examinations were performed to measure height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Height and weight were assessed using a standardized height-weight measuring device, with participants standing barefoot on the equipment. Trained physicians supervised the measurement process and documented the data.

Clinical and Biochemical Measurements

Blood pressure measurements were conducted in a private examination room. Participants were instructed to sit quietly for 5 minutes prior to measurement, after which three readings were recorded at 10-minute intervals.

Venous blood samples were collected from participants for analyzing four blood lipid parameters (total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)) and fasting blood glucose (FPG). Participants were required to fast for more than 8 hours before blood collection, which was performed by trained physicians. All samples were stored at −80°C until uniform processing, and subsequent testing was carried out using a Hitachi automatic blood analyzer.

Detection of Serum Exposures by LC-MS/MS

Sample Preparation

Serum samples were collected and kept on ice until centrifugation at 3000 rpm (4°C, 10 min) upon arrival at the lab. The separated serum was aliquoted into polypropylene tubes and stored at –80°C. Before extraction, 500 μL of each sample was spiked with isotope-labeled internal standards (eg, diisobutyl phthalate-D4, atrazine-D5) to assess extraction efficiency and correct for matrix effects. Liquid–liquid extraction was carried out by adding 3 mL of ethyl acetate/hexane (1:1, v/v) containing 0.6% (v/v) formic acid, followed by vortexing (3 min) and centrifugation (5000×g, 4°C, 10 min). The upper organic layer (2.5 mL) was collected, and the aqueous phase was re-extracted with 2 mL of fresh solvent. The combined organic extracts (~4.2 mL) were evaporated under nitrogen at 30°C, reconstituted in 200 μL LC-grade methanol, and stored overnight at –20°C or 4°C. On the day of analysis, samples were centrifuged (12,000 rpm, 4°C, 10 min), and 100 μL of supernatant was spiked with 10 ng of additional internal standards prior to LC-MS/MS analysis.

Chromatographic and Mass Spectrometric Conditions

Chromatographic separation was performed on an Xtimate C18 column (3 μm, 4.6×150 mm) with a matching guard column (4.6×10 mm), maintained at 40°C; the autosampler was kept at 4°C to prevent analyte degradation. In positive ion mode, mobile phase A was water containing 0.1% (v/v) formic acid and 8 mM ammonium formate, and mobile phase B was methanol: acetonitrile (85:15, v/v) with 0.1% (v/v) formic acid. The gradient started at 40% B, ramped to 80% B in 5 min, reached 100% B by 11 min, held until 30 min, then re-equilibrated to 40% B within 0.1 min and held until 35 min. In negative ion mode, mobile phase A contained 0.1% (v/v) ammonia and 8 mM ammonium formate in water, while mobile phase B remained unchanged. The gradient followed a similar profile but completed re-equilibration by 26 min.

The flow rate was 0.4 mL/min, and 10 μL of sample was injected. Analysis was carried out using a Shimadzu LC-40D XS UHPLC system coupled to an LCMS-8060NX triple quadrupole mass spectrometer with an electrospray ionization (ESI) source operating in multiple reaction monitoring (MRM) mode. For positive mode, ESI settings were: spray voltage +4.5 kV, desolvation temperature 300°C, drying gas 15 L/min at 325°C, and collision gas (Ar) pressure 270 kPa. In negative mode, spray voltage was –3.5 kV, with other parameters unchanged. MRM transitions for all 202 target compounds were optimized via flow injection analysis and literature validation to ensure high sensitivity and selectivity (see Supplementary Table 1).

Quality Assurance and Quality Control

To ensure the reliability and reproducibility of our data, rigorous quality assurance/quality control (QA/QC) procedures were implemented throughout the analytical process. Blank samples (containing only extraction solvent) were analyzed intermittently between real samples to monitor carry-over and contamination. Calibration curves were constructed using matrix-matched standards across a concentration range of 0.5–10,000 ng/L, with a weighting factor of 1/x applied during linear regression to improve fitting accuracy at low concentrations. The correlation coefficients (R^2) for all calibration curves exceeded 0.99. Method validation was performed according to international bioanalytical method validation guidelines. The limit of quantification (LOQ) for all target analytes was confirmed to be within the range of 0.5–10 ng/L, ensuring sensitive detection of trace-level exposure biomarkers. Matrix effects were evaluated by comparing peak areas of post-extraction spiked samples with those of neat standards, and values were found to be within an acceptable range (±15%). Recovery experiments were conducted at three different concentration levels (low, medium, high), yielding recovery rates between 70% and 120%, with relative standard deviations (RSDs) below 15%. Intra-day and inter-day

precision and accuracy were assessed by analyzing QC samples on three consecutive days. All results met the acceptance criteria, with intra- and inter-day RSDs less than 10%.

