Hygiene and Environmental Health Advances 12 (2024) 100112

Contents lists available at ScienceDirect

Hygiene and Environmental Health Advances

journal homepage: www.elsevier.com/locate/heha

Associations between exposure to multiple environmental chemicals and metabolic syndrome: A mixture analysis

Ruiqiang Li [a], Xiaoyi Lin [a], Tingyu Lu [a], Jiao Wang [a], Ying Wang [a], Lin Xu [a,b,c,*]

[a] School of Public Health, Sun Yat-sen University, Guangzhou, China
[b] School of Public Health, the University of Hong Kong, Hong Kong
[c] Institute of Applied Health Research, University of Birmingham, Birmingham, UK

A R T I C L E I N F O

Keywords:
Phenols
Polycyclic aromatic hydrocarbons
Metals
Phthalates
Metabolic syndrome

A B S T R A C T

Exposure to environmental chemicals is prevalent. While previous studies reported associations between multiple chemical exposures and metabolic syndrome (MetS), they did not comprehensively account for correlations among exposures. We used machine learning methods including Boruta algorithm and least absolute shrinkage and selection operator (LASSO) regression, combined with weighted quartiles sum (WQS) regression to investigate the associations of phenols, polycyclic aromatic hydrocarbons (PAHs), metals, and phthalates with MetS and its components. Data were drawn from the 2005–2012 National Health and Nutrition Examination Survey (NHANES). The mean (standard deviation (SD)) age of 2596 participants was 48.4 (17.9) years. After adjusting for age, sex, body mass index, race/ethnicity, marital status, education, poverty income ratio, physical activity, smoking, and alcohol, higher 2-Phenanthrene (2-PHE) and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) concentrations were associated with a higher odds of the MetS (odds ratio (OR) = 4.26, 95 % confidence interval (CI) 2.40–7.58 per ng/mL, and 3.24, 1.75–6.02 per ng/L, respectively). WQS index for environmental chemicals was positively associated with the MetS (OR = 1.31, 95 % CI 1.09–1.57). Moreover, we observed consistent and stronger positive associations with MetS (OR = 1.54, 95 % CI 1.04–2.30) in current smokers. Exposure to phenols, PAHs, metals, and phthalates was positively associated with an increase in metabolic syndrome and its components, which was more pronounced in current smokers.

1. Introduction

Metabolic syndrome (MetS) is a multifactorial disorder (Eckel et al., 2005), While previous studies have mainly focused on lifestyle and genetic factors (Cornier et al., 2008; Kassi et al., 2011), increasing attention is now being paid to environmental factors, including phenols and phthalates (Zhan et al., 2022), polycyclic aromatic hydrocarbons (PAHs) (Li et al., 2023a) and heavy metals (Deyssenroth et al., 2018). These pollutants, derived from combustion processes, industrial emissions (Bulka et al., 2019; Kim et al., 2013b), plastic and personal care products (Zhang et al., 2019), are pervasive in air, water, food and household items (Yilmaz et al., 2020). Recent studies reported positive associations of environmental pollutant exposure and MetS (Eze et al., 2015; Ren and Tong, 2008). For example, developmental exposure to phthalates was associated with a higher risk of MetS (Neier et al., 2019). Moreover, exposure to PAHs was associated with higher risks of hypertension and obesity (Poursafa et al., 2017), and exposure to bisphenol A (BPA) (Teppala et al., 2012) and metals such as mercury (Hg) and cadmium (Cd) was associated with a higher risk of MetS (Jeong, 2018; Roy et al., 2017).

Despite these findings, most studies focus on individual pollutants, overlooking the cumulative impact of chemical mixtures. Our study addresses this by employing advanced machine learning techniques to analyze the non-linear interactions among phenols, phthalates, PAHs, and heavy metals. This approach enables the assessment of combined exposures and their collective effects on MetS, providing a more comprehensive understanding of the environmental contributors to its risk.

Given the widespread exposure to multiple environmental pollutants and their potential combined impact on MetS, we hypothesize that simultaneous exposure to phenols, phthalates, PAHs, and heavy metals is significantly associated with a higher risk of MetS. We further hypothesize that these associations can be more accurately characterized using advanced machine learning that account for complex, non-linear

* Corresponding author at: School of Public Health, Sun Yat-sen University, 74 Zhongshan 2nd Road, Guangzhou, Guangdong Province, China.
E-mail address: xulin27@mail.sysu.edu.cn (L. Xu).

https://doi.org/10.1016/j.heha.2024.100112
Received 21 February 2024; Received in revised form 18 September 2024; Accepted 4 October 2024
Available online 5 October 2024

interactions among exposures. The primary objectives of the study are to: (1) assess the independent and combined effects of these pollutants on MetS risk, (2) explore their complex interactions, and (3) quantify the relative contribution of these exposures using weighted quantile sum (WQS) regression models.

2. Materials and methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is a large-scale program administered by the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the non-institutionalized U.S. population. The survey includes demographic information, dietary habits, and interviews on health-related issues. In addition, NHANES includes a physical examination component with physiological measurements and laboratory tests (Liu et al., 2022b). NHANES was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants volunteered (Ashley et al., 2020). The study used population data from the 2005–2012 cycle. We excluded participants aged under 20 years and those with missing data on any of the key variables, including environmental chemicals, demographic characteristics and MetS components, resulting in a final sample of 2596 participants for this study (Supplementary Fig. 1).

2.2. Measurements of environmental chemicals

Our analyses included data on environmental chemicals from four NHANES cycles, covering the period from 2005 to 2012. Urine samples were processed, dispensed, and frozen at −20 degrees Celsius until assayed. To avoid bias in the estimation of the types of substances below the limit of detection (LOD), only samples with detectable environmental contaminants in at least 65 % of the samples were included in our analyses (Johnson et al., 2021; Saadati et al., 2013). Results below the detection limit are expressed as the detection limit divided by the square root of two (Aimuzi et al., 2023). A total of 28 environmental pollutants were included, including three phenols, nine PAHs, three metals, and 11 phthalates (Supplementary Table 1). Laboratory test methods for phenols, PAHs, metals, and phthalates and the 28 adopted environmental chemicals are described in detail in the Supplementary Material.

2.3. Assessment of MetS and its components

MetS was defined by the presence of at least three of the following conditions: hypertension, hypertriglyceridemia, low HDL-C, hyperglycemia, and central obesity (Yoon et al., 2021). The specific diagnostic criteria were as follows (Grundy et al., 2004): (1) hypertension: systolic blood pressure (SBP) $\geq$ 130 mmHg, diastolic blood pressure (DBP) $\geq$85 mmHg, or undergoing antihypertensive therapy; (2) central obesity: waist circumference $\geq$102 cm for men and $\geq$88 cm for women; (3) hyperglycemia: fasting blood glucose $\geq$100 mg/dL or receiving antihyperglycaemic therapy; (4) low HDL-C: serum HDL-C < 40 mg/dL for men and <50 mg/dL for women; (5) hypertriglyceridemia: serum triglycerides of $\geq$150 mg/dL.

