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Association between organophosphate esters exposure and the prevalence of hyperuricemia in US adults from NHANES 2011–2016

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Organophosphate esters (OPEs) exposure has potentially harmful effects on human health. However, the evidence between OPEs and hyperuricemia is insufficient. We aimed to assess the association between OPEs metabolites and the prevalence of hyperuricemia. Multivariable logistic regression, weighted quantile regression (WQS) model, and Bayesian kernel machine regression (BKMR) models were used to investigate the association of OPEs metabolites with the risk of hyperuricemia. Mediation analysis was conducted to assess whether inflammation mediated the effects of OPEs on the prevalence of hyperuricemia. The multivariable logistics regression indicated that bis (1,3-dichloro-2-propyl) phosphate (BDCPP) and bis-2-chloroethyl phosphate (BCEP) were positively correlated with the risk of hyperuricemia. In WQS and BKMR analyses, OPEs mixtures presented a positive association with the risk of hyperuricemia, with BDCPP being the primary contributor. C-reactive protein (CRP) and monocytes were found to mediate the association between BDCPP and the risk of hyperuricemia prevalence, with 8.46% and 3.97% of the mediated proportion, respectively. Our study revealed that OPEs mixtures were positively correlated with the prevalence of hyperuricemia, with BDCPP identified as the most significant contributor. Inflammation was a potential mechanism mediating the effect of BDCPP exposure on the risk of hyperuricemia.

Keywords Hyperuricemia, Organophosphate esters, Inflammation, NHANES, OPEs

Hyperuricemia represents a common chronic disease characterized by metabolic disorders of serum uric acid levels[1]. Recently, an increased incidence of hyperuricemia was observed in several epidemiological studies, which caused burden to over 38 million adults in the US[2]. Moreover, recent studies have identified hyperuricemia as a critical risk factor for various diseases including kidney failure, metabolic syndrome, and hypertension[3–5]. Previous studies demonstrated that genetics and diet were the main contributors to hyperuricemia[6]. However, controlling those traditional risk factors did not prevent the increased morbidity of hyperuricemia in recent years. Growing evidence has implicated that environmental pollutants are related to the prevalence of hyperuricemia[7,8]. Thus, it is imminent to discover novel environmental factors in the development of hyperuricemia.

Organophosphate esters (OPEs) represent a category of triphosphate esters characterized by alkyl or aryl groups in both halogenated and nonhalogenated forms[9]. As substitutes for brominated flame retardants, OPEs are extensive applicated in various industrial, construction, and consumer goods. OPEs are easily released into adjacent microenvironments, including dust, soil, water, and food items[10,11]. Consequently, individuals are

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commonly exposed to OPEs inadvertently via breathing, consuming, and skin interaction[12]. Previous studies have shown that OPEs typically transform diester or hydroxylated metabolites, which can be swiftly and effectively detected in urine. As a result, urinary metabolites of OPEs are regarded as suitable biomarkers for assessing exposure levels and associated risks in human[13]. However, a growing body of researches have confirmed that OPEs cause adverse health effects, including the development of diabetes, hypertension, and chronic kidney disease (CKD)[14–16]. Nevertheless, the relationships and mechanisms between OPEs and hyperuricemia have not yet been investigated.

The pathogenesis of hyperuricemia is highly complex, and remains elusive. Numerous studies have indicated that inflammation is involved in the progression of hyperuricemia[17,18]. Additionally, it has been reported that OPEs can induce inflammatory responses, which are implicated in the development of several diseases[19,20]. Consequently, we propose that OPEs were associated with the prevalence of hyperuricemia, with inflammation being a plausible underlying mechanism. First, logistic regression model was employed to evaluate the association between single OPEs and the prevalence of hyperuricemia from the National Health and Nutrition Examination Survey (NHANES) database 2011–2016. Second, the roles of OPEs co-exposure in hyperuricemia were further explored using weighted quantile regression (WQS) and Bayesian kernel machine regression (BKMR) models. Finally, we performed a mediation analysis to investigate the potential mechanism between OPEs and the prevalence of hyperuricemia.

Methods

Study population

The NHANES database is a cross-sectional survey that collects data on population demographics, dietary intake, physical assessments, survey responses, and laboratory examinations[21–23]. This study included publicly accessible data from 29,902 individuals aged 18–80 years in the NHANES 2011–2016. Participants under 18 years old ($n = 695$), lacking data on urinary OPEs metabolites ($n = 23202$) and uric acid data ($n = 1556$) were excluded. Additionally, participants who were pregnant or had missing covariate information were removed from the analysis ($n = 742$). Finally, 3707 individuals with comprehensive data were included in this study. The participant selection process flowchart was shown in Fig. 1.

OPEs metabolites measurements

As shown in Supplementary Table 1, diphenyl phosphate (DPHP), bis (1,3-dichloro-2-propyl) phosphate (BDCPP), bis-2-chloroethyl phosphate (BCEP), bis(1-choloro-2-propyl) phosphate (BCPP), and di-n-butyl phosphate (DBUP) were included for further statistical analysis due to the detection rates ≥ 50%. OPEs levels lower than the limit of detection (LOD) were represented as LOD/√2. The urinary specimens were preserved at -70 ℃ until assayed. Quantification of urinary OPEs metabolites relied on isotope dilution-electrospray ionization tandem mass spectrometry detection. The measurements were followed by strict quality control to ensure accuracy and reliability[15,24,25].

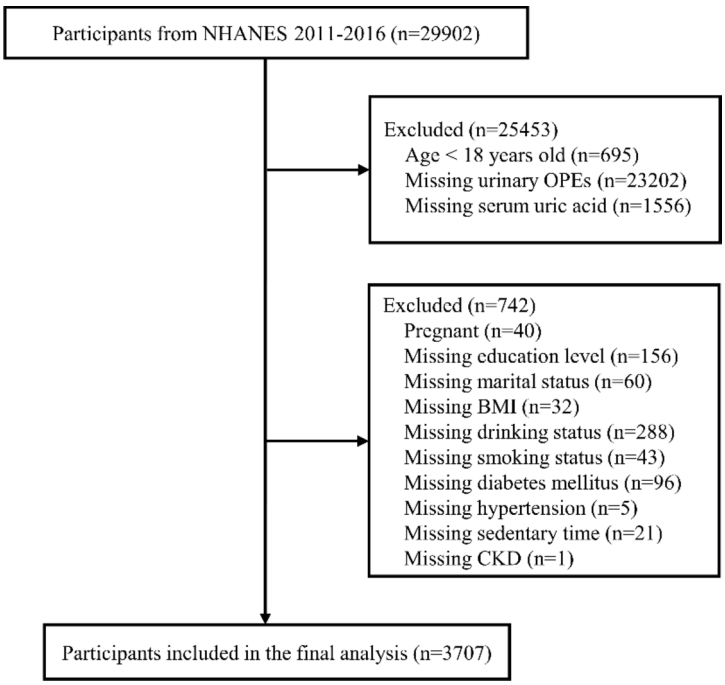

Fig. 1. Flowchart of participants included in this study. NHANES, National Health and Nutrition Examination Survey; OPEs, organophosphate esters; BMI, body mass index; CKD, chronic kidney disease.