Statistical Analysis

All statistical analyses were conducted using R software (version 4.5.1). The raw data obtained from chromatographic-mass spectrometric analysis were processed using LabSolutions (version 5.120), from which key parameters–including retention time (RT), mass-to-charge ratio (m/z), ion peak intensity, and ion peak area–were extracted. To meet the assumption of normality, the peak areas of all detected pollutants were subjected to logarithmic transformation prior to further analysis. Participants' body mass index (BMI) was calculated based on their measured height and weight. Individuals were categorized into two groups according to the Chinese classification criteria: a normal weight group (BMI < 24 kg/m^2) and an overweight group (BMI ≥ 24 kg/m^2).[21] To minimize potential confounding due to differences in age and gender, propensity score matching (PSM) was performed. Propensity scores were estimated using logistic regression, and a 1:1 matching algorithm was applied. After matching, a final sample of 214 participants was included in the analysis, with 107 individuals in each group. To compare baseline clinical and demographic characteristics between the two groups, independent samples *t*-tests were used for continuous variables, and chi-square tests were applied for categorical variables. Given that the log-transformed exposure variables met the assumption of normality, independent samples t-tests were also employed to identify exposures that significantly differed between the normal weight and overweight groups. To evaluate the association between each significantly different exposure and the risk of overweight, multivariate logistic regression models were fitted, adjusting for potential confounders including gender, age, FPG, SBP, DBP, TC, TG, HDL, and LDL levels. Weighted Quantile Sum (WQS) and Bayesian Kernel Machine Regression (BKMR) models were applied to assess the combined effects of multiple differential exposures on the risk of overweight, with adjustment for the aforementioned metabolic indicators. A two-sided p-value < 0.05 was considered statistically significant.

Results

The Clinical Characteristics of Participants

Table 1 shows the baseline characteristics of the overweight group and the normal group along with the differences between the two groups. Due to the PSM, there was no statistically significant difference in gender and age between the two groups. Furthermore, height, SBP, DBP, TG, FPG, and LDL did not differ significantly between the groups. The most pronounced differences were observed in weight and BMI, which were inherent grouping criteria. Additionally, there were significant differences in TC and HDL, with participants in the overweight group exhibiting higher levels of both TC and HDL. These two factors should be adjusted for in subsequent analyses.

Differences in Exposures Between the Two Groups

Using LC-MS/MS, a total of 202 effective exposures were identified. After log2 transformation, intergroup comparisons were performed to identify differential exposures between the overweight and normal groups. As shown in Supplementary Table 2, there were significant differences in 67 exposures between the two groups. By applying a cut-off of absolute fold change ≥ 1, we identified 13 exposures, of which 10 were elevated in the overweight group and 3 were elevated in the normal group (Figure 1B). Additionally, PCA analysis indicated that there were significant differences in the distribution of exposures between the overweight and normal groups (Figure 1A).

Correlation Between Differential Exposures and Clinical Indicators

We conducted a correlation analysis between the identified 13 differential exposures and clinical data. The results indicated a significant correlation between BMI and 5 of the exposures (Figure 2A). Specifically, PFBS (1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonic acid), TDCIPP (Tris(1,3-dichloropropan-2-yl) phosphate), TBOEP (Tris(2-butoxyethyl) phosphate), and TBC (1,3,5-Triazine-2,4,6-trione tris(2,3-dibromopropyl) ester) showed positive correlations with BMI, while IPPD (N-(Propan-2-yl)-N′-phenylbenzene-1,4-diamine) exhibited a negative correlation (Figure 2B). Additionally, the correlation network graph demonstrated that BMI, SBP, DBP, and weight were correlated with these exposures (Figure 2B).