2.4. Covariates

We initially included the following variables as covariates in our analysis, based on the directed acyclic graph (Supplementary Fig. 2) and previous literatures (Che et al., 2023; Li et al., 2023b; Lo et al., 2021): age, sex, race/ethnicity, education, marital status, poverty income ratio (PIR), BMI, smoking, physical activity, and alcohol intake. Specifically, age was treated as continuous. The classification of race/ethnicity included Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other/multi-racial groups, with the 'Other' category encompassing individuals identifying as Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, or those reporting more than one race. PIR represented the ratio of household income to the poverty threshold and was considered a categorical variable with three levels: <1, 1 $\leq$ PIR $\leq$ 3, and PIR > 3. Marital status includes married/cohabiting, widowed/divorced, separated/never married. Educational attainment was categorized as follows: less than 9th grade, 9th–11th grade, high school graduation/General Educational Development (GED) or equivalent, some college/associate's degree, college or higher. Physical activity was assessed through self-reported responses to questions regarding the frequency and intensity of exercise, such as ``In the past 30 days, how often did you engage in vigorous physical activities for at least 10 min at a time?'' and ``In the past 30 days, how often did you engage in moderate-intensity physical activities for at least 10 min at a time?''. Alcohol intake was assessed by asking participants, ``Have you ever consumed at least 12 alcoholic drinks in your lifetime?'' and ``During the past 12 months, how many days did you have at least one alcoholic drink?''. Never smokers were individuals who had smoked fewer than 100 cigarettes in their lifetime, while former smokers were those who had smoked more than 100 cigarettes but were not currently smoking at the time of the survey. Current smokers referred to individuals with a history of smoking over 100 cigarettes and still actively smoking during the survey period.

2.5. Statistical analysis

For demographic characteristics, mean and standard deviation (SD) were used to represent continuous variables, while proportions indicating the presence or absence of MetS were employed for categorical variables. For normally distributed data, we used the *t*-test, and for skewed variables, the Wilcoxon rank sum test was used for between-group comparisons. For the test of differences in categorical variables, we used the chi-square test. Given that the distributions of all environmental chemicals were right-skewed, we applied a natural logarithmic transformation (ln-transformation) to enhance the normality of the data. We also adjusted the environmental chemical concentrations based on urinary creatinine levels to account for varying dilution levels in urine samples. The MetS and its components were analyzed as binary outcomes. We compared the distribution of various environmental chemicals by the presence of the MetS and its components. Additionally, survey weights were applied to ensure that the results reflect nationally representative estimates.

In addition, we constructed regularized partial correlation networks to capture the association between pairs of environmental chemicals. Graphical lasso was used to estimate the sparse inverse covariance matrix (Epskamp and Fried, 2018). The method introduces L1 regularisation to achieve matrix sparsity, which pushes some elements of the inverse covariance matrix to zero. This sparse inverse covariance matrix reveals the direct relationship between variables, independent of other variables' indirect correlations. In a biased correlation network graph, each node represents an environmental chemical, and the weights of the edges indicate the biased correlation coefficients, with red edges representing positive correlations, while blue edges indicating negative correlations.

To explore in depth the association of multiple environmental chemicals with MetS and its components, we employed a composite statistical approach. First, for the association of individual environmental chemicals with MetS, we used standard multivariable logistic regression with post hoc false discovery rate (FDR) correction (Benjamini and Hochberg, n.d.) to reduce false positive rate caused by multiple comparisons. Next, we applied the LASSO regression, Boruta algorithm, and extreme gradient boosting (XGBoost) regression for feature selection, aiming to identify the most relevant environmental chemicals related to MetS. Environmental chemicals identified across all three methods were selected for the final analysis. Finally, we used WQS regression to estimate the cumulative effect of the screened environmental chemical mixtures on MetS. We further stratified the analysis by smoking status to explore potential effect modification due to smoking.

We also conducted several sensitivity analyses, as follows. (1) We also used quantile based g-computation (QGC) and random forest (RF) model to investigate the effect weights of different environmental chemicals on MetS. (2) Given the potential interactions between environmental chemicals, we also introduced the h-statistic to detect potential interactions between these chemicals (Jerome and Bogdan, n.d.). A value of 0 for the h-statistic indicates no interaction, whereas a value of 1 indicates that the observed changes can be explained entirely by interactions between the input features. (3) A restricted cubic spline generalized additive model (GAM) was used to fit univariate exposure-response relationship curves. Detailed methods of LASSO regression, Boruta algorithm, XGBoost regression, WQS, QGC and RF model were described in Supplementary Material. All data analyses were performed in R 4.3.1 with a significance level of 0.05.

3. Results

3.1. Demographic characteristics

The mean (standard deviation (SD)) age of 2596 participants was 48.4 (17.9) years. 49.7 % were men. Compared to those without Mets, participants with MetS were older, had higher proportion of non-Hispanic white ethnicity and lower education, were married/living with partner, had lower PIR, higher BMI, lower physical activity, more current smokers and alcohol users (*P* form <0.001 to 0.001) (Table 1). The concentrations of four environmental chemical groups including 28 chemicals by MetS and its components were shown in Supplementary Table 2.

3.2. Association of individual environmental chemicals with MetS

After adjusting for age, sex, body mass index, race/ethnicity, marital status, education, poverty income ratio, physical activity, alcohol, and smoking, higher 2-Phenanthrene (2-PHE) and mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) levels were associated with an higher odds of MetS (OR = 4.26, 95 % CI 2.40–7.58 per ng/L, and 3.24, 1.75–6.02 per ng/mL, respectively). Additionally, 2-PHE was associated with a higher odds of hyperglycemia, low HDL-C, hypertriglyceridemia and central obesity. Of the three metals, only higher Hg was associated with higher odds of hyperglycemia (1.15, 1.00–1.31 per ug/L). Furthermore, higher Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) was associated with higher odds of low HDL-C (1.47, 1.01–2.12 per ng/mL) and hypertension (1.67, 1.11–2.53 per ng/mL) (Fig. 1, Supplementary Table 3). The correlations between these 28 environmental chemicals were ranged from −0.27 to 0.54, with chemicals of the same category tend to cluster together, and showing positive correlations (Fig. 2).

3.3. Environment chemicals associated with MetS by feature selection

Using LASSO regression, Boruta algorithm and XGBoost regression, we identified 16, 15, and 10 environmental chemicals associated with MetS, respectively. Comparing the screening results from these three methods, we found nine environmental chemicals identified by all. These nine environmental chemicals included four categories, as follows: (1) phenols (benzophenone-3 (BP-3)), (2) PAHs (2-Naphthalene (2-NAP), 3-Phenanthrene (3-PHE), 2-Phenanthrene (2-PHE), 1-Pyrene (1-PYR)), (3) metals (lead (Pb)), and (4) phthalates (mono-(2-ethyl)-hexyl phthalate (MEHP), MEHHP, MECPP) (Table 2, Supplementary Fig. 3).

Table 1
Sample characteristics in all participants and by the presence of metabolic syndrome (MetS).

