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Association between endocrine disrupting chemicals exposure and diabetic kidney disease in adults

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ABSTRACT

Background: Diabetic kidney disease (DKD) is a global public health concern. Environmental factors are increasingly recognized as significant risk factors that cannot be overlooked, and certain environmental pollutants exhibit endocrine-disrupting properties. Previous research on the association between endocrine-disrupting chemicals (EDCs) and DKD has been notably limited.

Methods: This study investigated the association between exposure to 25 EDC metabolites and DKD in 1421 U.S. adults from the 2015–2018 National Health and Nutrition Examination Survey (NHANES). We used logistic regression, restricted cubic spline regression, weighted quantile sum (WQS) regression, and bayesian kernel machine regression (BKMR) models to assess the association between individual and co-exposure to multiple EDCs and DKD. Subgroup analyses and interaction tests were performed to investigate whether this association was stable across the population. Additionally, mediation analysis was used to explore the mediating role of serum globulins in the association between Pb exposure and DKD.

Results: In logistic regression models, N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA), N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine (MHBMA3), Phenylglyoxylic acid (PGA), and lead (Pb) were significantly positively associated with diabetes. Restricted cubic spline (RCS) analyses also revealed significant non-linear positive associations between 2HPMA, MHBMA3, and DKD. Perfluorohexane sulfonic acid (PFHxS), n-perfluorooctanoic acid (n-PFOA), n-perfluorooctane sulfonic acid (n-PFOS), and Perfluoromethylheptane sulfonic acid isomers (Sm-PFOS) were significantly negatively associated with DKD. Furthermore, co-exposure to metals and metalloid was positively associated with DKD in both the WQS regression and the BKMR models, with Pb as the primary contributing factor. Mediation analysis showed that globulin mediated the association between Pb exposure and DKD, with a mediation proportion of 7.25 % ($P = 0.046$). Co-exposure to perfluoroalkyl and polyfluoroalkyl substances (PFASs) was negatively correlated with DKD, and subgroup analyses revealed that this correlation was more pronounced in the obese group (BMI $\geq$30 kg/m^2). The BKMR analysis revealed potential interactions among various chemical compounds, such as N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA), 2-Methylhippuric acid (2MHA), N-Acetyl-S-(4-hydroxy-2-methyl-2-butenyl)-L-cysteine (IPM3), mercury (Hg), and cadmium (Cd), in a model simulating co-exposure to metals and metalloid, as well as to volatile organic compound metabolites (mVOCs).

Conclusion: The findings suggest an association between individual or co-exposure to EDC metabolites and DKD, providing valid evidence for DKD prevention from the perspective of EDCs exposure. However, more prospective studies are needed to elucidate the potential mechanisms underlying these findings.

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1. Introduction

Diabetes mellitus (DM) is one of the most common and fastest-growing diseases globally, with an estimated 578 million people worldwide projected to have diabetes by 2030 (Saeedi et al., 2019). Diabetic kidney disease (DKD), a major microvascular complication of DM, is characterized by persistent albuminuria and a decline in glomerular filtration rate (GFR), significantly contributing to end-stage kidney disease (Fu et al., 2019; Lin et al., 2018). DKD represents a major global health challenge with a substantial economic burden (Reutens, 2013). Therefore, investigating factors that influence DKD is critical for slowing its progression and improving the quality of life for patients.

Certain metals, metalloids, volatile organic compounds (VOCs), and perfluoroalkyl and polyfluoroalkyl substances (PFASs) are endocrine-disrupting chemicals (EDCs) that can interfere with hormone functions, induce oxidative stress, and increase the risk of metabolic disturbances (Cano et al., 2021; Liu et al., 2012; Wei et al., 2023). DKD is a common manifestation of underlying systemic diseases, such as metabolic syndrome and endocrine disorders.

Emerging studies have shown that VOCs emitted from industrial activities and transportation are linked to various health problems, including kidney and liver damage (Aivalioti et al., 2010). Certain VOCs, such as BTEXS (benzene, toluene, ethylbenzene, xylene, and styrene) and chlorinated benzenes, are nephrotoxic (Aivalioti et al., 2010; den Besten et al., 1991; Shi et al., 2013). In an environmental study, urinary VOC metabolites (mVOCs) were found to be associated with renal damage, such as albuminuria and a reduced estimated Glomerular Filtration Rate (eGFR) (Lee et al., 2020).

Trace metals and metalloids, such as cadmium (Cd), arsenic (As), lead (Pb), and mercury (Hg), found in industrial waste and food, act as endocrine disruptors and are linked to chronic diseases, including diabetes and kidney disease (Błażewicz et al., 2024; Clemens and Ma, 2016). Cd, As, and Hg act as endocrine disruptors, elevating the risk of metabolic syndrome, insulin resistance, type 2 diabetes, and associated kidney diseases by affecting signaling pathways such as PI3K/AKT, PPARγ, and NF-κB/PTEN (Haidar et al., 2023). A study by Antonio Planchart et al. found that Pb-exposed cultured islets of Langerhans exhibited decreased cell viability, impaired insulin secretion, and higher baseline insulin levels and reactive oxygen species (ROS). Pb exposure in adolescents and adults can cause insulin resistance (Planchart et al., 2018). Selenoprotein levels show a U-shaped relationship with insulin sensitivity; both low and high selenium levels may increase the risk of type 2 diabetes (Rayman, 2012; Zhang et al., 2023). Inflammatory responses and oxidative stress play key roles in the pathogenesis of DKD (Brownlee, 2005; Jha et al., 2016). Experimental evidence indicates that Fyn phosphorylation, which regulates transglutaminase 2 phosphorylation, affects autophagy and p53 signaling in DKD development (Uehara et al., 2023). Furthermore, globulins may impact DKD via inflammation and oxidative stress (Khater et al., 2021; Wang et al., 2022). Pb exposure induces ROS generation and promotes inflammatory responses. Hence, we evaluated whether serum globulins and oxidative stress markers mediate the relationship between Pb and DKD.