Table 1 The Clinical Characteristics of All Participants

	Normal Group (N=107)	Overweight Group (N=107)	Overall (N=214)	P
Gender				0.785
Female (n, %)	54 (50.47%)	52 (48.60%)	106	
Male (n, %)	53 (49.53%)	55 (51.40%)	108	
Age (years)				0.877
Mean (SD)	55.7 (9.57)	55.5 (9.42)	55.6 (9.48)	
Median [Min, Max]	56.0 [36.0, 83.0]	55.0 [36.0, 83.0]	55.0 [36.0, 83.0]	
Height (m)				0.331
Mean (SD)	1.66 (0.07)	1.65 (0.08)	1.66 (0.07)	
Median [Min, Max]	1.66 [1.50, 1.86]	1.66 [1.46, 1.84]	1.66 [1.46, 1.86]	
Weight (kg)				<0.001
Mean (SD)	61.6 (7.28)	69.5 (6.81)	65.2 (8.10)	
Median [Min, Max]	61.0 [44.5, 80.7]	70.5 [53.7, 82.5]	65.6 [44.5, 82.5]	
BMI (Kg/m2)				<0.001
Mean (SD)	22.2 (1.59)	25.4 (0.940)	23.6 (2.07)	
Median [Min, Max]	22.6 [16.9, 24.0]	25.2 [24.0, 29.1]	23.8 [16.9, 29.1]	
SBP (mmHg)				0.999
Mean (SD)	120 (11.9)	120 (10.6)	120 (11.3)	
Median [Min, Max]	120 [94.0, 140]	122 [100, 139]	120 [94.0, 140]	
DBP (mmHg)				0.361
Mean (SD)	74.7 (7.57)	73.8 (6.78)	74.3 (7.22)	
Median [Min, Max]	74.0 [60.0, 90.0]	74.0 [56.0, 90.0]	74.0 [56.0, 90.0]	
FPG (mmol/L)				0.286
Mean (SD)	5.32 (0.40)	5.38 (0.42)	5.35 (0.41)	
Median [Min, Max]	5.37 [4.29, 6.05]	5.38 [3.65, 6.09]	5.38 [3.65, 6.09]	
TC (mmol/L)				0.010
Mean (SD)	4.44 (0.50)	4.21 (0.77)	4.34 (0.64)	
Median [Min, Max]	4.50 [3.17, 5.16]	4.39 [0.940, 5.17]	4.47 [0.94, 5.17]	
TG (mmol/L)				0.086
Mean (SD)	0.99 (0.31)	1.07 (0.34)	1.03 (0.32)	
Median [Min, Max]	0.930 [0.39, 1.70]	1.04 [0.25, 1.70]	0.995 [0.25, 1.70]	
HDL (mmol/L)				0.019
Mean (SD)	1.35 (0.25)	1.28 (0.18)	1.32 (0.222)	
Median [Min, Max]	1.34 [0.76, 2.01]	1.28 [0.84, 1.70]	1.30 [0.76, 2.01]	
LDL (mmol/L)				0.291
Mean (SD)	2.39 (0.42)	2.32 (0.54)	2.36 (0.48)	
Median [Min, Max]	2.46 [1.05, 3.12]	2.39 [0.86, 3.12]	2.44 [0.86, 3.12]	

Abbreviations: BMI, body mas index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fatsing plasma glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Correlation Between 13 Exposures and Risk of Overweight

We employed multivariable logistic regression (adjusting for sex, age, SBP, DBP, FPG, TC, TG, HDL, and LDL) to analyze the correlation between each exposure and the risk of overweight. As shown in Figure 3, TBOEP had the highest association with increased overweight risk among the 13 exposures (OR = 2.40, 95% C.I. = 1.79~3.33). This was followed by TBC (OR = 1.56, 95% C.I. = 1.33~1.86), (Methanediyldibenzene-4,1-diyl bis(dihydrogen phosphate)) BPM (OR = 1.47, 95% C.I. = 1.25~1.77), PFBS (OR = 1.42, 95% C.I. = 1.19~1.71), TDCIPP (OR = 1.37, 95% C.I. = 1.17~1.62), (3-(3,5-dichlorophenyl)-2,4-dioxo-N-(propan-2-yl)imidazolidine-1-carboxamide)T35DMPP (OR = 1.31, 95% C.I. = 1.12~1.55), (Pentadecafluorooctanoic acid) PFOA (OR = 1.25, 95% C.I. = 1.09~1.43), (Bis(1-chloro-2-propyl) phosphate) BCIPP (OR = 1.22, 95% C.I. = 1.09~1.38), ((6aR,10aR)-6,6,9-Trimethyl-3-pentyl-6,6a,7,8,10a-