Characteristics	Total (*n* = 2596)	No MetS (*n* = 1817)	MetS (*n* = 779)	*P*-value
Age [years, mean (SD)]	48.4 (17.9)	45.1 (17.7)	55.2 (16.2)	**<0.001**
Sex [*n* (%)]				0.20
Men	1291 (49.7)	881 (50.6)	410 (48.0)	
Women	1305 (50.3)	860 (49.4)	445 (52.0)	
Race/ethnicity [*n* (%)]				**<0.001**
Mexican American	412 (15.9)	252 (14.5)	160 (18.7)	
Other Hispanic	225 (8.7)	156 (9.0)	69 (8.1)	
Non-Hispanic White	1241 (47.8)	809 (46.5)	432 (50.5)	
Non-Hispanic Black	515 (19.8)	362 (20.8)	153 (17.9)	
Other/multi-racial	203 (7.8)	162 (9.2)	41 (4.8)	
Education [*n* (%)]				**<0.001**
Less than 9th grade	277 (10.7)	156 (9.0)	121 (14.2)	
9th-11th grade	390 (15.0)	233 (13.4)	157 (18.4)	
High School grad/GED or equivalent	601 (23.2)	370 (21.3)	231 (27.0)	
College or AA degree	718 (27.7)	504 (28.9)	214 (25.0)	
College Grad or Above	610 (23.4)	478 (27.4)	132 (15.4)	
Marital Status [*n* (%)]				**<0.001**
Married/living with partner	1589 (61.2)	1041 (59.8)	548 (64.1)	
Widowed/divorced/ separated	549 (21.1)	332 (19.1)	217 (25.4)	
Single/never married	458 (17.7)	368 (21.1)	90 (10.5)	
Poverty income ratio [*n* (%)]				**<0.001**
<1	532 (20.5)	341 (19.6)	191 (22.3)	
1–3	1070 (41.2)	682 (39.2)	388 (45.4)	
>3	994 (38.3)	718 (41.2)	276 (32.3)	
BMI [kg/m2, mean (SD)]	29.0 (6.6)	27.1 (5.8)	33.0 (6.5)	**<0.001**
Physical activity [*n* (%)]				**<0.001**
Low	1275 (49.1)	759 (43.6)	516 (60.4)	
High	1321 (50.9)	982 (56.4)	339 (39.6)	
Smoking [*n* (%)]				**<0.001**
Never	1403 (54.0)	1002 (57.6)	401 (46.9)	
Former	633 (24.4)	376 (21.6)	257 (30.1)	
Current	560 (21.6)	363 (20.8)	197 (23.0)	
Alcohol [*n* (%)]				**0.001**
No	1788 (68.9)	1237 (71.1)	551 (64.4)	
Yes	808 (31.1)	504 (28.9)	304 (35.6)	

Note: Continuous variables were presented as mean±standard deviation (SD). Categorical variables were presented as *n* (%). MetS, metabolic syndrome; BMI, body mass index. Values in bold font are statistically significant ($P < 0.05$).

3.4. Association of multiple environmental chemicals with MetS

The nine environmental chemicals identified were included in the WQS regression to generate a composite index for combined exposure (i.e., WQS index). The WQS index showed a positive association with MetS (OR = 1.31, 95 % CI: 1.09–1.57), hyperglycemia (1.30, 1.10–1.55), low HDL-C (1.20, 1.01–1.43), hypertriglyceridemia (1.32, 1.12–1.55), and central obesity (1.51, 1.16–1.98) (Table 3). No association with hypertension was observed. Of the five outcomes showing significant associations, 2-PHE showed the highest estimated weight regarding the associations with MetS, hyperglycemia, hypertriglyceridemia, and central obesity (Fig. 3, Supplementary Figs. 4 and 5), with WQS weights being 0.46, 0.28, 0.56, and 0.53, respectively, while 2-NAP showed the highest estimated weight for low HDL-C (WQS weight = 0.49) (Supplementary Table 4).

In addition, the WQS index showed a significant interaction with smoking status in terms of the association with MetS (P for interaction =

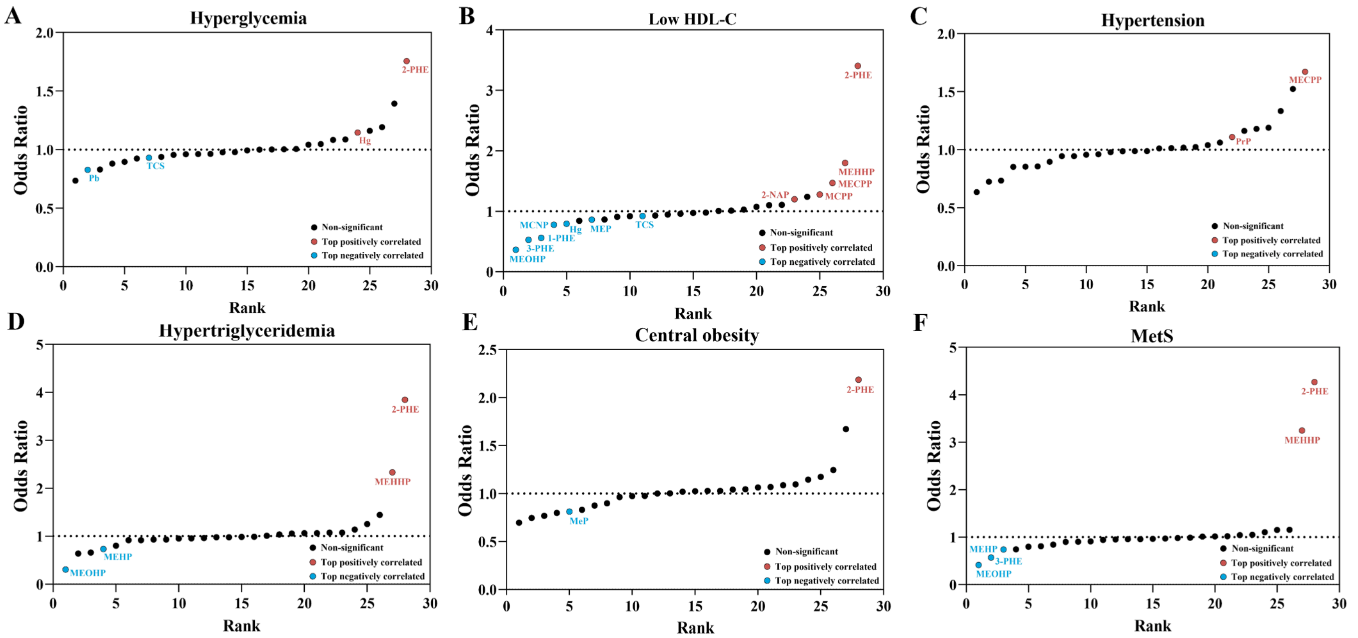

Fig. 1. Associations between environmental chemicals and hyperglycemia (A), Low HDL-C (B), hypertension (C), hypertriglyceridemia (D), central obesity (E), and MetS (F) in logistic regression.
Note: (1) Red indicates a positive correlation between the environmental chemical and MetS or its components, while blue indicates a negative correlation. (2) All models were adjusted for age, sex, race/ethnicity, education, marital status, poverty income ratio, BMI, physical activity, smoking, alcohol.