PFASs are widely used in industrial and consumer products, such as polishes and food packaging (Shankar et al., 2011). Animal and in vitro experiments have shown that exposure to PFASs may cause congestion and edema in the renal parenchyma of rats, as well as alterations in endothelial cell permeability, which in turn affects renal function (Cui et al., 2009; Hu et al., 2003). Previous epidemiological studies on PFASs and renal function have produced mixed results. One study found a negative correlation between certain PFASs and eGFR (Shankar et al., 2011), while another observed an inverted U-shaped relationship between PFASs and eGFR during the progression of chronic kidney disease (Jain and Ducatman, 2019a).

Humans in industrial or heavily trafficked areas may be exposed to both VOCs and metals in certain environments. Several epidemiologic studies have explored the association between VOCs or metals and kidney or diabetic nephropathy. However, few have investigated the co-exposure to VOCs and metals in relation to DKD. Upon reviewing the references, we found that there might be competing binding and binding reactions between VOCs and metals (Bridges and Zalups, 2005; Clarkson and Magos, 2006; Wu et al., 2021). Therefore, it is valuable and meaningful to explore the association between co-exposure to both substances and DKD. Unfortunately, we could not explore the association between the co-exposure of PFASs, mVOCs, metals, and metalloids with DKD due to sample size limitations.

Most studies have focused on the effects of individual chemicals, but real-world exposure involves multiple chemicals, which may interact in additive, synergistic, or antagonistic ways. We employed logistic regression, restricted cubic spline (RCS) regression, weighted quantile sum (WQS), and Bayesian Kernel Machine Regression (BKMR) models to explore both the correlation between individual EDCs and DKD, as well as the correlation between four exposure models (co-exposure to PFASs, co-exposure to mVOCs, co-exposure to metals and metalloid, and a combined co-exposure model encompassing mVOCs, metals, and metalloid) and DKD. Additionally, we further explored the possible mediators between EDCs and DKD.

2. Method

2.1. Study design and participants

Data for this study were obtained from NHANES, a nationally representative cross-sectional survey conducted by the National Center for Health Statistics (NCHS) to assess the nutritional status and health of adults and children in the United States. The study protocol was approved by the Institutional Review Board of the NCHS, and written consent was obtained from all participants (https://www.cdc.gov/nchs/nhanes/irba98.htm). Based on the available data on EDCs and diabetes diagnostics, we included two cycles (2015–2018) of NHANES data for analysis. Among the 19,225 participants, 7937 participants under 20 years of age and 125 pregnant participants were initially excluded. Next, we excluded 810 participants with missing urinary albumin to creatinine ratio (ACR) data, 3 with missing diabetes diagnostic information, 8663 without a diabetes diagnosis, and 266 without any urinary mVOCs, blood metals/metalloids or serum PFAS metabolites data. Finally, 1421 participants were included in this study (Fig. 1).

2.2. Exposure ascertainment

The study measured the concentrations of urinary volatile organic compound metabolites (mVOCs), blood metals and metalloids, and serum perfluoroalkyl and polyfluoroalkyl substances (PFASs) in samples from NHANES participants, with only chemicals having a detection rate of $\geq$ 85 % considered for the study of their association with DKD. Ultimately, 15 urinary mVOCs (2MHA, 3,4-MHA, AAMA, AMCA, ATCA, SBMA, CEMA, DHBMA, 2HPMA, 3HPMA, IPM3, MA, MHBMA3, PGA, and HPMM), 5 serum PFASs (PFHxS, PFNA, n-PFOA, n-PFOS, and Sm-PFOS), and 5 blood metals and metalloid (Lead (Pb), Cadmium (Cd), Mercury (Hg), Selenium (Se) and Manganese (Mn)) were evaluated in this study. Abbreviations and full titles for each EDC metabolite are provided in the Supplementary Material. EDC concentrations below the lower detection limit (LLOD) are assigned a value equal to LLOD/$\sqrt{2}$, as recommended by NHANES (Hornung and Reed, 1990; Lei et al., 2023). The mVOCs in urine were measured by ultra-performance liquid chromatography coupled with electrospray tandem mass spectrometry (UPLC-ESI/MSMS). The metals and metalloids in whole blood were measured directly by mass spectrometry following a simple dilution sample preparation step. Serum PFASs were measured by online solid phase extraction coupled with high-performance liquid chromatography-turbo ionspray ionization-tandem mass spectrometry (online SPE-HPLC-TIS-MS/MS). Detailed information on the EDC laboratory methodology is provided in the Supplementary Material or on the