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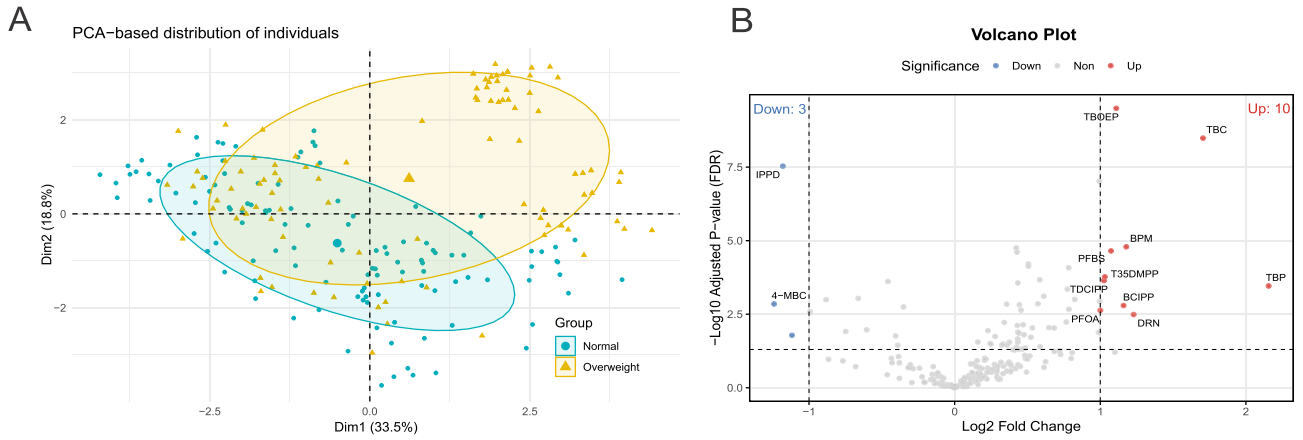

Figure 1 Differences in exposures between the two groups.
Notes: (**A**) The distribution of individuals based on PCA; (**B**) The Volcano Plot between overweight and normal groups.