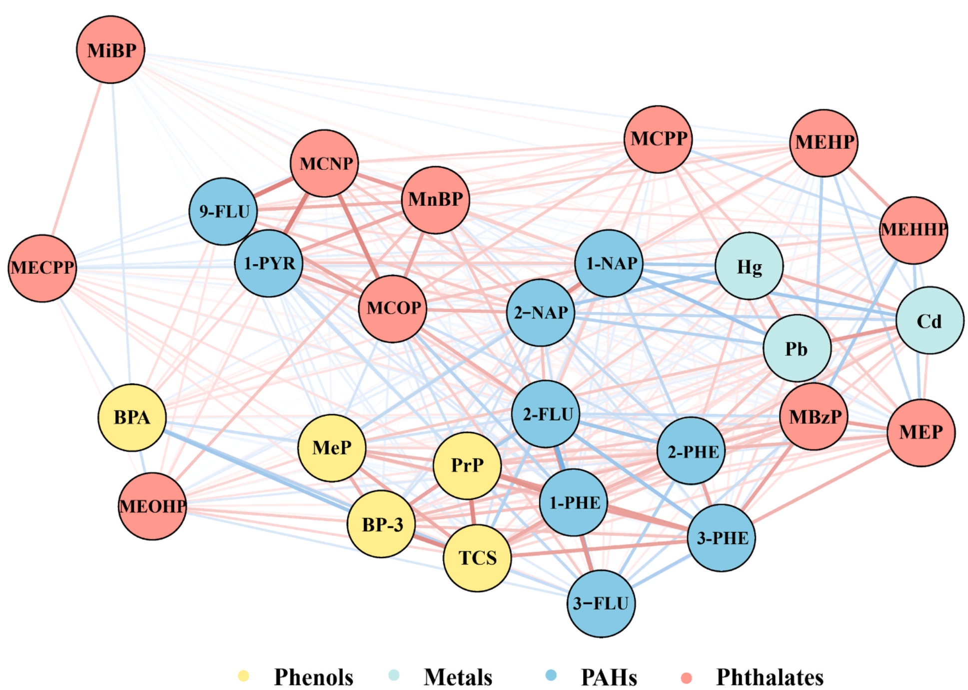

Fig. 2. Regularized partial correlation network.
Note: (1) Red edges indicate positive correlations and blue edges indicate negative correlations. (2) Edge weights indicate partial correlation coefficients.

0.01). After stratifying by smoking status, the association of WQS index with MetS was more pronounced in the current smokers than the never smokers (OR and 95 % CI 1.54 (1.04–2.30) versus 1.27 (0.94–1.73)) (Table 4). Specifically, we observed consistent and stronger positive associations with hypertriglyceridemia (OR = 1.71, 95 % CI 1.22–2.40) and low HDL-C (1.40, 1.06–1.85) in current smokers. In the current smokers, the first three greatest estimated weights of MetS-related chemicals were 2-PHE (WQS weight = 0.33), 1-PYR (WQS weight = 0.22), and Pb (WQS weight = 0.18) (Supplementary Table 5).

3.5. *Sensitivity analyses*

First, in the QGC model, we observed that chemicals such as 2-PHE, MEHHP, and Pb continued to carry more weight in association with MetS and its components (Supplementary Fig. 6, Supplementary Table 6). Second, we assessed the importance of environmental

Table 2
Association of environmental chemicals with MetS using LASSO regression, Boruta algorithm, and XGBoost regression.

Environmental chemicals		LASSO regression[†]	Boruta algorithm[†]	XGBoost regression[†]
Phenols (ng/mL)	BPA	√	×	×
	BP-3	√	√	√
	TCS	√	×	×
	MeP	×	×	×
	PrP	√	×	×
PAHs (ng/L)	1-NAP	√	√	×
	2-NAP	√	√	√
	3-FLU	×	√	√
	2-FLU	×	√	×
	3-PHE	√	√	√
	1-PHE	×	√	×
	2-PHE	√	√	√
	1-PYR	√	√	√
	9-FLU	√	√	×
Metals (ug/L)	Cd	×	×	×
	Pb	√	√	√
	Hg	√	×	×
Phthalates (ng/mL)	MCNP	×	×	×
	MCOP	×	×	×
	MnBP	√	×	×
	MEP	×	×	×
	MEHP	√	√	√
	MBzP	×	×	×
	MCPP	×	×	×
	MEHHP	√	√	√
	MEOHP	×	√	×
	MiBP	×	×	×
	MECPP	√	√	√

MetS, metabolic syndrome; PAHs, polycyclic aromatic hydrocarbons; LASSO regression, least absolute shrinkage and selection operator regression; XGBoost regression, extreme gradient boosting regression.

[†] : ``√'' and ``×'' represent whether the environmental chemical was associated with MetS, respectively.

Table 3
Associations of WQS index with MetS and its components.

Outcome	WQS direction[‡]	OR (95 % CI)[†]	*P*-value
Hyperglycemia	N	1.15 (0.96–1.37)	0.14
	P	1.30 (1.10–1.55)	**0.003**
Low HDL-C	N	0.95 (0.79–1.14)	0.61
	P	1.20 (1.01–1.43)	**0.04**
Hypertension	N	0.99 (0.86–1.14)	0.85
	P	1.01 (0.84–1.21)	0.94
Hypertriglyceridemia	N	0.97 (0.79–1.20)	0.81
	P	1.32 (1.12–1.55)	**<0.001**
Central obesity	N	1.51 (1.11–2.06)	0.01
	P	1.51 (1.16–1.98)	**0.002**
MetS	N	1.11 (0.88–1.39)	0.39
	P	1.31 (1.09–1.57)	**0.003**

MetS, metabolic syndrome; Low HDL-C, low high density cholesterol; OR, Odds Ratio; CI, confidence interval; WQS, weighted quantile sum. Values in bold font are statistically significant ($P < 0.05$).

[†] All models were adjusted for age, sex, race/ethnicity, education, marital status, poverty income ratio, BMI, physical activity, smoking, alcohol.

[‡] "N" and "P" indicate the association in WQS analyses was assumed in negative and positive direction, respectively.

chemicals using the RF model and observed that 2-PHE and MEHHP remained the two most important environmental chemicals in their effects on MetS (Supplementary Fig. 7). Third, h-statistic results suggested that there was no significant interaction between the different environmental chemicals (Supplementary Figure 8). Fourth, a positive association was observed between 2-PHE, MEHHP, and MetS and its components in the dose-response analysis (Supplementary Figs. 9–14).

4. Discussion

Using a robust statistical methodology that included machine learning and regression models, our study demonstrated that higher exposure to phenols, PAHs, metals, and phthalates was associated with higher odds of MetS and its components. Moreover, a composite index (WQS index) derived from nine identified chemicals demonstrated positive associations with MetS and some of its components, with more pronounced effects noticed among current smokers. Our results highlight the critical public health implication of addressing environmental pollutants as modifiable risk factors for MetS.