Hyperuricemia

Serum specimens collected from participants were stored at -30 °C until they were shipped and analyzed. The concentrations of serum uric acid were quantified using a timed endpoint method on the DxC800 analyzer. The definition of hyperuricemia was serum uric acid concentrations equal to or exceeding 416 μmol/L (7.0 mg/dL) for males or 357 μmol/L (6.0 mg/dL) for females[7,26–28].

Inflammatory biomarkers

Blood samples collected at the NHANES mobile examination centers were utilized to measure complete blood count parameters using the Beckman Coulter method. In the NHANES 2015–2016 survey cycles, C-reactive protein (CRP) levels were measured using Beckman UniCel analyzers. For individuals with values below the detection limit, the imputed value was calculated as LOD/$\sqrt{2}$. Based on previous studies, we selected CRP, neutrophils, monocytes, and lymphocytes for mediation analysis[18,29,30].

Covariates

We have selected the following variables as probable covariates in our study, as there are some extraneous factors that may impact the outcomes. The covariates in our study included age, gender, ethnicity, body mass index (BMI), education level, marital status, drinking status, smoking status, sedentary time, diabetes mellitus, hypertension, and CKD according to previous studies[8]. BMI was defined as body weight relative to height (kg/m^2), and individuals with BMI > 25 kg/m^2 were classified as overweight. Smoking status: non-smokers had < 100 cigarettes in life, while smokers had > 100 cigarettes in life. Drinking status: drinkers consumed at least 12 alcoholic drinks annually, while non-drinkers had fewer than 12 drinks per year. Participants who reported diabetes or hypertension on the questionnaire were categorized accordingly. CKD was characterized by estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or albumin to creatinine ratio (ACR) > 30 mg/g.

Statistical analysis

Due to the intricate survey structure in NHANES, we used weighted data to accurately represent the survey sample characteristics[31]. We summarized the sociodemographic characteristics of individuals through descriptive analyses. The concentrations of OPEs metabolites and inflammatory biomarkers underwent ln-transformed before statistical analysis due to their skewed distribution. Additionally, we performed Pearson's correlation analysis to investigate the correlations among urinary OPEs metabolites.

Logistic regression analysis was used to investigate the relationship between individual OPEs metabolites and the risk of hyperuricemia. We constructed univariate and multivariate logistic regressions to adjust for multiple confounding factors. Additionally, we categorized OPEs metabolites into quartiles, using the lowest quartile as the reference group. To assess linear trends, *P* for trend value was calculated quartile as ordinal variables. Given the challenges posed by the intercorrelations among the components in mixtures, we employed WQS and BKMR to evaluate the impact of OPEs metabolites on hyperuricemia prevalence. In this WQS analysis, we randomly partitioned all measurements into two datasets, with 40% designated for training and 60% for validation via 10,000 bootstrap iterations. The weighted linear index was derived to demonstrate the overall effect of all OPEs metabolites and the weight assigned to each OPEs metabolites.

Moreover, we applied BKMR with 10,000 bootstrap iterations, a non-parametric approach performed kernel machine regression, to evaluate both single and overall effects of OPEs metabolites on the hyperuricemia risk. First, we examined the relationship between OPEs metabolites mixtures and the prevalence of hyperuricemia when compared to 50th percentiles. Secondly, we computed posterior inclusion probabilities (PIPs) to assess the relative significance of individual OPEs metabolites within the mixtures. Third, the exposure-response function illustrated the association of each OPEs metabolite and the risk of hyperuricemia with the other OPEs metabolites held at 50th percentiles. Fourth, the individual impact of OPEs metabolites was demonstrated using the single-exposure effect, which quantified the response change when a specific OPEs metabolite was at the 75th percentile compared to its 50th percentile, while keeping other OPEs metabolites at their 25th, 50th, and 75th percentiles. Finally, interactions were examined by assessing the parallelism of slopes in bivariate exposure-response functions.

Mediation analysis involving 1000 bootstrap simulations was undertaken to explore the role of inflammatory biomarkers in the associations between OPEs metabolites and the prevalence of hyperuricemia. The assessment of potential mediation effects followed the identification of significant associations among OPEs metabolites exposure, inflammatory biomarkers, and hyperuricemia prevalence. Specifically, we estimated the total effect (TE) of BDCPP on hyperuricemia, as well as its decomposition into direct effect (DE) and indirect effect (IE), where the latter represents the portion of the effect mediated by inflammatory biomarkers. The proportion mediated was calculated as IE/TE, reflecting the extent to which inflammatory biomarkers contributed to the association.

All statistical analyses were carried out using R software, with statistical significance set at a two-tailed *P* value less than 0.05. R packages including "survey," "gWQS," "bkmr," and "mediation" were utilized for the construction of sampling-weighted logistic regression model, WQS model, BKMR model, and mediation analysis, respectively.

Results

Participants characteristics

As presented in Table 1 and 750 individuals (20.23%) were diagnosed with hyperuricemia. Individuals with hyperuricemia showed higher levels of BDCPP and BCEP, as well as statistically significant differences in age, gender, ethnicity, BMI, smoking status, sedentary time, diabetes mellitus, hypertension, and CKD when compared to those without hyperuricemia. As shown in Supplementary Fig. 1, Pearson correlations among the