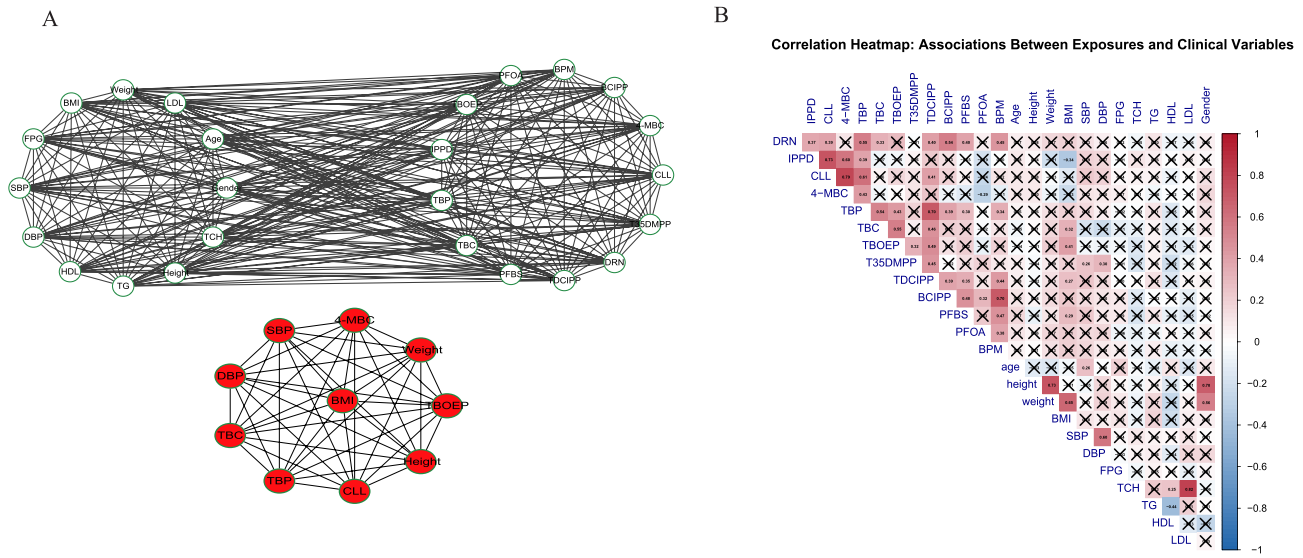

Figure 2 Correlation between differential exposures and clinical indicators.
Notes: (**A**) Network diagram of correlations between environmental exposures and clinical characteristics; (**B**) Heatmap of correlations between environmental exposures and clinical characteristics.

pentahydro-benzo [c] chromen-1-ol) DRN (OR = 1.16, 95% C.I. = 1.05~1.22), and (Tributyl phosphate) TBP (OR = 1.13, 95% C.I. = 1.06~1.22). In contrast, (N′-(3-chloro-4-methylphenyl)-N,N-dimethylurea) CLL (OR = 0.89, 95% C.I. = 0.82~0.98), (1,7,7-Trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one) 4-MBC (OR = 0.84, 95% C.I. = 0.76~0.94), and IPPD (OR = 0.58, 95% C.I. = 0.45~0.72) showed negative correlations with the risk of being overweight.

WQS Model Analysis of the Overall Effect of 13 Exposures on the Risk of Overweight

Using the WQS model, we analyzed the correlation between the overall effect of the 13 differential exposures and the risk of being overweight. After adjusting for covariates such as gender, age, FPG, TC, TG, HDL, LDL, SBP, and DBP, the results indicated that the overall effect of the 13 exposures significantly increased the risk of overweight, with an OR of 2.329 (95% C.I. = 1.771~3.065). As shown in Figure 3, TBOEP had the highest weight at 0.322, followed by PFOA (0.198), PFBS (0.118), TBC (0.105), and BCIPP (0.094) (Figure 4).

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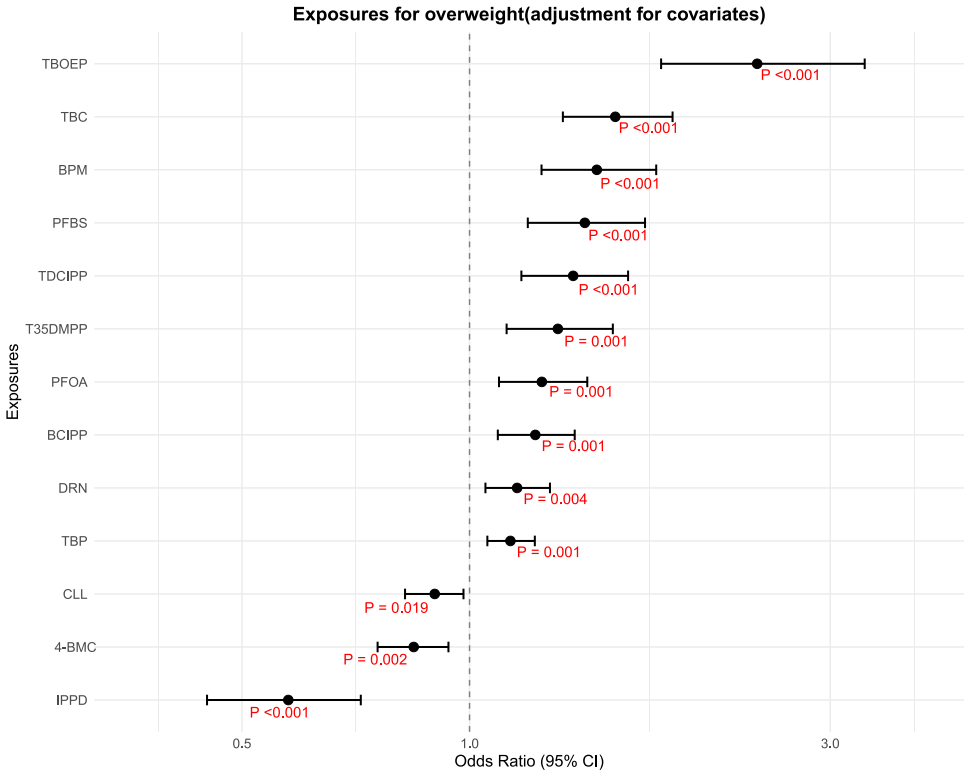

Figure 3 Correlation between 13 exposures and risk of overweight. All models adjusted sex, gender, SBP, DBP, TC, TG, LDL, HDL and FPG.