Phenols, PAHs, metals, and phthalates are widely recognized as EDCs (Braun, 2017; Fan et al., 2023) that can significantly impact health through various mechanisms (Monneret, 2017; Sun et al., 2022). A recent study showed that the association of EDCs with MetS was primarily through disruption of insulin and glucose metabolism (Vanni et al., 2021). For example, phenols and phthalates have been involved in pancreatic β-cell dysfunction, increasing the risk of obesity and insulin resistance through mechanisms involving oxidative stress and inflammation (Lin et al., 2011). Furthermore, proteomic studies showed that phthalates and their metabolites interfere with lipid storage mechanisms, leading to impaired insulin sensitivity and adipokines secretion (Ellero-Simatos et al., 2011; Liu et al., 2022a). Furthermore, proteomic studies showed that phthalates and their metabolites interfere with lipid storage mechanisms, leading to impaired insulin sensitivity and adipokines secretion (Blüher, 2012; Piya et al., 2013). Disruption of adipokine secretion by phthalates may thus contribute to the development of insulin resistance and obesity (Hsia et al., 2022; Schaffert et al., 2022), particularly in populations with high environmental exposure (Liu et al., 2022a; Xu et al., 2021).

Similarly, PAHs are highly soluble in lipids, easily absorbed by the gastrointestinal tract, and tend to accumulate in adipose tissue across various organs (Kumari et al., 2023). Existing experimental evidence indicates that exposure to PAHs affects lipid metabolism in adipose tissue, leading to an increase in body weight and fat mass (Irigaray et al., 2006). Furthermore, PAHs may form more active metabolites when metabolized by host cell enzymes, resulting in stronger toxicity (Shimada and Fujii-Kuriyama, 2004). Previous studies showed that higher levels of PAH exposure were associated with higher prevalence of MetS components, such as increased waist circumference, hyperglycemia, and dyslipidemia (Li et al., 2023c; Shahsavani et al., 2021). Phthalates have been shown to disrupt endocrine functions, leading to long-term metabolic disturbances such as insulin resistance and dyslipidemia, primarily through oxidative stress pathways (Kim et al., 2013a). In contrast, PAHs were associated with hypertension and obesity via mechanisms involving inflammation and oxidative stress, contributing to a higher risk of MetS (Mallah et al., 2021; Zhou et al., 2023). Furthermore, exposure to metals such as mercury and cadmium might impair insulin signalling and exacerbate oxidative stress, thereby increasing the risk of MetS (Masenga et al., 2023).The impact of metal exposure on metabolic health also warrants attention. Metals such as arsenic, cadmium, and lead have also been identified as significant contributors to MetS development. These metals disrupt insulin signaling pathways, leading to insulin resistance and impaired glucose metabolism (Paithankar et al., 2021). Chronic exposure to these metals was associated with increased oxidative stress, inflammation, and mitochondrial dysfunction, all of which are key factors in the pathogenesis of MetS (Haidar et al., 2023). A recent review and meta-analysis reinforced the association between metal exposure and MetS risk, highlighting the need for continued monitoring and regulation of these environmental contaminants (Caito and Aschner, 2015).

Our study showed that 2-PHE and MEHHP had the greatest weights among the nine environmental chemicals in the association with MetS after accounting for the context of mixed exposures. 2-PHE is a category of PAHs that predominantly permeates the human physiological system via various environmental vectors, including tobacco smoke inhalation,

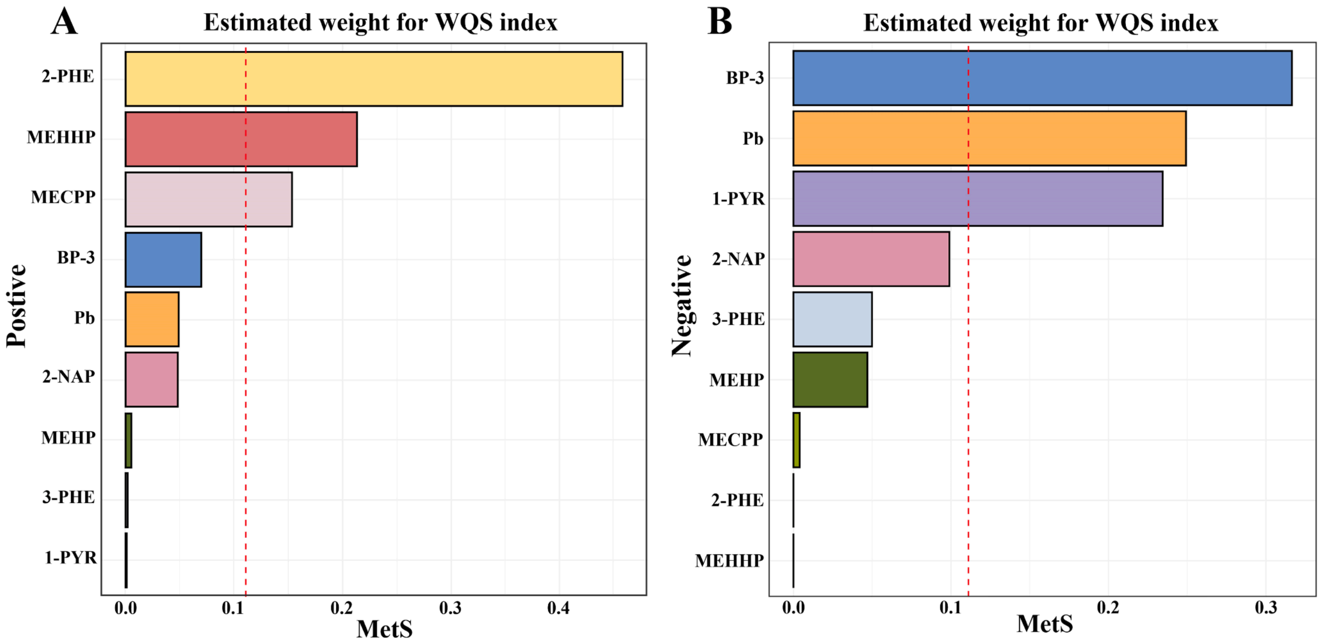

Fig. 3. Index weights from WQS model regression on association between different categories of environmental chemicals and MetS.
Note: (1) Two independent WQS indices were generated, one modelled in the positive direction (A) and one modelled in the opposite direction to the MetS (B). (2) The red dashed line is the reference standard for the weighting measure: 1/N. N is the type of environmental pollutant. (3) All models were adjusted for age, sex, race/ethnicity, education, marital status, poverty income ratio, BMI, physical activity, smoking, alcohol.

Table 4
Associations of WQS index with MetS and its components by smoking status.