Variables	Total ($n=3707$)	Non-Hyperuricemia ($n=2957$)	Hyperuricemia ($n=750$)	*P*-value
Age, (years)	47 (32, 61)	47 (32, 60)	51 (33, 65)	0.006
Gender, n (%)				0.001
Male	1857 (50.09%)	1443 (48.39%)	413 (57.10%)	
Female	1851 (49.91%)	1514 (51.61%)	337 (42.90%)	
Ethnicity, n (%)				0.003
Mexican America	515 (8.29%)	446 (8.96%)	69 (5.53%)	
Non-Hispanic White	1527 (66.73%)	1192 (65.99%)	335 (69.79%)	
Non-Hispanic Black	749 (10.79%)	575 (10.57%)	174 (11.68%)	
Other Hispanic	406 (6.05%)	342 (6.45%)	64 (4.42%)	
Other	510 (8.14%)	402 (8.03%)	108 (8.59%)	
BMI, n (%)				< 0.001
< 25 kg/m^2	1085 (30%)	961 (33.50%)	124 (15.61%)	
≥ 25 kg/m^2	2622 (70%)	1996 (66.50%)	626 (84.39%)	
Education level, n (%)				0.331
Middle school or lower	336 (5.51%)	268 (5.36%)	68 (6.12%)	
High school	1257 (29.66%)	992 (29.00%)	265 (32.37%)	
College or more	2114 (64.83%)	1697 (65.64%)	417 (61.51%)	
Marital status, n (%)				0.185
Never married	513 (12.94%)	416 (13.44%)	97 (10.89%)	
Married	2058 (59.55%)	1650 (59.69%)	408 (58.96%)	
Other	1136 (27.51%)	891 (26.87%)	245 (30.14%)	
Drinking status, n (%)				0.383
No	1063 (22.63%)	863 (22.97%)	200 (21.24%)	
Yes	2644 (77.37%)	2094 (77.03%)	550 (78.76%)	
Smoking status, n (%)				0.041
No	2092 (56.44%)	1696 (57.58%)	396 (51.74%)	
Yes	1615 (43.56%)	1261 (42.42%)	354 (48.26%)	
Sedentary time (minutes)	360 (240, 540)	360 (240, 540)	420 (300, 600)	0.002
Diabetes mellitus, n (%)				< 0.001
No	3219 (90.71%)	2609 (92.01%)	610 (85.35%)	
Yes	488 (9.29%)	348 (7.99%)	140 (14.65%)	
Hypertension, n (%)				< 0.001
No	2354 (67.74%)	1992 (71.39%)	362 (52.72%)	
Yes	1353 (32.26%)	965 (28.61%)	388 (47.28%)	
CKD, n (%)				< 0.001
No	3047 (84.95%)	2539 (88.21%)	508 (71.54%)	
Yes	660 (15.05%)	418 (11.79%)	242 (28.46%)	
Ln DPHP (ug/L)	-0.27 (-1.04, 0.48)	-0.29 (-1.05, 0.49)	-0.22 (-0.97, 0.45)	0.785
Ln BDCPP (ug/L)	-0.20 (-1.11, 0.69)	-0.26 (-1.14, 0.62)	0.01 (-0.87, 0.94)	< 0.001
Ln BCEP (ug/L)	-0.95 (-1.84, -0.11)	-0.99 (-1.95, -0.18)	-0.71 (-1.55, 0.24)	< 0.001
Ln BCPP (ug/L)	-2.04 (-2.65, -1.11)	-2.10 (-2.65, -1.12)	-1.83 (-2.65, -0.97)	0.071
Ln DBUP (ug/L)	-2.53 (-2.65, -1.43)	-2.65 (-2.65, -1.43)	-2.26 (-2.65, -1.35)	0.318

Table 1. Characteristics of the participants. The continuous variables were presented as survey-weighted median (interquartile range, IQR). The categorical variables were presented as survey-weighted number and percentages. BMI, body mass index; CKD, chronic kidney disease; DPHP, diphenyl phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BCEP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; DBUP, dibutyl phosphate. Significant values are in bold.

five OPEs metabolites were statistically significant, with coefficients ranging from 0.22 to 0.51. These correlations emphasized the necessity of considering metabolites' interrelationships when assessing their single and overall effects.

Logistic regression model

As presented in Table 2, the logistic regression model was to investigated the association between each OPEs metabolite and the prevalence of hyperuricemia. When OPEs metabolites were treated as continuous variables, BDCPP (Crude model OR: 1.17, 95% CI:1.07–1.28, $P < 0.001$; Model I OR: 1.17, 95% CI: 1.07–1.29, $P = 0.002$;

OPEs (ug/L)	Crude Model		Model I		Model II	
	Crude OR (95%CI)	*P*-value	Adjusted OR (95%CI)	*P*-value	Adjusted OR (95%CI)	*P*-value
Ln DPHP	1.01 (0.94–1.09)	0.785	1.02 (0.94–1.11)	0.620	1.01 (0.93–1.10)	0.761
Q1	Reference		Reference		Reference	
Q2	1.15 (0.85–1.55)	0.371	1.09 (0.82–1.45)	0.564	1.04 (0.76–1.43)	0.790
Q3	1.40 (0.97–2.02)	0.076	1.43 (0.98–2.08)	0.072	1.34 (0.91–1.98)	0.151
Q4	1.08 (0.81–1.44)	0.612	1.08 (0.78–1.49)	0.646	1.06 (0.76–1.48)	0.751
P for trend	0.429		0.396		0.488	
Ln BDCPP	1.17 (1.07–1.28)	< 0.001	1.17 (1.07–1.29)	0.002	1.17 (1.07–1.29)	0.003
Q1	Reference		Reference		Reference	
Q2	1.09 (0.70–1.69)	0.709	1.05 (0.67–1.66)	0.829	1.07 (0.68–1.68)	0.771
Q3	1.30 (0.89–1.89)	0.176	1.33 (0.89–1.97)	0.168	1.30 (0.88–1.91)	0.195
Q4	1.65 (1.15–2.39)	0.010	1.66 (1.12–2.46)	0.015	1.62 (1.09–2.38)	0.023
P for trend	0.003		0.005		0.008	
Ln BCEP	1.23 (1.13–1.34)	< 0.001	1.21 (1.10–1.33)	< 0.001	1.19 (1.09–1.31)	< 0.001
Q1	Reference		Reference		Reference	
Q2	1.44 (1.06–1.96)	0.023	1.50 (1.10–2.05)	0.015	1.59 (1.15–2.20)	0.010
Q3	1.40 (0.97–2.03)	0.083	1.39 (0.95–2.03)	0.095	1.35 (0.93–1.97)	0.126
Q4	2.16 (1.60–2.92)	< 0.001	2.06 (1.48–2.85)	< 0.001	2.00 (1.46–2.76)	< 0.001
P for trend	< 0.001		< 0.001		0.001	
Ln BCPP	1.10 (0.99–1.22)	0.064	1.06 (0.96–1.18)	0.272	1.04 (0.93–1.17)	0.492
Q1	Reference		Reference		Reference	
Q2	1.14 (0.73–1.78)	0.578	1.05 (0.68–1.63)	0.830	1.05 (0.69–1.63)	0.800
Q3	1.22 (0.93–1.61)	0.159	1.16 (0.87–1.53)	0.318	1.13 (0.83–1.53)	0.443
Q4	1.33 (1.01–1.75)	0.048	1.21 (0.90–1.62)	0.213	1.17 (0.86–1.59)	0.339
P for trend	0.042		0.192		0.313	
Ln DBUP	1.07 (0.94–1.23)	0.313	1.06 (0.92–1.22)	0.442	1.02 (0.89–1.17)	0.785
Q1	Reference		Reference		Reference	
Q2	0.68 (0.23–2.01)	0.490	0.70 (0.25–1.99)	0.510	0.71 (0.25–2.02)	0.529
Q3	1.14 (0.81–1.60)	0.447	1.11 (0.80–1.54)	0.533	1.09 (0.78–1.51)	0.631
Q4	1.15 (0.87–1.52)	0.338	1.12 (0.84–1.48)	0.452	1.02 (0.77–1.35)	0.898
P for trend	0.296		0.405		0.753	

Table 2. Multivariate logistic regression analysis of ln-transformed OPEs metabolites for the prevalence of hyperuricemia. The crude model did not adjust for any covariates. Model I was adjusted for age, gender, ethnicity, and BMI. Model II was adjusted for all covariates. OPEs, organophosphate esters; DPHP, diphenyl phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BCEP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; DBUP, dibutyl phosphate; OR, odds ratio; CI, confidence interval; BMI, body mass index. Significant values are in bold.