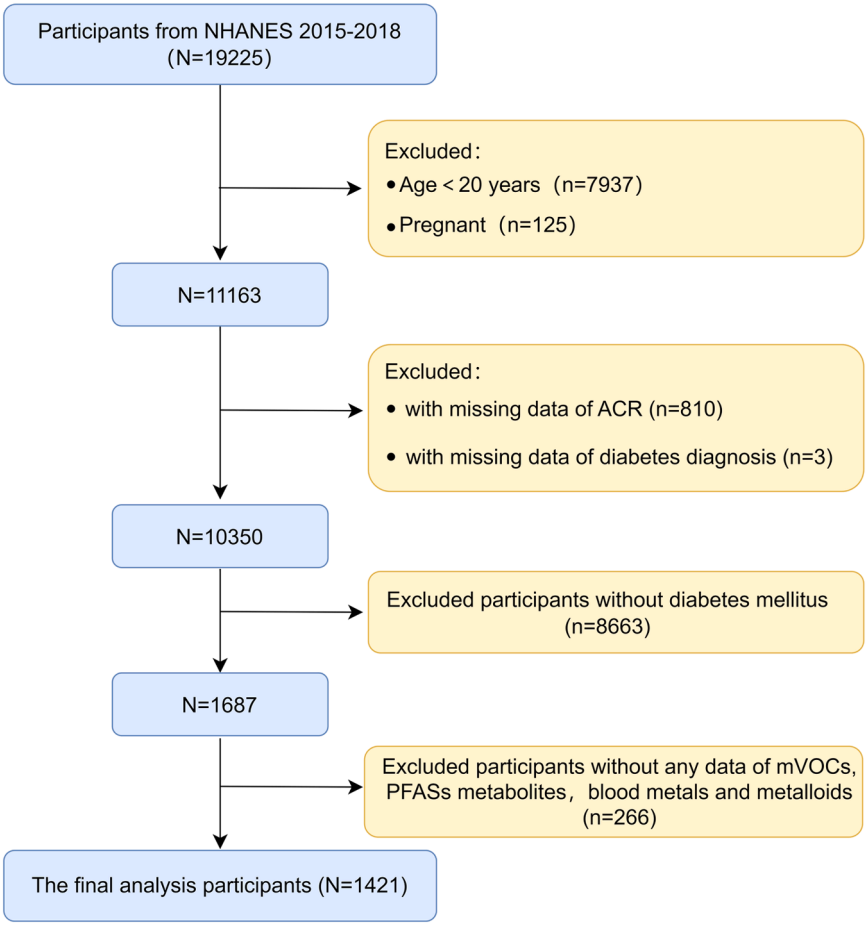

Fig. 1. The flowchart for screening participants from NHANES 2015–2018; Abbreviations: ACR, albumin to creatinine ratio; mVOCs, volatile organic compound metabolites; PFASs, Perfluoroalkyl and polyfluoroalkyl substances.

NHANES website (http://www.cdc.gov/nchs/nhanes). Urine mVOC samples were first corrected by urinary creatinine and then log-transformed, whereas serum PFASs, blood metals and metalloid samples were log-transformed directly to achieve a normal distribution.

2.3. Definition of diabetic kidney disease

Based on the available NHANES questionnaire and laboratory data, and by the criteria set by the American Diabetes Association and previous studies, individuals meeting any of the following criteria were classified as having diabetes mellitus: (1) fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L, or (2) glycosylated hemoglobin A1c (HbA1c) $\geq$ 6.5 %, or (3) a prior diagnosis of diabetes mellitus, or (4) current use of medications for diabetes treatment (American Diabetes Association, 2021). Diagnostic criteria for diabetic kidney disease (DKD): (1) Confirmed diagnosis of diabetes, and (2) urine albumin to creatinine ratio (ACR) $\geq$ 30 mg/g or estimated glomerular filtration rate (eGFR) $\leq$ 60 mL/min/1.73 m^2, or both (De Boer et al., 2011). For eGFR calculation, we utilized the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009), as follows:

$$\text{eGFR CKD}-\text{EPI}\ (\text{mL/ min /1.73 m}^2) = 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where Scr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum value of Scr/κ or 1, and max indicates the maximum value of Scr/κ or 1.

2.4. Potential confounders

Confounders were selected based on previous research findings and clinical expertise (Guo et al., 2022, 2023; Lei et al., 2023; Li et al., 2023; Lv et al., 2023), as well as utilizing the EmpowerStats software: a covariate is included if it satisfies either of the following criteria: either the inclusion of the covariate in the base model or its removal from the full model has an impact on the regression coefficient of X that is greater than 10 %, or the p-value for the regression coefficient of the covariate with respect to Y is less than 0.1. Based on this criterion, we finalized the covariates to be considered in the study to include age, sex, race, education level, marital status, poverty-income ratio (PIR), body mass index (BMI), hypertension, hyperlipidemia, smoking status, alcohol intake, physical activity (PA), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), homeostatic model assessment of insulin resistance (HOMA-IR), serum creatinine (SCR), hemoglobin A1c (HbA1c), serum uric acid (SUA), blood urea nitrogen (BUN), and high-sensitivity c-reactive protein (hs-CRP).

Among these covariates, Race was categorized into the following five groups: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other Race. In addition to this, education level was categorized as less than high school graduate, high school graduate or equivalent, above high school. Marital status was categorized as marry/conhabity, widowed/divorced/separated, and never. PIR was categorized into three groups (<1.3, 1.3–3.5, $\geq$3.5). BMI (kg/m^2) was specifically calculated as weight (kg) divided by the square of height (m). Hypertension was defined as systolic blood pressure (SBP) $\geq$ 130 mmHg and/or diastolic blood pressure (DBP) $\geq$ 80 mmHg after three consecutive measurements (Whelton et al., 2018) or a previous

diagnosis of hypertension. Hyperlipidemia was defined as total cholesterol (TC) ≥ 240 mg/dL, triglycerides (TG) ≥ 200 mg/dL, low-density lipoproteins (LDL-C) ≥ 160 mg/dL, high-density lipoproteins (HDL-C) < 40 mg/dL, or a previous diagnosis of hyperlipidemia. Based on the questionnaire data, smoking status was categorized into the following three groups: never (<100 cigarettes in lifetime), former (≥100 cigarettes in lifetime, but now quit), and current (≥100 cigarettes in lifetime, still smoking) (Liu et al., 2024). Alcohol intake was categorized as none (never drink alcohol), moderate (≤1 drink/day for women and ≤2 drinks/day for men), and heavy (>1 drink/day for women and >2 drinks/day for men) (Chen et al., 2019). Based on the physical activity questionnaire data we categorized PA into the following four groups based on the amount of time spent in moderate to vigorous physical activity (MVPA) per week: no MVPA (<10 points/week), some MVPA (10–149 points/week), meets MVPA (150–300 points/week), exceeds MVPA (>300 points/week) (Gorzelitz et al., 2022; Piercy et al., 2018). In addition, the homeostasis model assessment of insulin resistance (HOMA-IR) is calculated by multiplying fasting plasma insulin by fasting plasma glucose and dividing by 22.5 (Wallace et al., 2004). The specific formulas for calculating the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) are as follows (Cheng et al., 2023):

$$SII = (\text{platelet count} \times \text{neutrophil count})/\text{lymphocyte count}$$

$$SIRI = (\text{neutrophil count} \times \text{monocyte count})/\text{lymphocyte count}$$

Finally, we employed multiple imputations for the missing demographic covariates to fill in the missing values.