Smoking status	WQS direction‡	Hyperglycemia OR (95 % CI)†	Low HDL-C OR (95 % CI)†	Hypertension OR (95 % CI)†	Hypertriglyceridemia OR (95 % CI)†	Central obesity OR (95 % CI)†	MetS OR (95 % CI)†
Never	N	1.09 (0.89–1.33)	0.73 (0.54–1.01)	1.08 (0.83–1.42)	0.87 (0.67–1.12)	1.06 (0.69–1.62)	0.92 (0.73–1.15)
	P	1.24 (0.94–1.63)	0.91 (0.70–1.18)	1.25 (0.94–1.65)	1.19 (0.94–1.52)	1.05 (0.72–1.53)	1.27 (0.94–1.73)
Former	N	0.85 (0.59–1.22)	1.14 (0.75–1.74)	1.28 (0.87–1.87)	1.04 (0.72–1.50)	1.24 (0.70–2.19)	1.12 (0.77–1.64)
	P	1.24 (0.86–1.78)	**1.61 (1.06–2.47)**	1.19 (0.85–1.67)	0.84 (0.60–1.16)	1.27 (0.69–2.35)	1.30 (0.87–1.93)
Current	N	1.12 (0.75–1.67)	0.83 (0.55–1.25)	1.02 (0.73–1.43)	1.18 (0.85–1.64)	1.18 (0.62–2.24)	0.92 (0.55–1.54)
	P	1.22 (0.86–1.74)	**1.40 (1.06–1.85)**	1.02 (0.65–1.61)	**1.71 (1.22–2.40)**	1.50 (0.85–2.63)	**1.54 (1.04–2.30)**

MetS, metabolic syndrome; Low HDL-C, low high density cholesterol; OR, Odds Ratio; CI, confidence interval; WQS, weighted quantile sum. Values in bold font are statistically significant ($P < 0.05$).
† All models were adjusted for age, sex, race/ethnicity, education, marital status, poverty income ratio, BMI, physical activity, alcohol.
‡ "N" and "P" indicate the association in WQS analyses was assumed in negative and positive direction, respectively.

atmospheric pollutant exposure, and culinary processes (Joksić et al., 2022). Exposure to environmental chemicals such as 2-PHE and MEHHP may influence metabolic health through multiple pathways. 2-PHE, a polycyclic aromatic hydrocarbon, is known to disrupt endocrine functions, potentially by interacting with estrogen receptors (Haverinen et al., 2021; Sun et al., 2021; Zhang et al., 2016), thereby affecting metabolic processes linked to MetS. Experimental studies have suggested that PAHs like 2-PHE may alter lipid metabolism and promote adipogenesis, leading to increased fat accumulation and insulin resistance (Irigaray et al., 2006; Mustieles et al., 2017). Similarly, MEHHP, a metabolite of phthalates, is implicated in metabolic disruption via the activation of peroxisome proliferator-activated receptor alpha (PPARα), which may play an important role in lipid metabolism and oxidative stress responses (Feige et al., 2010). This activation may contribute to the development of insulin resistance and other components of MetS (Perez-Diaz et al., 2024). The pronounced associations of 2-PHE and MEHHP with MetS observed in our study likely reflet their specific endocrine-disrupting properties and their widespread environmental presence. In contrast, other chemicals may exhibit weaker associations due to their differing metabolic pathways, exposure routes, or less significant effects on key metabolic processes. For example, chemicals with lower bioavailability or weaker receptor-binding affinities might not elicit as strong a metabolic response, resulting in non-significant associations.

Our findings also indicate that the association between multiple environmental chemical exposure and MetS were more pronounced in current smokers, suggesting that smoking-induced oxidative stress may amplify the adverse effects of endocrine-disrupting chemicals on metabolic health (Caliri et al., 2021; Lee et al., 2022). These results highlight the importance of considering both lifestyle and environmental factors in MetS prevention strategies. We recommend that policymakers strengthen regulatory efforts to reduce environmental pollutants and promote tobacco control measures, while healthcare providers should prioritize screening and education on reducing exposure to harmful chemicals. Further studies are warranted to explore the combined effects of EDCs and smoking on MetS and to evaluate the effectiveness of interventions aimed at mitigating these risks.

Our research possessed numerous strengths. To our understanding, this study represents the initial attempt to comprehensively explore the association of phenols, PAHs, metals, and phthalates on MetS and its components. Furthermore, we used a robust statistical framework integrating multiple methods to analyze the single and cumulative effects of different environmental chemicals on MetS and its components. However, some limitations warrant consideration. First, due to the cross-sectional nature of this study, causal associations between environmental chemicals and MetS cannot be confirmed, although the inverse direction, i.e., the presence of MetS led to the exposure of environmental chemicals, is very unlikely. Second, biomonitoring of urine could not accurately quantify exposure to more toxic PAHs, thus compromising precision in estimating PAH exposure. Finally, concentrations of metabolites in urine at a single time point may not be representative of long-term exposure and may not accurately reflect associations with progressive changes leading to MetS.

5. Conclusion

In conclusion, our mixture analysis revealed a significant and novel association between exposure to multiple environmental chemicals, including phenols, PAHs, metals, and phthalates, and an increased risk of metabolic syndrome and its components. This association was particularly pronounced in current smokers, suggesting a higher vulnerability in this group to the harmful effects of these exposures. These findings underscore the urgent need for targeted preventive and regulatory interventions to reduce chemical exposures, especially in high-risk groups such as smokers, to address the rising public health burden of metabolic diseases in the context of increasing environmental challenges.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by National Center for Health Statistics (NCHS) and the NCHS Institutional Review Board (IRB). The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Funding

This work was funded by the National Natural Science Foundation of China (82373661).

CRediT authorship contribution statement

Ruiqiang Li: Writing – review & editing, Writing – original draft, Conceptualization. **Xiaoyi Lin:** Resources, Data curation. **Tingyu Lu:** Validation, Software. **Jiao Wang:** Software, Methodology. **Ying Wang:** Resources, Data curation. **Lin Xu:** Writing – review & editing, Validation, Supervision, Project administration.

Declaration of competing interest

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heha.2024.100112.