Model II OR: 1.17, 95% CI: 1.07–1.29, $P = 0.003$) and BCEP (Crude model OR: 1.23, 95% CI:1.13–1.34, $P < 0.001$; Model I OR: 1.21, 95% CI: 1.10–1.33, $P < 0.001$; Model II OR: 1.19, 95% CI: 1.09–1.31, $P < 0.001$) were positively correlated with risk of hyperuricemia. When divided into quartiles, a positive association was observed between the highest quartile of BDCPP and the prevalence of hyperuricemia (Crude model OR: 1.65, 95% CI: 1.15–2.39, $P = 0.010$; Model I OR: 1.66, 95% CI: 1.12–2.46, $P = 0.015$; Model II OR: 1.62, 95% CI: 1.09–2.38, $P = 0.023$) when compared to the lowest quartile. Additionally, BCEP was also positively associated with the prevalence of hyperuricemia (Crude model OR: 2.16, 95% CI: 1.60–2.92, $P < 0.001$; Model I OR: 2.06, 95% CI: 1.48–2.85, $P < 0.001$; Model II OR: 2.00, 95% CI: 1.46–2.76, $P < 0.001$). The trends for BDCPP and BCEP were statistically significant, while DPHP, BCPP, and DBUP were not associated with the prevalence of hyperuricemia.

WQS model

As shown in Supplementary Table 2, the WQS model demonstrated a positive association between OPEs metabolites mixtures and the risk of hyperuricemia in Model I (OR: 1.18, 95% CI: 1.05–1.34, $P = 0.007$) and Model II (OR: 1.17, 95% CI: 1.03–1.33, $P = 0.013$). Moreover, Fig. 2 illustrated the contributions of each OPEs metabolite to the positive associations in the fully adjusted WQS index. Notably, BDCPP had the highest weight in the positive model (weight = 0.57), while BCEP (weight = 0.18), DBUP (weight = 0.12), BCPP (weight = 0.10), and DPHP (weight = 0.03) had relatively smaller contributions to the WQS index.

BKMR model

In Fig. 3, the concentrations of OPEs mixtures at or above the 50th percentile exhibited an increased prevalence of hyperuricemia. As indicated in Supplementary Table 3, BDCPP was identified as the primary contributor

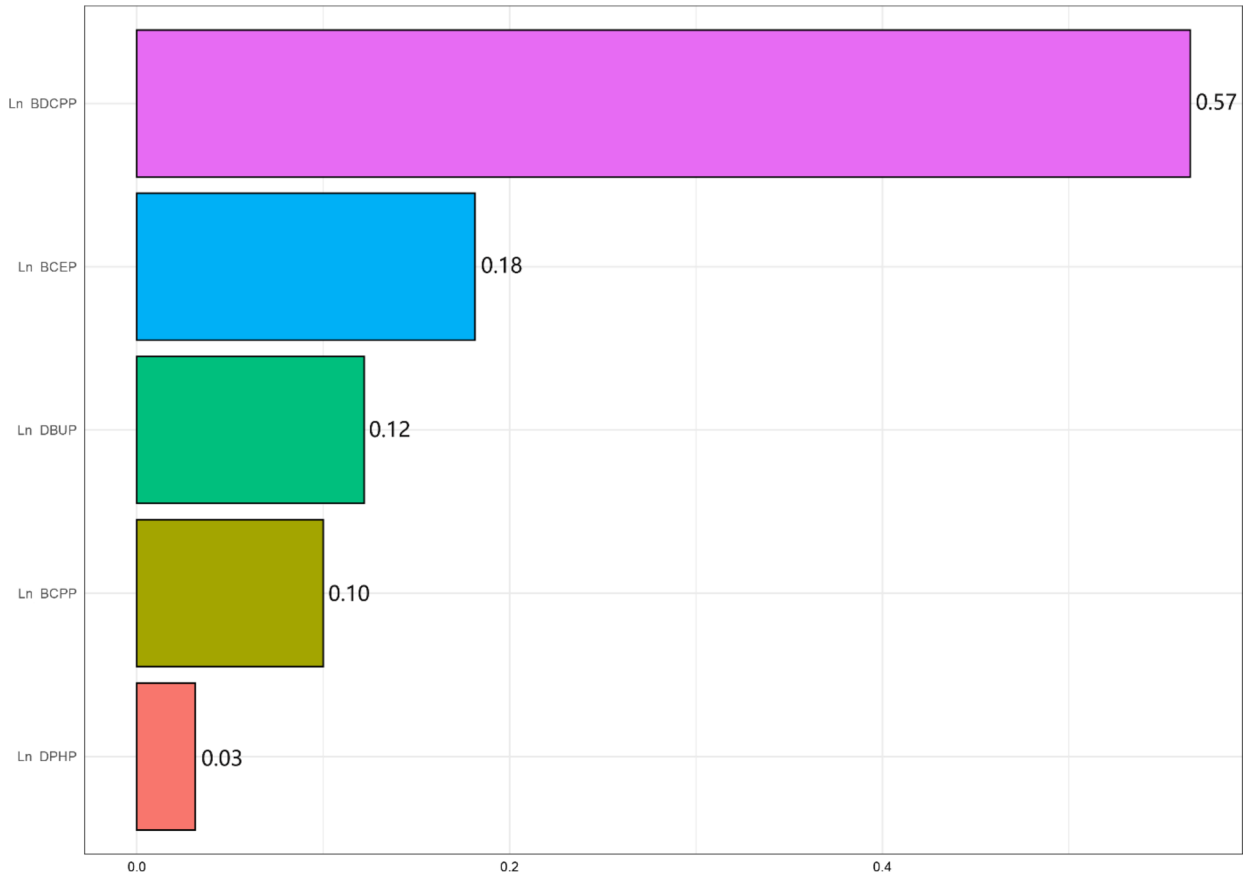

Fig. 2. The WQS model regression index weights of OPEs metabolites on the prevalence of hyperuricemia. This model adjusted for all covariates. WQS, weighted quantile sum regression; OPEs, organophosphate esters; DPHP, diphenyl phosphate; BDCPP, bis(1,3-dichloro-2-propyl) phosphate; BCEP, bis(2-chloroethyl) phosphate; BCPP, bis(1-chloro-2-propyl) phosphate; DBUP, dibutyl phosphate.

to the elevated prevalence of hyperuricemia, with a PIP of 0.72. Figure 4 displayed the exposure–response functions for the five single OPEs metabolites. BDCPP and BCEP exhibited positive associations with the prevalence of hyperuricemia when the other OPEs metabolites were held at their 50th percentile. As depicted in Supplementary Fig. 2, the single-exposure function demonstrated that BDCPP was positively correlated with the prevalence of hyperuricemia, whereas BCEP, DBUP, BCPP, and DPHP did not exhibit statistically significant effects on the risk of hyperuricemia. Supplementary Fig. 3 indicated that there were interactions among BDCPP, BCEP, and DPHP in the parallel exposure–response functions.