2.5. Statistical analysis

In descriptive analyses, we analyzed continuous and categorical variables with the *t*-test and the chi-square test, respectively, reporting mean and standard deviation for continuous variables and frequency (n) and percentage (%) for categorical variables. The concentrations of blood metals and metalloid, serum PFASs, and urinary creatinine-corrected mVOCs, after log transformation, are divided into quartiles (Q1: $P_{0–25}$, Q2: $P_{25–50}$, Q3: $P_{50–75}$, Q4: $P_{75–100}$). Logistic regression models were used to scrutinize the connection between log-transformed EDC metabolites and DKD, and the strength of the association was determined with the odds ratio (OR) and confidence interval (CI). Three regression models were utilized as follows: Model 1 was unadjusted for covariates; Model 2 enhanced Model 1 by including age, sex, race, education level, marital status, PIR, and BMI; and Model 3 further augmented Model 2 by integrating hypertension, hyperlipidemia, smoking status, alcohol intake, physical activity, SII, SIRI, HOMA-IR, SCR, HbA1c, SUA, BUN, hs-CRP.

To further investigate the dose-response relationship between EDCs and DKD, we employed a restricted cubic spline (RCS) model using the R package "rcssci." Four knots were set at the 5th, 35th, 65th, and 95th percentiles in the models, respectively.

In addition, we conducted subgroup analyses of log-transformed EDC metabolites and examined their interactions with age, gender, body mass index, HbA1c, and HOMA-IR.

Weighted quantile sum (WQS) regression was applied to analyze the association of four co-exposure patterns (co-exposure to 15 mVOCs, co-exposure to 5 metals and metalloid, co-exposure to 5 PFASs, and a combined co-exposure model encompassing 15 mVOCs, 5 metals and metalloid) with DKD. R package ("gWQS") grouping the different metabolites of EDCs in each exposure mode into ordered variables (quartiles), with 60 % of the participants as the validation set and 40 % of the participants as the training set, and 1000 bootstrap runs were performed to calculate the weighted linear index which represented whole body burden of chemicals co-exposure. Additionally, the weights of individual EDC metabolites (ranging from 0 to 1) calculated by the model showed the extent of their contribution to the WQS index.

We applied Bayesian Kernel Machine Regression (BKMR) (Bobb et al., 2015) to investigate (1) the combined effect of co-exposure to 15 mVOCs, co-exposure to 5 metals and metalloid, co-exposure to 5 PFASs, and co-exposure model encompassing 15 mVOCs, 5 metals and metalloid, these four types of co-exposure patterns on DKD, (2) the impact of each chemical as part of the co-exposure of EDCs on DKD, and (3) potential interactions between the different chemicals. The BKMR combines Bayesian and statistical approaches by iteratively regressing exposure-response functions with a Gaussian kernel function to fully account for potential nonlinear relationships and interactions among EDC metabolites. Based on the similar exposure sources and the collinearity among chemicals identified by Pearson's correlation, we further grouped the log-transformed EDC metabolites within each of the four exposure patterns previously identified. Among the co-exposure to 15 mVOCs model: group 1 included 3HPMA, IPM3, MHBMA3, HPMM, group 2 included 2MHA, 3,4-MHA, AMCA, DHBMA, 2HPMA, MA, PGA, and group 3 included AAMA, ATCA, SBMA, CEMA. The co-exposure to 5 metals and metalloid model: Pb and Cd were categorized in group 1, while Hg, Se, and Mn were categorized in group 2. The co-exposure to 5 PFASs model: Sm-PFOS, n-PFOS were categorized in group 1, with PFHxS, PFNA, and n-PFOA categorized in group 2. The co-exposure to 15mVOCs and 5 metals and metalloid model: we categorized 2MHA, 3, 4-MHA, AAMA, AMCA, ATCA, SBMA, CEMA, DHBMA, 2HPMA, 3HPMA, IPM3, MA, MHBA3, PGA, and HPMM into group1, whereas Pb, Cd, Hg, Se, and Mn were grouped into group2. The BKMR model calculated the group posterior inclusion probability (groupPIP) for the probability of inclusion between each co-exposure group and the conditional posterior inclusion probability (condPIP) for the probability of inclusion of each chemical within the group after 10,000 iterations using a hierarchical variable selection approach. The PIP values represented the significance of the contribution of individual exposure variables to the outcome.

After adjusting for all covariates, we examined the potential mediating effect of serum globulins and oxidative stress products (serum bilirubin, gamma-glutamyl transferase) on the association between Pb exposure and DKD using parallel mediation analysis (utilizing the R package "mediation"). In our research, we applied the quasi-Bayesian Monte Carlo method with 1000 simulations based on normal approximation for parallel mediation analysis. The total effect (TE) of Pb (X) on DKD (Y) was divided into direct effect (DE) and indirect effect (IE), with the ratio of IE to TE representing the proportion of mediation mediated by the mediator (M).

All analyses and plots were performed with the use of R software (version 4.3.1), EmpowerStats (http://www.empowerstats.com), 'Wu Kong' platform (https://www.omicsolution.com/wkomics/main), and GraphPad Prism (version 9.0.0). $P < 0.05$ was statistically significant.