References

Aimuzi, R., Xie, Z., Qu, Y., Jiang, Y., Luo, K., 2023. Associations of urinary organophosphate esters metabolites and diet quality with nonalcoholic/metabolic dysfunction-associated fatty liver diseases in adults. Ecotoxicol. Environ. Saf. 254, 114720.
Ashley, D.L., Smith, M.M., Silva, L.K., Yoo, Y.M., De Jesús, V.R., Blount, B.C., 2020. Factors associated with exposure to trihalomethanes, NHANES 2001–2012. Environ. Sci. Technol. 54, 1066–1074.
Benjamini, Y., Hochberg, Y., Controlling the false discovery rate: a practical and powerful approac.
Blüher, M., 2012. Clinical relevance of adipokines. Diabetes Metab. J. 36, 317–327.
Braun, J.M., 2017. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat. Rev. Endocrinol. 13, 161–173.
Bulka, C.M., Persky, V.W., Daviglus, M.L., Durazo-Arvizu, R.A., Argos, M., 2019. Multiple metal exposures and metabolic syndrome: a cross-sectional analysis of the national health and nutrition examination survey 2011–2014. Environ. Res. 168, 397–405.
Caito, S.W., Aschner, M., 2015. Mitochondrial redox dysfunction and environmental exposures. Antioxid. Redox Signal 23, 578–595.
Caliri, A.W., Tommasi, S., Besaratinia, A., 2021. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat. Res. Rev. Mutat. Res. 787, 108365.
Che, Z., Jia, H., Chen, R., Pan, K., Fan, Z., Su, C., Wu, Z., Zhang, T., 2023. Associations between exposure to brominated flame retardants and metabolic syndrome and its components in U.S. adults. Sci. Total. Environ. 858, 159935.
Cornier, M.A., Dabelea, D., Hernandez, T.L., Lindstrom, R.C., Steig, A.J., Stob, N.R., Van Pelt, R.E., Wang, H., Eckel, R.H., 2008. The metabolic syndrome. Endocr. Rev. 29, 777–822.
Deyssenroth, M.A., Gennings, C., Liu, S.H., Peng, S., Hao, K., Lambertini, L., Jackson, B. P., Karagas, M.R., Marsit, C.J., Chen, J., 2018. Intrauterine multi-metal exposure is associated with reduced fetal growth through modulation of the placental gene network. Environ. Int. 120, 373–381.
Eckel, R.H., Grundy, S.M., Zimmet, P.Z., 2005. The metabolic syndrome. Lancet 365, 1415–1428.
Ellero-Simatos, S., Claus, S.P., Benelli, C., Forest, C., Letourneur, F., Cagnard, N., Beaune, P.H., de Waziers, I., 2011. Combined transcriptomic-(1)H NMR metabonomic study reveals that monoethylhexyl phthalate stimulates adipogenesis and glyceroneogenesis in human adipocytes. J. Proteome Res. 10, 5493–5502.
Epskamp, S., Fried, E.I., 2018. A tutorial on regularized partial correlation networks. Psychol. Methods 23, 617–634.
Eze, I.C., Schaffner, E., Foraster, M., Imboden, M., von Eckardstein, A., Gerbase, M.W., Rothe, T., Rochat, T., Künzli, N., Schindler, C., Probst-Hensch, N., 2015. Long-term exposure to ambient air pollution and metabolic syndrome in adults. PLoS One 10, e0130337.
Fan, Y., Tao, C., Li, Z., Huang, Y., Yan, W., Zhao, S., Gao, B., Xu, Q., Qin, Y., Wang, X., Peng, Z., Covaci, A., Li, Y., Xia, Y., Lu, C., 2023. Association of endocrine-disrupting chemicals with all-cause and cause-specific mortality in the U.S.: a prospective cohort study. Environ. Sci. Technol. 57, 2877–2886.
Feige, J.N., Gerber, A., Casals-Casas, C., Yang, Q., Winkler, C., Bedu, E., Bueno, M., Gelman, L., Auwerx, J., Gonzalez, F.J., Desvergne, B., 2010. The pollutant diethylhexyl phthalate regulates hepatic energy metabolism via species-specific PPARalpha-dependent mechanisms. Environ. Health Perspect. 118, 234–241.
Grundy, S.M., Brewer Jr., H.B., Cleeman, J.I., Smith Jr., S.C., Lenfant, C., 2004. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 109, 433–438.
Haidar, Z., Fatema, K., Shoily, S.S., Sajib, A.A., 2023. Disease-associated metabolic pathways affected by heavy metals and metalloid. Toxicol. Rep. 10, 554–570.
Haverinen, E., Fernandez, M.F., Mustieles, V., Tolonen, H., 2021. Metabolic syndrome and endocrine disrupting chemicals: an overview of exposure and health effects. Int. J. Environ. Res. Public Health 18, 13047.
Hsia, T.I., Huang, P.C., Chen, H.C., Lo, Y.C., Chang, W.T., Jou, Y.Y., Huang, H.B., 2022. Relationships among phthalate exposure, oxidative stress, and insulin resistance in young military soldiers: a cumulative risk assessment and mediation approach. Environ. Int. 165, 107316.
Irigaray, P., Ogier, V., Jacquenet, S., Notet, V., Sibille, P., Méjean, L., Bihain, B.E., Yen, F. T., 2006. Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. FEBS J. 273, 1362–1372.
Jeong, H.S., 2018. The relationship between workplace environment and metabolic syndrome. Int. J. Occup. Environ. Med. 9, 176–183.
Jerome, H.F., Bogdan, E.P., Predictive learning via rule ensembles.
Johnson, C.L., Jazan, E., Kong, S.W., Pennell, K.D., 2021. A two-step gas chromatography-tandem mass spectrometry method for measurement of multiple environmental pollutants in human plasma. Environ. Sci. Pollut. Res. Int. 28, 3266–3279.
Jokšić, A., Tratnik, J.S., Mazej, D., Kocman, D., Stajnko, A., Eržen, I., Horvat, M., 2022. Polycyclic aromatic hydrocarbons (PAHs) in men and lactating women in Slovenia: results of the first national human biomonitoring. Int. J. Hyg. Environ. Health 241, 113943.
Kassi, E., Pervanidou, P., Kaltsas, G., Chrousos, G., 2011. Metabolic syndrome: definitions and controversies. BMC Med. 9, 48.
Kim, J.H., Park, H.Y., Bae, S., Lim, Y.H., Hong, Y.C., 2013a. Diethylhexyl phthalates is associated with insulin resistance via oxidative stress in the elderly: a panel study. PLoS One 8, e71392.
Kim, K.H., Jahan, S.A., Kabir, E., Brown, R.J., 2013b. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ. Int. 60, 71–80.
Kumari, A., Upadhyay, V., Kumar, S., 2023. A critical insight into occurrence and fate of polycyclic aromatic hydrocarbons and their green remediation approaches. Chemosphere 329, 138579.

Lee, K.I., Han, Y., Ryu, J.S., In, S.M., Kim, J.Y., Park, J.S., Kim, J.S., Kim, J., Youn, J., Park, S.R., 2022. Tobacco smoking could accentuate epithelial-mesenchymal transition and Th2-type response in patients with chronic rhinosinusitis with nasal polyps. Immune Netw. 22, e35.

Li, H., Yao, C., He, C., Yu, H., Yue, C., Zhang, S., Li, G., Ma, S., Zhang, X., Cao, Z., An, T., 2023a. Coking-produced aromatic compounds in urine of exposed and nonexposed populations: exposure levels, source identification, and model-based health implications. Environ. Sci. Technol. 57, 15379–15391.

Li, W., Chen, D., Peng, Y., Lu, Z., Kwan, M.P., Tse, L.A., 2023b. Association between metabolic syndrome and mortality: prospective cohort study. JMIR Public Health Surveill. 9, e44073.

Li, W., Chen, D., Peng, Y., Lu, Z., Wang, D., 2023c. Association of polycyclic aromatic hydrocarbons with systemic inflammation and metabolic syndrome and its components. Obesity (Silver Spring) 31, 1392–1401.

Lin, Y., Wei, J., Li, Y., Chen, J., Zhou, Z., Song, L., Wei, Z., Lv, Z., Chen, X., Xia, W., Xu, S., 2011. Developmental exposure to di(2-ethylhexyl) phthalate impairs endocrine pancreas and leads to long-term adverse effects on glucose homeostasis in the rat. Am. J. Physiol. Endocrinol. Metab. 301, E527–E538.

Liu, L., Li, X., Wu, M., Yu, M., Wang, L., Hu, L., Li, Y., Song, L., Wang, Y., Mei, S., 2022a. Individual and joint effects of metal exposure on metabolic syndrome among Chinese adults. Chemosphere 287, 132295.