Mediation analysis

As shown in Supplementary Table 4, we assessed the relationships between urinary BDCPP and plasma levels of CRP, neutrophils, monocytes, and lymphocytes. Multiple linear regression revealed a positive association between BDCPP and CRP (β: 0.07, 95% CI: 0.01, 0.12, $P=0.016$), neutrophils (β: 0.01, 95% CI: 7.62e-04, 0.02, $P=0.035$), monocytes (β: 0.01, 95% CI: 1.97e-03, 0.02, $P=0.016$) after adjusted all covariates, respectively. As presented in Supplementary Table 5, CRP (OR: 1.25, 95% CI: 1.10, 1.42, $P<0.001$), neutrophils (OR: 1.32, 95% CI: 1.05, 1.65, $P=0.017$), and monocytes (OR: 1.59, 95% CI: 1.23, 2.05, $P<0.001$) exhibited a positive association with the prevalence of hyperuricemia after adjusting for all covariates. No statistically significant association was observed between lymphocytes and urinary BDCPP, or between lymphocytes and the prevalence of hyperuricemia. Additionally, we further assessed whether inflammation could mediate the association between BDCPP and the risk of hyperuricemia through mediation analysis. As presented in Table 3, CRP (OR: 2.03e-03, 95% CI: 2.95e-04, 0.00, $P=0.020$) and monocytes (OR: 6.69e-04, 95% CI: 5.55e-05, 0.00, $P=0.032$) significantly mediated the BDCPP induced the prevalence of hyperuricemia, accounting for 8.46% and 3.97% of the mediated proportion, respectively. However, we did not observe a significant mediating effect of neutrophils and lymphocytes in the relationships between BDCPP and the prevalence of hyperuricemia.

Discussion

Hyperuricemia is considered a significant contributor to various diseases and impacts the quality of life of people worldwide[2,32,33]. OPEs exposure have become a serious public health concern due to the reproductive, neurotoxic and carcinogenic effects[34–36]. However, there is currently no research to demonstrate the relationship

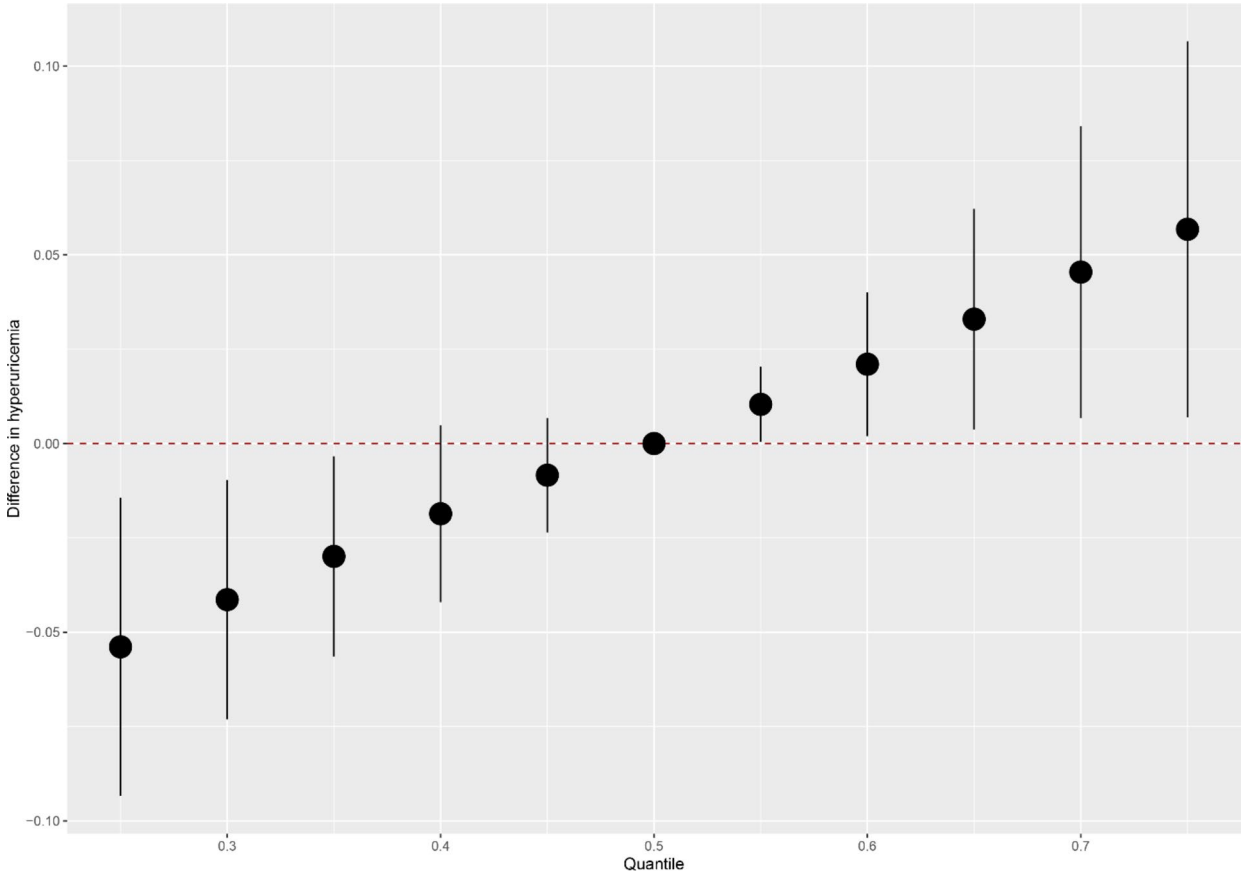

Fig. 3. Overall effect of OPEs metabolites mixtures on the prevalence of hyperuricemia in BKMR model. All OPEs metabolites at specific percentiles were compared to their 50th percentile. This model included adjustments for all covariates. OPEs, organophosphate esters; BKMR, Bayesian kernel machine regression.

between OPEs and the prevalence of hyperuricemia. In this study, we found that urinary BDCPP and BCEP levels were elevated in participants with hyperuricemia, and these two OPEs were positively correlated with the prevalence of hyperuricemia in the logistic regression model. Moreover, a positive effect of OPEs mixtures on the risk of hyperuricemia was revealed, and BDCPP had the greatest weight in the WQS model. Furthermore, the BKMR model showed that OPEs mixtures were correlated with the elevated risk of hyperuricemia, with BDCPP identified as the most significant contribution. Additionally, we also discovered that inflammation mediated the association between BDCPP and hyperuricemia prevalence. Therefore, our results suggested that BDCPP exposure increased the prevalence of hyperuricemia via inflammation.