3. Results

3.1. Participant characteristics and EDC metabolites profiles

1421 participants with diabetes mellitus were enrolled in NHANES 2015–2018. The demographic characteristics of the two groups, DKD participants (n = 575) and non-DKD participants (n = 846) are shown in Table 1. The results indicated that there were statistically significant differences between the two groups in age, sex, race, marital status, PIR, smoking status, alcohol intake, hypertension, HbA1c, HOMA-IR, hs-CRP, ACR, Scr, eGFR, SUA, BUN, SII, SIRI, Hb (hemoglobin), ALB (albumin), ALP (alkaline phosphatase), ALT(alanine aminotransferase), GLB (Globulin), LDH (lactate dehydrogenase), potassium, iron, TC, TG, HDL-C and LDL-C. The DKD group was more likely to be older, male, non-Hispanic white, and have hypertension compared to the non-DKD group. In addition, participants with DKD typically had higher levels of HbA1c, HOMA-IR, TyG index (triglyceride glucose index), hs-CRP, SUA, BUN, ALP, TG, GLB, LDH, potassium, SII, and SIRI, and lower levels of ALT, TC, HDL-C, LDL-C, and iron (all $p < 0.05$).

Table 1
Characteristics of the patients with Diabetes mellitus in the NHANES 2015–2018.

Characteristics		Non-DKD (n = 846)	DKD (n = 575)	P-value
Age (years)		59.50 ± 12.47	66.48 ± 11.61	< 0.001
Sex, n (%)	Male	444 (52.48)	342 (59.48)	0.009
	Female	402 (47.52)	233 (40.52)	
Race, n (%)	Mexican American	164 (19.38)	100 (17.39)	0.001
	Other Hispanic	106 (12.53)	56 (9.74)	
	Non-Hispanic White	223 (26.36)	212 (36.87)	
	Non-Hispanic Black	202 (23.88)	119 (20.70)	
	Other Race	151 (17.85)	88 (15.30)	
Education level, n (%)	Less than high school graduate	241 (28.49)	170 (29.57)	0.573
	High school graduate or equivalent	196 (23.17)	143 (24.87)	
	Above high school	409 (48.34)	262 (45.56)	
Marital status, n (%)	Marry/ Conhabity	554 (65.48)	332 (57.74)	< 0.001
	Widowed/ Divorced/ Separated	206 (24.35)	199 (34.61)	
	Never	86 (10.17)	44 (7.65)	
PIR, n (%)	< 1.3	259 (30.61)	201 (34.96)	0.004
	1.3–3.5	347 (41.02)	255 (44.35)	
	≥ 3.5	240 (28.37)	119 (20.69)	
Smoking status, n (%)	Never	447 (52.84)	275 (47.83)	0.022
	Former	274 (32.39)	227 (39.48)	
	Now	125 (14.77)	73 (12.69)	
Alcohol intake, n (%)	None	173 (20.45)	152 (26.44)	0.026
	Moderate	229 (27.07)	151 (26.26)	
	Heavy	444 (52.48)	272 (47.30)	
Hypertension, n (%)	No	315 (37.23)	137 (23.83)	< 0.001
	Yes	531 (62.77)	438 (76.17)	
Hyperlipidemia, n (%)	No	557 (65.84)	360 (62.61)	0.212
	Yes	289 (34.16)	215 (37.39)	
PA, n (%)	No MVPA	521 (61.58)	394 (68.52)	0.062
	Some MVPA	160 (18.91)	88 (15.30)	
	Meets MVPA	103 (12.18)	56 (9.74)	
	Exceeds MVPA	62 (7.33)	37 (6.44)	
BMI (kg/m^2)		32.07 ± 7.35	32.37 ± 7.62	0.453
HbA1c		7.22 ± 1.56	7.81 ± 1.98	< 0.001
HOMA-IR		8.21 ± 10.76	11.71 ± 19.13	< 0.001
TyG index		8.97 ± 0.84	9.16 ± 0.81	< 0.001
hs-CRP (mg/L)		5.45 ± 8.91	7.30 ± 14.89	0.004
ACR (mg/g)		10.88 ± 6.59	393.62 ± 1051.29	< 0.001
Scr (mg/dL)		0.84 ± 0.23	1.27 ± 0.95	< 0.001
eGFR(mL/min/ 1.73 m^2)		92.99 ± 20.01	68.15 ± 28.92	< 0.001
SUA (μmol/L)		321.96 ± 87.58	362.36 ± 100.17	< 0.001
BUN (mmol/L)		21.77 ± 25.87	26.26 ± 38.38	0.009
SII		515.16 ± 344.57	594.77 ± 424.60	< 0.001
SIRI		1.31 ± 0.96	1.70 ± 1.33	< 0.001
Hb(g/L)		139.78 ± 14.28	134.57 ± 17.69	< 0.001
ALB (g/L)		41.12 ± 3.57	39.79 ± 4.01	< 0.001
ALP (IU/L)		78.63 ± 27.23	85.93 ± 32.00	< 0.001
AST(U/L)		24.75 ± 30.43	23.67 ± 14.05	0.423
ALT(U/L)		25.90 ± 18.55	23.29 ± 16.23	0.006
TC (mg/dL)		182.21 ± 47.48	172.73 ± 44.27	< 0.001
TG (mg/dL)		135.02 ± 95.88	146.71 ± 127.76	0.049
HDL-C(mg/dL)		49.52 ± 15.73	46.86 ± 13.68	< 0.001
LDL-C(mg/dL)		105.08 ± 41.50	96.42 ± 36.58	< 0.001
GLB(g/L)		30.20 ± 4.65	31.80 ± 5.33	< 0.001
LDH (U/L)		144.30 ± 35.24	158.55 ± 47.64	< 0.001
Potassium(mmol/ L)		4.05 ± 0.39	4.23 ± 0.46	< 0.001
Iron (μmol/L)		14.41 ± 6.07	13.67 ± 5.52	0.020

Mean ± SD for continuous variables: P - value was calculated by the *t*-test.
n (%) for categorical variables: P- value was calculated by the chi-square test.
Abbreviations: PIR, poverty-income ratio; BMI, body mass index; PA, physical activity; MVPA: moderate-to-vigorous physical activity; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, hemoglobin A1c; TyG index, triglyceride glucose index; hs-CRP, high-sensitivity C-reactive protein; ACR, albumin to creatinine ratio; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; BUN, blood urea nitrogen; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; Hb, hemoglobin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; GLB, globulin; LDH, lactate dehydrogenase.