Liu, S., Pai, M.P., Lester, C.A., 2022b. Medication use among U.S. adults after bariatric surgery: a population-based analysis of NHANES 2015–2018. Diabetes Care 45, e54–e55.

Lo, K., Yang, J.L., Chen, C.L., Liu, L., Huang, Y.Q., Feng, Y.Q., Yang, A.M., 2021. Associations between blood and urinary manganese with metabolic syndrome and its components: cross-sectional analysis of National Health and Nutrition Examination Survey 2011–2016. Sci. Total. Environ. 780, 146527.

Mallah, M.A., Mallah, M.A., Liu, Y., Xi, H., Wang, W., Feng, F., Zhang, Q., 2021. Relationship between polycyclic aromatic hydrocarbons and cardiovascular diseases: a systematic review. Front. Public Health 9, 763706.

Masenga, S.K., Kabwe, L.S., Chakulya, M., Kirabo, A., 2023. Mechanisms of oxidative stress in metabolic syndrome. Int. J. Mol. Sci. 24, 7898.

Monneret, C., 2017. What is an endocrine disruptor? C. R. Biol. 340, 403–405.

Mustieles, V., Fernández, M.F., Martin-Olmedo, P., González-Alzaga, B., Fontalba-Navas, A., Hauser, R., Olea, N., Arrebola, J.P., 2017. Human adipose tissue levels of persistent organic pollutants and metabolic syndrome components: combining a cross-sectional with a 10-year longitudinal study using a multi-pollutant approach. Environ. Int. 104, 48–57.

Neier, K., Cheatham, D., Bedrosian, L.D., Gregg, B.E., Song, P.X.K., Dolinoy, D.C., 2019. Longitudinal metabolic impacts of perinatal exposure to phthalates and phthalate mixtures in mice. Endocrinology 160, 1613–1630.

Paithankar, J.G., Saini, S., Dwivedi, S., Sharma, A., Chowdhuri, D.K., 2021. Heavy metal associated health hazards: an interplay of oxidative stress and signal transduction. Chemosphere 262, 128350.

Perez-Diaz, C., Uriz-Martínez, M., Ortega-Rico, C., Leno-Duran, E., Barrios-Rodríguez, R., Salcedo-Bellido, I., Arrebola, J.P., Requena, P., 2024. Phthalate exposure and risk of metabolic syndrome components: a systematic review. Environ. Pollut. 340, 122714.

Piya, M.K., McTernan, P.G., Kumar, S., 2013. Adipokine inflammation and insulin resistance: the role of glucose, lipids and endotoxin. J. Endocrinol. 216, T1–t15.

Poursafa, P., Moosazadeh, M., Abedini, E., Hajizadeh, Y., Mansourian, M., Pourzamani, H., Amin, M.M., 2017. A systematic review on the effects of polycyclic aromatic hydrocarbons on cardiometabolic impairment. Int. J. Prev. Med. 8, 19.

Ren, C., Tong, S., 2008. Health effects of ambient air pollution–recent research development and contemporary methodological challenges. Environ. Health 7, 56.

Roy, C., Tremblay, P.Y., Ayotte, P., 2017. Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature. Environ. Res. 156, 747–760.

Saadati, N., Abdullah, M.P., Zakaria, Z., Sany, S.B., Rezayi, M., Hassonizadeh, H., 2013. Limit of detection and limit of quantification development procedures for organochlorine pesticides analysis in water and sediment matrices. Chem. Cent. J. 7, 63.

Schaffert, A., Karkossa, I., Ueberham, E., Schlichting, R., Walter, K., Arnold, J., Blüher, M., Heiker, J.T., Lehmann, J., Wabitsch, M., Escher, B.I., von Bergen, M., Schubert, K., 2022. Di-(2-ethylhexyl) phthalate substitutes accelerate human adipogenesis through PPARγ activation and cause oxidative stress and impaired metabolic homeostasis in mature adipocytes. Environ. Int. 164, 107279.

Shahsavani, S., Fararouei, M., Soveid, M., Hoseini, M., Dehghani, M., 2021. The association between the urinary biomarkers of polycyclic aromatic hydrocarbons and risk of metabolic syndromes and blood cell levels in adults in a Middle Eastern area. J. Environ. Health Sci. Eng. 19, 1667–1680.

Shimada, T., Fujii-Kuriyama, Y., 2004. Metabolic activation of polycyclic aromatic hydrocarbons to carcinogens by cytochromes P450 1A1 and 1B1. Cancer Sci. 95, 1–6.

Sun, J., Fang, R., Wang, H., Xu, D.X., Yang, J., Huang, X., Cozzolino, D., Fang, M., Huang, Y., 2022. A review of environmental metabolism disrupting chemicals and effect biomarkers associating disease risks: where exposomics meets metabolomics. Environ. Int. 158, 106941.

Sun, K., Song, Y., He, F., Jing, M., Tang, J., Liu, R., 2021. A review of human and animals exposure to polycyclic aromatic hydrocarbons: health risk and adverse effects, photo-induced toxicity and regulating effect of microplastics. Sci. Total. Environ. 773, 145403.

Teppala, S., Madhavan, S., Shankar, A., 2012. Bisphenol a and metabolic syndrome: results from NHANES. Int. J. Endocrinol. 2012, 598180.

Vanni, R., Bussuan, R.M., Rombaldi, R.L., Arbex, A.K., 2021. Endocrine disruptors and the induction of insulin resistance. Curr. Diabetes Rev. 17, e102220187107.

Xu, P., Liu, A., Li, F., Tinkov, A.A., Liu, L., Zhou, J.C., 2021. Associations between metabolic syndrome and four heavy metals: a systematic review and meta-analysis. Environ. Pollut. 273, 116480.

Yilmaz, B., Terekeci, H., Sandal, S., Kelestimur, F., 2020. Endocrine disrupting chemicals: exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. Rev. Endocr. Metab. Disord. 21, 127–147.

Yoon, S.J., Kim, S.K., Lee, N.Y., Choi, Y.R., Kim, H.S., Gupta, H., Youn, G.S., Sung, H., Shin, M.J., Suk, K.T., 2021. Effect of Korean Red Ginseng on metabolic syndrome. J. Ginseng Res. 45, 380–389.

Zhan, W., Yang, H., Zhang, J., Chen, Q., 2022. Association between co-exposure to phenols and phthalates mixture and infertility risk in women. Environ. Res. 215, 114244.

Zhang, Y., Dong, S., Wang, H., Tao, S., Kiyama, R., 2016. Biological impact of environmental polycyclic aromatic hydrocarbons (ePAHs) as endocrine disruptors. Environ. Pollut. 213, 809–824.

Zhang, Y., Dong, T., Hu, W., Wang, X., Xu, B., Lin, Z., Hofer, T., Stefanoff, P., Chen, Y., Wang, X., Xia, Y., 2019. Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity: comparison of three statistical models. Environ. Int. 123, 325–336.

Zhou, S., Li, X., Dai, Y., Guo, C., Peng, R., Qin, P., Tan, L., 2023. Association between polycyclic aromatic hydrocarbon exposure and blood lipid levels: the indirect effects of inflammation and oxidative stress. Environ. Sci. Pollut. Res. Int. 30, 123148–123163.