In recent years, increasing researches has focused on the effects of environmental pollutants on the development of hyperuricemia[7,37,38]. As potential ecological and environmental pollutants, excessive OPEs exposure adversely affect human health. Luo et al. found a positive association between the mixture of OPEs and an increased prevalence of metabolic syndrome in men[14]. Hu et al. revealed that OPEs exposure contributed to increased blood pressure in young individuals[16]. Furthermore, renal function was indispensable for maintaining uric acid homeostasis, as the kidney was responsible for excreting uric acid[6]. Recent studies demonstrated that exposure to OPEs led to renal dysfunction. Kang et al. revealed that urinary BCEP, BDCIPP, and DNBP were correlated with the elevated risk of CKD[15]. David et al. demonstrated that TDCPP exposure caused cytostasis and cell toxicity in the human kidney proximal tubule[39]. Additionally, polybrominated diphenyl ethers, as traditional flame retardants that were generally replaced by OPEs, activated xanthine oxidase and upregulated purine metabolism, resulting in increased uric acid production[40]. Hence, it is reasonable to hypothesize that OPEs exposure might potentially lead to hyperuricemia. Based on extensive population samples, we revealed that OPEs mixtures were linked to an elevated risk of hyperuricemia in different statistical models, with BDCPP considered as the main contributor.

The mechanism of hyperuricemia is complex, with chronic inflammation regarded as a typical pathophysiological process[41]. Wasilewska et al. observed that serum inflammatory markers were increased in hyperuricemia patients[42]. Kaspar et al. demonstrated that CRP was positively associated with hyperuricemia in the US population[18]. Klück et al. established that human mononuclear cells contributed to the hyperinflammatory phenotype of patients with hyperuricemia[43]. Recently, it has been reported that inflammation played a vital role in the effects of OPEs exposure on various disorders. Welch et al. showed that prolonged exposure to consumer products containing OPEs was correlated with increased inflammation in pregnant women[19]. Hu et

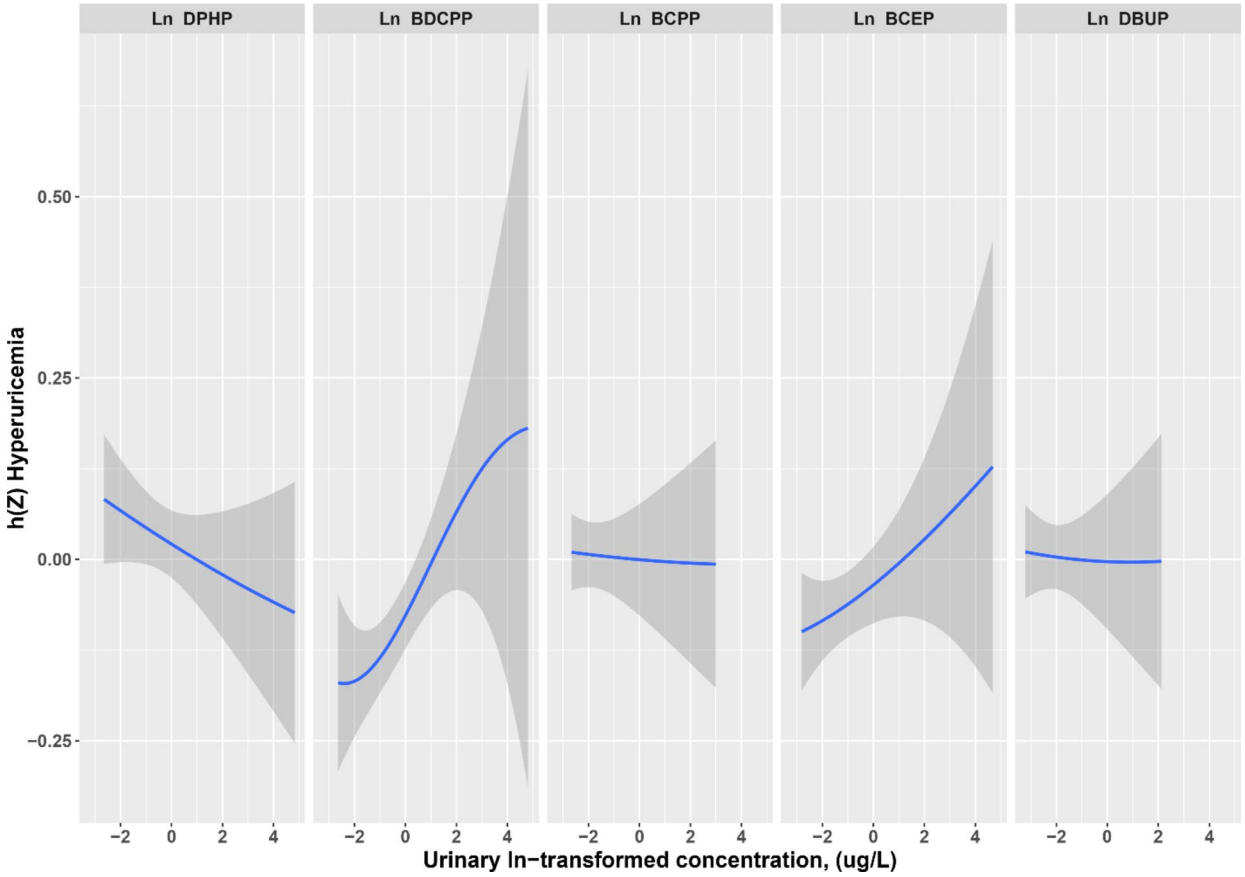

Fig. 4. Univariate exposure–response function between each OPEs metabolite and the prevalence of hyperuricemia when the other OPEs metabolites were fixed at 50th percentiles. This model adjusted for all covariates.

Pathways	Indirect effect	95% CI	*P*-value	Mediation proportions	95% CI	*P*-value
BDCPP → CRP→ Hyperuricemia	2.03e-03	2.95e-04, 0.00	0.020	8.46%	0.01, 0.36	0.020
BDCPP → Neutrophils → Hyperuricemia	1.11e-04	-4.25e-04, 0.00	0.610	0.67%	-0.03, 0.05	0.612
BDCPP → Monocytes → Hyperuricemia	6.69-04	5.55e-05, 0.00	0.032	3.97%	2.40-03, 0.13	0.034
BDCPP → Lymphocytes → Hyperuricemia	-2.29e-05	-2.89e-04, 0.00	0.862	0.14%	-2.33e-02, 0.01	0.864

Table 3. Mediating effects and proportions of inflammation biomarkers between BDCPP exposure and the prevalence of hyperuricemia. This model included adjustments for all covariates. BDCPP, bis(1,3-dichloro-2-propyl) phosphate; CRP, C-reactive protein; CI, confidence interval. Significant values are in bold.

al. reported that airway inflammation served as a mediator factor linking OPEs and lung function in individuals aged 6–79 years[20]. However, the precise mechanism elucidating the relationship between OPEs and the risk of hyperuricemia remains undetermined. In this study, we observed that BDCPP exposure was positively associated with inflammatory markers, including CRP, neutrophils, and monocytes using linear regression. Moreover, we found positive effects of CRP, neutrophils, and monocytes on the prevalence of hyperuricemia using the logistic regression model. Additionally, mediation analysis demonstrated that CRP and monocytes played a significant role in mediating the relationship between OPEs exposure and the prevalence of hyperuricemia. Thus, these results indicated that inflammation might be a crucial mechanism involved in the effects of OPEs on the prevalence of hyperuricemia.