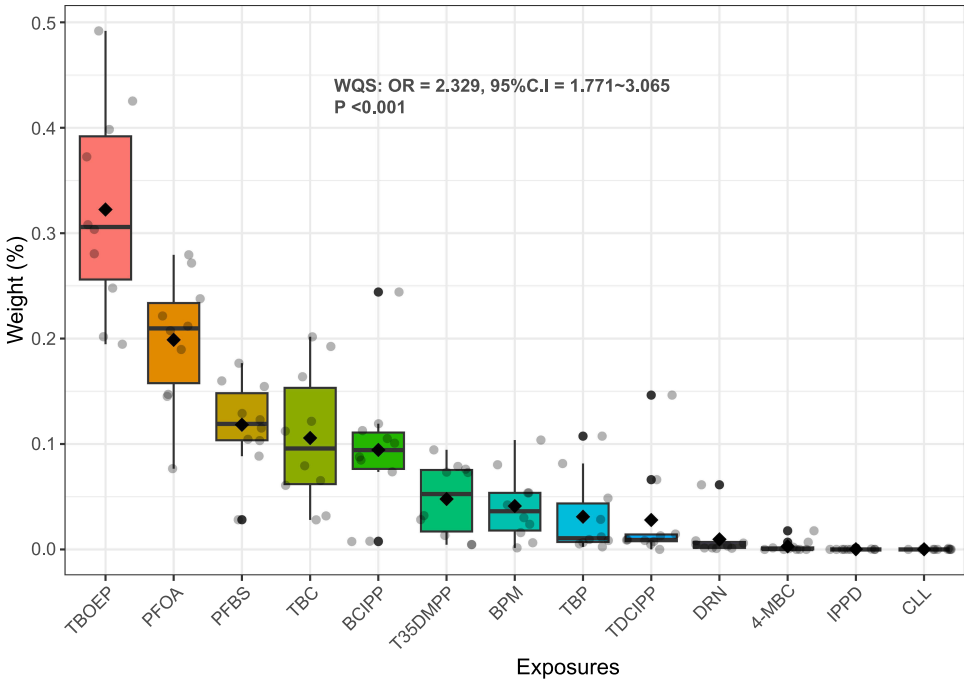

Figure 4 WQS model analysis of the overall effect of 13 exposures on the risk of overweight. Model adjusted sex, gender, SBP, DBP, TC, TG, LDL, HDL and FPG.

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BKMR Model Analysis of the Correlation Between 13 Exposures and the Risk of Overweight

Figure 5 illustrates the relationship between the 13 exposures and overweight. As shown in Figure 5A, with increasing levels of the exposures TBC, BCIPP, PFOA, and TBOEP, the risk of being overweight gradually increases, demonstrating a positive correlation. In contrast, the relationship between DRN and TBP with overweight is non-linear, forming an inverted V shape. IPPD and 4-MBC exhibit a negative correlation with overweight. Figure 5B shows the overall effect of the exposures on overweight, which also follows an inverted V shape. In the 0.25 to 0.5 quantile range, the risk of overweight increases with higher exposure levels; however, in the 0.6 to 0.9 quantile range, the risk of overweight decreases as exposure levels rise.

Discussion

In this study involving 214 samples from the northern Chinese population, we detected 202 types of environmental exposure substances in the blood. Multivariate logistic analysis revealed that 10 environmental exposure substances may be risk factors affecting overweight, while 3 environmental exposure substances showed a negative correlation with overweight. Further analysis using WQS and BKMR models indicated that the overall effect of these exposure substances is to increase the risk of overweight.