The geometric mean concentrations and distribution characteristics of the metabolites of EDCs are presented in Table S1 of the Supplementary Material. The results showed that the detection rates of urinary creatinine-corrected mVOCs ranged from 89.35 % to 100 %, serum PFASs ranged from 96.09 % to 98.77 %, and the detection rates of blood metals and metalloid detection rate was 85.55–100 %. In addition to this, the highest geometric mean concentration of urinary creatinine-corrected mVOCs was DHBMA, while HPMM, 3HPMA, and PGA were ranked second, third, and fourth in that order. n-PFOS and Sm-PFOS had the highest concentrations in PFASs. The results showed that the concentration of Se was almost more than 20 times higher than other blood trace elements among the blood metals and metalloids detected.

3.2. Association between EDC metabolites and DKD

We grouped EDC metabolites into quartiles (Q1: $P_{0–25}$, Q2: $P_{25–50}$, Q3: $P_{50–75}$, Q4: $P_{75–100}$) after urinary creatinine correction and Log transformed and then evaluated the association between individual EDCs and DKD by logistic regression models. The results showed that exposure to EDC metabolites was significantly associated with DKD (Table 2 and Supplementary Table S2).

There were significant associations between mVOCs and DKD. In model 3, adjusted for all covariates, 2HPMA (Q2, Q3, Q4), MHBMA3 (Q3, Q4), and PGA (Q4) showed significant associations with DKD and were similar to the significance observed in the unadjusted model 1. Compared to the first quartile (Q1), 2HPMA (Q4, OR: 2.43, 95 % CI: 1.12–5.24), MHBMA3 (Q4, OR: 2.63, 95 % CI: 1.16–5.98), and PGA (Q4, OR: 2.59, 95 % CI: 1.20–5.57) were positively correlated with DKD. Additionally, significant dose-response relationships were observed for

Table 2
Associations between EDCs and diabetic kidney disease, NHANES 2015–2018.

		Model 1 (OR 95 %CI)	P	Model 2 (OR 95 %CI)	P	Model 3 (OR 95 %CI)	P
mVOCs (Log ng/mg CR) [b]							
2HPMA							
	Q1	Ref.	0.252	Ref.	0.103	Ref.	0.066
	Q2	1.64 (0.96, 2.81)		**2.44 (1.34, 4.45)**		**3.34 (1.59, 6.98)**	
	Q3	**2.05 (1.21, 3.50)**		**3.05 (1.68, 5.51)**		**3.78 (1.84, 7.77)**	
	Q4	1.46 (0.85, 2.50)		**1.89 (1.04, 3.44)**		**2.43 (1.12, 5.24)**	
MHBMA3							
	Q1	Ref.	**0.029**	Ref.	**0.016**	Ref.	**0.006**
	Q2	1.14 (0.65, 2.00)		1.15 (0.63, 2.09)		0.95 (0.46, 1.95)	
	Q3	**3.12 (1.82, 5.34)**		**3.02 (1.69, 5.38)**		**2.48 (1.25, 4.96)**	
	Q4	**1.82 (1.06, 3.13)**		**2.01 (1.12, 3.63)**		**2.63 (1.16, 5.98)**	
PGA							
	Q1	Ref.	**0.008**	Ref.	0.059	Ref.	**0.022**
	Q2	0.87 (0.51, 1.49)		0.99 (0.55, 1.78)		1.61 (0.78, 3.34)	
	Q3	1.20 (0.71, 2.03)		1.14 (0.64, 2.05)		1.43 (0.69, 2.94)	
	Q4	**1.86 (1.11, 3.13)**		1.70 (0.94, 3.06)		**2.59 (1.20, 5.57)**	
PFASs (Log ng/mL) [c]							
PFHxS							
	Q1	Ref.	**0.028**	Ref.	**< 0.001**	Ref.	**0.001**
	Q2	0.68 (0.41, 1.13)		**0.48 (0.27, 0.85)**		**0.48 (0.25, 0.94)**	
	Q3	**0.51 (0.31, 0.86)**		**0.32 (0.18, 0.58)**		**0.35 (0.18, 0.70)**	
	Q4	0.61 (0.37, 1.01)		**0.34 (0.19, 0.62)**		**0.32 (0.16, 0.65)**	
n-PFOA							
	Q1	Ref.	**0.021**	Ref.	**0.001**	Ref.	**0.022**
	Q2	**0.42 (0.25, 0.72)**		**0.36 (0.20, 0.63)**		**0.46 (0.23, 0.93)**	
	Q3	**0.48 (0.28, 0.81)**		**0.37 (0.20, 0.67)**		**0.41 (0.20, 0.83)**	
	Q4	**0.53 (0.32, 0.88)**		**0.37 (0.21, 0.67)**		**0.43 (0.21, 0.86)**	
n-PFOS							
	Q1	Ref.	0.573	Ref.	0.063	Ref.	0.133
	Q2	0.84 (0.50, 1.39)		0.73 (0.42, 1.28)		0.91 (0.47, 1.78)	
	Q3	0.62 (0.37, 1.06)		**0.42 (0.23, 0.77)**		**0.49 (0.24, 0.99)**	
	Q4	0.94 (0.56, 1.56)		0.64 (0.35, 1.17)		0.67 (0.32, 1.40)	
Sm-PFOS							
	Q1	Ref.	0.511	Ref.	**0.007**	Ref.	**0.006**
	Q2	**0.51 (0.30, 0.87)**		**0.36 (0.20, 0.65)**		**0.37 (0.18, 0.73)**	
	Q3	0.72 (0.43, 1.20)		**0.43 (0.24, 0.80)**		**0.35 (0.17, 0.73)**	
	Q4	0.80 (0.48, 1.35)		**0.39 (0.21, 0.75)**		**0.33 (0.15, 0.72)**	
Metals and metalloid (Log ug/L) [d]							
Pb							
	Q1	Ref.	**< 0.001**	Ref.	**0.001**	Ref.	**0.006**
	Q2	**1.56 (1.11, 2.18)**		1.17 (0.82, 1.69)		1.19 (0.78, 1.82)	
	Q3	**1.99 (1.42, 2.78)**		**1.52 (1.06, 2.18)**		**1.56 (1.03, 2.36)**	
	Q4	**2.61 (1.87, 3.64)**		**1.77 (1.21, 2.58)**		**1.76 (1.13, 2.74)**	
Mn							
	Q1	Ref.	0.057	Ref.	0.546	Ref.	0.801
	Q2	0.80 (0.58, 1.10)		0.83 (0.59, 1.17)		0.97 (0.66, 1.45)	
	Q3	**0.62 (0.45, 0.86)**		**0.69 (0.49, 0.98)**		0.91 (0.60, 1.36)	
	Q4	0.77 (0.56, 1.06)		0.93 (0.65, 1.33)		1.07 (0.71, 1.62)	