Our study had the following strengths. Firstly, this study pioneered the exploration of the relationship between OPEs exposure and the prevalence of hyperuricemia. Secondly, we employed three complementary statistical models to demonstrate the robustness of our conclusions. Thirdly, we controlled various confounders to attain the authenticity of the results. However, our study also had limitations. Firstly, the cross-sectional nature of the study limits our ability to infer causality, and the observed associations could be subject to bias or confounding factors. Secondly, because of the incomplete information in the NHANES database, we were unable to account for all potential confounders in our study, such as high-purine diet and genetic factors. Finally,

a single measurement of OPEs level might not comprehensively capture the long-term accumulation of OPEs exposure. More longitudinal studies or randomized controlled trials are needed to validate our results in the future.

Conclusions

In this study, we found that OPEs mixtures positively correlated with the prevalence of hyperuricemia, with BDCPP identified as the primary contributor. Furthermore, inflammation was identified as a mediator involved in the effect of BDCPP on the prevalence of hyperuricemia. These findings provide a novel strategy for the prevention of hyperuricemia. Further research is required to support our results in diverse population.

Data availability

The datasets used for these analyses are publicly available (https:// www.cdc.gov/nchs/nhanes/index.htm).

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References

1. Chen-Xu, M., Yokose, C., Rai, S. K., Pillinger, M. H. & Choi, H. K. M.H., and Contemporary Prevalence of Gout and Hyperuricemia in the United States and Decadal Trends: The National Health and Nutrition Examination Survey 2007–2016. *Arthritis & rheumatology (Hoboken, N.J.) 71* (6), 991–999. (2019). https://doi.org/10.1002/art.40807
2. Hu, L. et al. U-Shaped association of serum uric acid with All-Cause and Cause-Specific mortality in US adults: A cohort study. *J. Clin. Endocr. Metab.* **105** (3), e597–e609. https://doi.org/2021122102222489700 (2020).
3. Odden, M. C., Amadu, A. R., Smit, E., Lo, L. & Peralta, C. A. Uric acid levels, kidney function, and cardiovascular mortality in US adults: National health and nutrition examination survey (NHANES) 1988–1994 and 1999–2002. *Am. J. Kidney Diseases: Official J. Natl. Kidney Foundation*. **64** (4), 550–557. https://doi.org/10.1053/j.ajkd.2014.04.024 (2014).
4. Mazidi, M., Katsiki, N., Mikhailidis, D. P. & Banach, M. The link between insulin resistance parameters and serum uric acid is mediated by adiposity. *Atherosclerosis* **270**, 180–186. https://doi.org/10.1016/j.atherosclerosis.2017.12.033 (2018).
5. Park, C. E. et al. Gender Difference in the Relationship between Uric Acid and Pulse Pressure among Korean Adults. *Clinical and Experimental Hypertension (New York, N.Y.*: 2019, *41* (6), 499–504. (1993). https://doi.org/10.1080/10641963.2018.1510944
6. Choi, H. K. et al. Population impact attributable to modifiable risk factors for hyperuricemia. *Arthritis Rheumatol. (Hoboken N J).* **72** (1), 157–165. https://doi.org/10.1002/art.41067 (2020).
7. Tan, Y. et al. Relationship between phthalates exposures and hyperuricemia in U.S. General population, a Multi-Cycle study of NHANES 2007–2016. *Sci. Total Environ.* **859**, 160208. https://doi.org/10.1016/j.scitotenv.2022.160208 (2023).
8. Tan, Y. et al. Yingyin Fu; Feng Huang; Lin Wen; Xueqiong Weng; Huojie Yao; Huanzhu Liang; Mincong Kuang; Chunxia Jing. Association between Blood Metal Exposures and Hyperuricemia in the U.S. General Adult: A Subgroup Analysis from NHANES. *Chemosphere 318*, 137873. (2023). https://doi.org/10.1016/j.chemosphere.2023.137873
9. Liu, M. et al. Exposure to novel brominated flame retardants and organophosphate esters and associations with thyroid cancer risk: A Case-Control study in Eastern China. *Environ. Sci. Technol.* **56** (24), 17825–17835. https://doi.org/10.1021/acs.est.2c04759 (2022).
10. Li, R. et al. Associations between organophosphate esters concentrations and markers of liver function in US adolescents aged 12–19 years: A mixture analysis. *Environ. Pollut.* **314**, 120255. https://doi.org/10.1016/j.envpol.2022.120255 (2022).
11. Luo, K., Aimuzi, R., Wang, Y., Nian, M. & Zhang, J. Urinary organophosphate esters metabolites, glucose homeostasis and prediabetes in adolescents. *Environ. Pollut.* **267**, 115607. https://doi.org/10.1016/j.envpol.2020.115607 (2020).
12. Craig, J. A. et al. Exposure of nail salon workers to phthalates, Di(2-Ethylhexyl) terephthalate, and organophosphate esters: A pilot study. *Environ. Sci. Technol.* **53** (24), 14630–14637. https://doi.org/10.1021/acs.est.9b02474 (2019).
13. Wuet, X. Organophosphate ester exposure among Chinese waste incinerator workers: urinary levels, risk assessment and associations with oxidative stress. *Sci. Total Environ.* **854**, 158808. https://doi.org/10.1016/j.scitotenv.2022.158808 (2023).
14. Luo, K. et al. Exposure to organophosphate esters and metabolic syndrome in adults. *Environ. Int.* **143**, 105941. https://doi.org/10.1016/j.envint.2020.105941 (2020).
15. Kang, H., Lee, J., Pyo, J., Lee & Choi, K. Urinary metabolites of organophosphate esters (OPEs) are associated with chronic kidney disease in the general US population, NHANES 2013–2014. *Environ. Int.* **131**, 105034. https://doi.org/10.1016/j.envint.2019.105034 (2019).
16. Hu, L. et al. Association of exposure to organophosphate esters with increased blood pressure in children and adolescents. *Environ. Pollut.* **295**, 118685. https://doi.org/10.1016/j.envpol.2021.118685 (2022).
17. Eswar Krishnan. Interaction of inflammation, hyperuricemia, and the prevalence of hypertension among adults free of metabolic syndrome: NHANES 2009–2010. *J. Am. Heart Association*. **3** (2), e000157. https://doi.org/10.1161/JAHA.113.000157 (2014).
18. Kaspar, C. D. W., Lu, J., Hyperuricemia, E. B. M. & Index Female sex, and albuminuria increase the probability of elevated High-Sensitivity C-Reactive protein: results from the National health and nutrition examination survey 2015–2018. *Front. Public. Health*. **9**, 689219. https://doi.org/10.3389/fpubh.2021.689219 (2021).
19. Welch, B. M. et al. Longitudinal exposure to consumer product chemicals and changes in plasma Oxylipins in pregnant women. *Environ. Int.* **157**, 106787. https://doi.org/10.1016/j.envint.2021.106787 (2021).
20. Hu, P. et al. Organophosphate esters, airway inflammation, and lung function among U.S. Participants: A nationally representative Cross-Sectional study from NHANES, 2011–2012. *Sci. Total Environ.* **892**, 164755. https://doi.org/10.1016/j.scitotenv.2023.164755 (2023).
21. Weng, X. et al. Association between mixed exposure of phthalates and cognitive function among the U.S. Elderly from NHANES 2011–2014: three statistical models. *Sci. Total Environ.* **828**, 154362. https://doi.org/10.1016/j.scitotenv.2022.154362 (2022).
22. Bai, J. et al. Mixed exposure to phenol, Parabens, pesticides, and phthalates and insulin resistance in NHANES: A mixture approach. *Sci. Total Environ.* **851** (Pt 2), 158218. https://doi.org/10.1016/j.scitotenv.2022.158218 (2022).
23. Pang, K. et al. Higher total cholesterol concentration May be associated with better cognitive performance among elderly females. *Nutrients* **14** (19), 4198. https://doi.org/10.3390/nu14194198 (2022).
24. Boyle, M., Buckley, J. P. & Quirós-Alcalá, L. Associations between urinary organophosphate ester metabolites and measures of adiposity among U.S. Children and adults: NHANES 2013–2014. *Environ. Int.* **127**, 754–763. https://doi.org/10.1016/j.envint.2019.03.055 (2019).
25. Luo, K. et al. Associations between organophosphate esters and sex hormones among 6–19-Year old children and adolescents in NHANES 2013–2014. *Environ. Int.* **136**, 105461. https://doi.org/10.1016/j.envint.2020.105461 (2020).
26. Niu, Z. et al. Kidney function decline mediates the adverse effects of Per- and Poly-Fluoroalkyl substances (PFAS) on uric acid levels and hyperuricemia risk. *J. Hazard. Mater.* **471**, 134312. https://doi.org/10.1016/j.jhazmat.2024.134312 (2024).