POPs are a diverse group of pollutants with distinct chemical properties, which can be categorized into two main sources: a) intentionally produced POPs, including organochlorine pesticides and industrial chemicals such as polychlorinated biphenyls (PCBs); and b) unintentionally generated substances, including polycyclic aromatic hydrocarbons (PAHs), dioxins, and furans.[22] These compounds are characterized by their persistence in the environment, making them difficult to degrade, and they can accumulate in the food chain, leading to long-term residues in both the environment and biological organisms. POPs can activate key regulatory factors such as peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα), promoting adipocyte differentiation and lipid accumulation, thereby increasing the risk of obesity. In this study, we identified BCIPP, PFOA, and TBOEP as influential factors contributing to overweight in the northern Chinese population. Previous studies support our findings; for example, a study conducted in South Korea revealed that BCIPP is the pollutant with the highest concentration in urinary metabolites, with levels exceeding those previously reported in other countries, such as the USA and China.[23] Additionally, articles based on the NHANES database have indicated that BCIPP is a risk factor for obesity.[24] PFOA has also been identified as a risk factor for obesity. Research indicates that for every 1 ng/mL increase in maternal serum PFOA concentration during pregnancy, there is a corresponding increase of 2.0% (95% C.I: 0.3%; 3.7%) in total fat mass for girls, and an increase of 3.8% (95% C.I: 0.6%; 7.0%) in abdominal fat mass.[25] Furthermore, obesity serves as

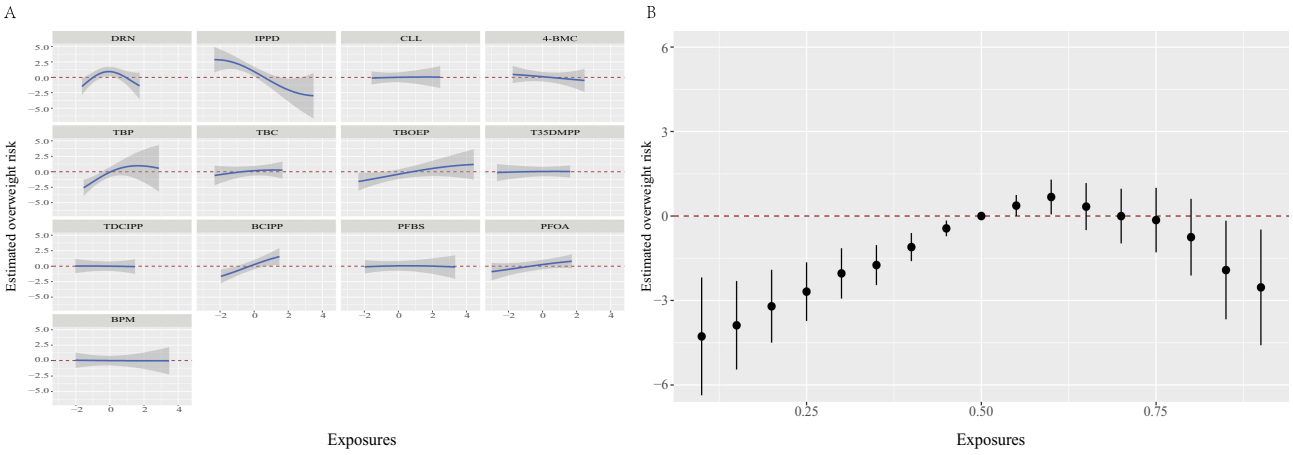

Figure 5 BKMR model analysis of the correlation between 13 exposures and the risk of overweight. Model adjusted sex, gender, SBP, DBP, TC, TG, LDL, HDL and FPG.
Notes: (**A**) The correlation between each of the 13 exposures and overweight; (**B**) The overall effect of the 13 exposures on overweight.