Model 1: unadjusted.
Model 2: adjusted for age, sex, race, education level, marital status, PIR, BMI.
Model 3: Model 2 + hypertension, hyperlipidemia, smoking status, alcohol intake, PA, SII, SIRI, HOMA-IR, SCR, HbA1c, SUA, BUN, hs-CRP.
[b] The concentrations of urine mVOCs were initially corrected for urinary creatinine and then subjected to logarithmic transformation to achieve a normal distribution ;
[c, d] The concentrations of serum PFASs, as well as blood metals and metalloid, were all log-transformed to achieve a normal distribution.
Abbreviations: EDCs, endocrine–disrupting chemicals; PFASs, perfluoroalkyl and polyfluoroalkyl substances; PIR, poverty-income ratio; BMI, body mass index; PA, physical activity; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; SCR, serum creatinine; SUA, serum uric acid; BUN, blood urea nitrogen; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; OR, odds ratio; CI, confidence interval. The bold font indicated statistical significance (P < 0.05), and P represented P for trend.

two mVOCs (i.e., MHBMA3, PGA) in relation to DKD (P for trend < 0.05). The RCS analysis revealed a nonlinear relationship between 2HPMA, MHBMA3, and DKD after adjusting for all covariates (P for nonlinearity were 0.031 and 0.011, respectively; Supplementary Fig. 1). As noted, MHBMA3 had an explicitly inverted U-shape relationship with DKD, while 2HPMA showed S-shaped dose-response curves with DKD.

PFASs were also found to be significantly linked to DKD. In model 3, apart from PFNA showing no correlation with DKD, PFHxS (Q2, Q3, Q4), n-PFOA (Q2, Q3, Q4), n-PFOS (Q3), and Sm-PFOS (Q2, Q3, Q4) were significantly negatively correlated with DKD, with roughly the same level of significance as in model 1. In the significant fourth quartile group, the OR values for PFHxS, n-PFOA, and Sm-PFOS were 0.32 (95 % CI: 0.16–0.65), 0.43 (95 %CI: 0.21–0.86), and 0.33 (95 %CI: 0.15–0.72) respectively. Meanwhile, the OR value for n-PFOS in the third quartile group was 0.49 (95 %CI: 0.24–0.99). Significant dose-response relationships were observed for 3 PFASs (except PFNA and n-PFOS) in relation to DKD (P for trend < 0.05). As shown in Supplementary Fig. 1, the RCS analysis indicated that the non-linear relationships between the five PFASs and DKD were not statistically significant (P for nonlinearity > 0.05).

Regarding metals and metalloid, in the unadjusted model 1, Pb (Q2, Q3, Q4) and Cd (Q3) were significantly positively correlated with DKD,

whereas Se (Q3) and Mn (Q3) were significantly negatively correlated with DKD, and Hg was not correlated. After adjusting for all covariates, only Pb (Q4, OR: 1.76, 95 % CI: 1.13–2.74) exposure remained significantly positively correlated with DKD (P for trend = 0.006). The RCS analysis revealed that the non-linear relationship between Pb and DKD was not statistically significant (P for nonlinearity was 0.962; Supplementary Fig. 1), and other metals showed no significant nonlinearity.

3.3. Subgroup analyses and interaction tests

After adjusting for covariates, the association between EDC metabolites (corrected for urinary creatinine and log-transformed) and DKD varied by age, sex, BMI, HbA1c, and HOMA-IR. A p-value for interaction < 0.05 indicates that the association between EDC metabolites and DKD differed across groups (Supplementary Table S3, S4, and Fig. 2).