27. Kuo, C. C. et al. Arsenic exposure, hyperuricemia, and gout in US adults. *Environ. Int.* **76**, 32–40. https://doi.org/10.1016/j.envint.2014.11.015 (2015).
28. Chen-Xu, M., Yokose, C., Rai, S. K., Pillinger, M. H. & Choi, H. K. Contemporary prevalence of gout and hyperuricemia in the united States and decadal trends: the National health and nutrition examination survey, 2007–2016. *Arthritis Rheumatol.* **71** (6), 991–999. https://doi.org/10.1002/art.40807 (2019).
29. Natsuko, P. D. et al. Differential gene expression of ABCG2, SLC22A12, IL-1β, and ALPK1 in peripheral blood leukocytes of primary gout patients with hyperuricemia and their comorbidities: A Case-Control study. *Eur. J. Med. Res.* **27** (1), 62. https://doi.org/10.1186/s40001-022-00684-1 (2022).
30. Ma, Q. et al. Soluble uric acid is an intrinsic negative regulator of monocyte activation in monosodium urate Crystal-Induced tissue inflammation. *J. Immunol. (Baltimore Md. : 1950)*. **205** (3), 789–800. https://doi.org/10.4049/jimmunol.2000319 (2020).
31. Che, Z. et al. Associations between exposure to brominated flame retardants and metabolic syndrome and its components in U.S. Adults. *Sci. Total Environ.* **858** (Pt 2), 159935. https://doi.org/10.1016/j.scitotenv.2022.159935 (2023).
32. Han, Y. et al. Hyperuricemia and gout increased the risk of Long-Term mortality in patients with heart failure: insights from the National health and nutrition examination survey. *J. Transl Med.* **21**, 463. https://doi.org/10.1186/s12967-023-04307-z (2023).
33. Han, F. et al. Association between serum uric acid levels and peripheral artery disease in Chinese adults with hypertension. *Front. Endocrinol.* **14**, 1197628. https://doi.org/10.3389/fendo.2023.1197628 (2023).
34. Liu, W. et al. Prenatal exposure to halogenated, Aryl, and alkyl organophosphate esters and child neurodevelopment at two years of age. *J. Hazard. Mater.* **408**, 124856. https://doi.org/10.1016/j.jhazmat.2020.124856 (2021).
35. Gao, F. et al. Exposure assessment of Aryl-Organophosphate esters based on specific urinary biomarkers and their associations with reproductive hormone homeostasis disruption in women of childbearing age. *Environ. Int.* **169**, 107503. https://doi.org/10.1016/j.envint.2022.107503 (2022).
36. Li, Y. et al. Positive correlation between human exposure to organophosphate esters and Gastrointestinal cancer in patients from Wuhan, China. *Ecotoxicol. Environ. Saf.* **196**, 110548. https://doi.org/10.1016/j.ecoenv.2020.110548 (2020).
37. Qin, X. D. et al. Positive Associations of Serum Perfluoroalkyl Substances with Uric Acid and Hyperuricemia in Children from Taiwan. *Environmental Pollution (Barking, Essex*: 2016, *212*, 519–524. (1987). https://doi.org/10.1016/j.envpol.2016.02.050
38. Yang, J. et al. Nickel exposure induces gut Microbiome disorder and serum uric acid elevation. *Environ. Pollut.* **324**, 121349. https://doi.org/10.1016/j.envpol.2023.121349 (2023).
39. Killilea, D. W., Chow, D., Xiao, S. Q., Li, C. & Stoller, M. L. Flame retardant Tris(1,3-Dichloro-2-Propyl)Phosphate (TDCPP) toxicity is attenuated by N-Acetylcysteine in human kidney cells. *Toxicol. Rep.* **4**, 260–264. https://doi.org/10.1016/j.toxrep.2017.05.003 (2017).
40. Yang, C., Wong, C. M., Wei, J., Chung, A. C. K. & Cai, Z. The brominated flame retardant BDE 47 upregulates purine metabolism and mitochondrial respiration to promote adipocyte differentiation. *Sci. Total Environ.* **644**, 1312–1322. https://doi.org/10.1016/j.scitotenv.2018.07.087 (2018).
41. Yang, X. et al. Uric acid induced inflammatory responses in endothelial cells via Up-Regulating(pro)Renin receptor. *Biomed. Pharmacotherapy = Biomedecine Pharmacotherapie*. **109**, 1163–1170. https://doi.org/10.1016/j.biopha.2018.10.129 (2019).
42. Wasilewska, A., Tenderenda, E., Taranta-Janusz, K., Tobolczyk, J. & Stypułkowska, J. Markers of systemic inflammation in children with hyperuricemia. *Acta Paediatr.* **101** (5), 497–500. https://doi.org/10.1111/j.1651-2227.2011.02582.x (2012).
43. Klück, V. et al. TGF-β is elevated in hyperuricemic individuals and mediates Urate-Induced hyperinflammatory phenotype in human mononuclear cells. *Arthritis Res. Ther.* **25** (1), 30. https://doi.org/10.1186/s13075-023-03001-1 (2023).

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The study protocol (Protocol Number: Protocol #2011-17) was approved by the NCHS Research Ethics Review Board (ERB) and all participants provided written informed consent prior to participation. (https://www.cdc.gov/nchs/nhanes/irba98.htm).

Additional information

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