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a significant mediating factor in the association between PFOA and non-alcoholic fatty liver disease (NAFLD). In the analysis of its correlation with NAFLD, PFOA demonstrated statistical significance, with OR ranging from 1.09 to 1.39.[26] This study also found that TBOEP had a more significant effect on overweight in both the WQS and BKMR analyses, although existing research on this topic is limited. TBOEP is widely present in the environment and in food.[27] A toxicity study conducted on zebrafish revealed that TBOEP not only exhibits reproductive toxicity in the maternal organism but can also transmit this toxicity to offspring, leading to developmental toxicity in juvenile fish—manifested by decreased heart rates, abnormal movements, increased mortality rates, and higher rates of deformities.[28] Another nested case-control study concerning gestational diabetes mellitus (GDM) indicated that TBEP (OR = 1.29, 95% CI = 1.04–1.60, P = 0.023) is associated with an increased risk of GDM.[29]

EDCs are defined as exogenous chemicals or chemical mixtures that can alter the functioning of the endocrine system, leading to adverse health effects on individuals, offspring, or populations.[30] This category includes, but is not limited to, synthetic drugs, estrogens, phytoestrogens, herbicides, pesticides, phenols, dioxins, and phthalates.[31] The mechanisms by which EDCs contribute to obesity are multifaceted, involving the disruption of energy metabolism, adipogenesis, and endocrine balance through various pathways.[32] Notably, exposure during critical developmental periods (such as the embryonic and neonatal stages) can have long-lasting effects and even transgenerational impacts that promote obesity.[33] In our study, we found that EDCs such as TBC, IPPD, and 4-MBC are associated with the risk of overweight. Notably, IPPD and 4-MBC exhibited a negative correlation, while TBC showed a positive association. TBC is classified as a novel brominated flame retardant (NBFR) and is a type of synthetic bromine-containing organic compound.[34] Due to its fire-retardant properties, TBC is widely used in industrial applications and is categorized as an endocrine disruptor (EDC) because it can interfere with hormonal signaling pathways in organisms.[35] TBC can enter the human body through contaminated air, water, dust, or the food chain. Research indicates that TBC affects the expression of insulin-like growth factors (IGF1 and IGF2) and their receptor (IGF1R),[36] disrupting cellular proliferation and survival signals, which can lead to endocrine disruption and damage to reproductive cells.

In this study, we utilized the PSM method to ensure no statistically significant differences in gender and age between the obese group and the normal-weight group. This is critical, as the accumulation of EDCs and POPs in the blood is age-dependent, and distinct physiological mechanisms in males and females contribute to variations in bodily EDC levels. Additionally, it is important to note that bloodborne exposures are interactive, a phenomenon well-documented in previous research. To assess the overall effects of these exposures, we employed methods capable of evaluating their cumulative impact: WQS and BKMR. Both methods indicated that overall exposure constitutes a risk factor for overweight, which aligns with prior reports.[37,38]

This study has several limitations. Firstly, it is a cross-sectional study; while we have identified endocrine-disrupting chemicals (EDCs) and persistent organic pollutants (POPs) as risk factors for overweight, we cannot establish a causal relationship from our findings. Additionally, the relatively small sample size limits our ability to rule out the presence of heterogeneity among participants. Moreover, our study was conducted in Xuzhou, a significant industrial city in Northern China, where dietary habits differ notably from those in Southern Chinese cities. As all samples were collected from local residents of Xuzhou, future research should consider the geographical and dietary influences when extrapolating our findings to broader populations. To validate these results, future large-scale population studies are needed.

In summary, our study identified 13 categories of environmental exposures detectable in blood samples that are associated with overweight, with TBC, BCIPP, PFOA, and TBOEP emerging as particularly notable contributors. Importantly, this association is not an isolated phenomenon; rather, the cumulative effect of these environmental exposures collectively elevates the risk of developing overweight.

Data Sharing Statement

All data generated or analyzed during this study are included in this manuscript.

Ethics Approval and Consent to Participate

The study was reviewed and approved by the ethics committee of the Xuzhou Central hospital. The NO. of ethics committee approval is XZXY-LK-20230718-0106.

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Author Contributions

Ying Liu: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing –Editing; Fenfen Ma: Data Curation, Investigation, Visualization, Writing – Original Draft, Writing –Editing; Zhifang Zhong: Resources, Project Administration, Supervision, Writing –Editing; Xuekui Liu: Methodology, Formal Analysis, Validation, Writing –Editing; Min Liu: Software, Validation, Writing – Review & Editing; Kexin Lou: Software, Validation, Project Administration, Writing – Original Draft, Writing – Review & Editing. All authors participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there is no conflict of interest associated with this study.

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