Among the mVOCs, we observed a significant difference in the association between DHBMA exposure and DKD among genders (P for interaction = 0.029), with a significant positive association in the male group (OR: 25.30, 95 % CI: 2.70–237.39) and a non-significant negative association in the female group (OR: 0.80, 95 % CI: 0.08–7.83). Additionally, we observed a significant interaction between 2HPMA and DKD

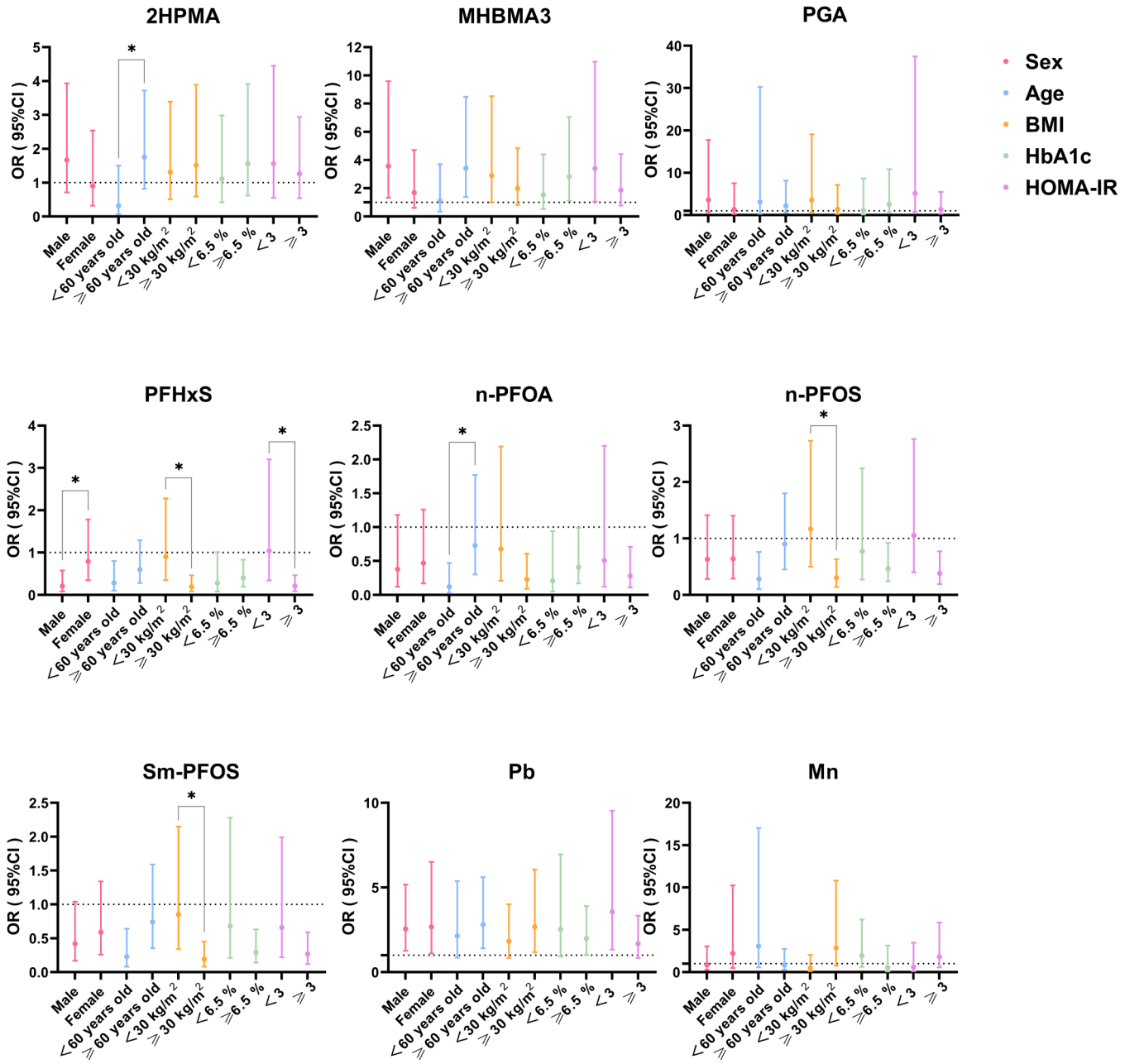

Fig. 2. Interactive effect of gender, age, BMI, HbA1c, HOMA-IR, and EDC metabolites on DKD. The urine mVOCs were initially corrected by urinary creatinine and then log-transformed to achieve a normal distribution. The serum PFASs, as well as blood metals and metalloid, were all log-transformed to achieve a normal distribution. This analysis was carried out using the logistic regression model. Covariates included age, sex, race, education level, marital status, poverty-income ratio, body mass index, hypertension, hyperlipidemia, smoking status, alcohol intake, physical activity, homeostatic model assessment of insulin resistance, hemoglobin A1c, high-sensitivity C-reactive protein, serum creatinine, serum uric acid, blood urea nitrogen, systemic immune-inflammation index, systemic inflammation response index. Abbreviations: EDCs, endocrine–disrupting chemicals; PFASs, perfluoroalkyl and polyfluoroalkyl substances; OR, odds ratio; CI, confidence interval. *P < 0.05 indicated that the interaction is significant.

in age subgroups (P for interaction = 0.037). The OR was 1.75 (95 %CI: 0.82–3.72) for the subgroup aged ≥ 60 years and 0.32 (95 %CI: 0.07–1.50) for the subgroup aged < 60 years. The association between mVOCs and DKD did not significantly vary across different BMI groups. No significant interactions were observed in subgroups stratified by HbA1c and HOMA-IR (P for interaction > 0.05), except DHBMA. In the subgroups with lower HbA1c and HOMA-IR, exposure to DHBMA was associated with a significantly higher risk of developing diabetic kidney disease (DKD) (OR: 15.48, 95 % CI: 1.03–231.82; OR: 22.51, 95 % CI: 1.80–280.89).

The results indicated a highly significant intergroup difference in PFASs. As gender varies, a significant difference in the association between PFHxS and DKD was observed (P for interaction = 0.041). Compared to the female group (OR: 0.79, 95 %CI: 0.35–1.78), the male group (OR: 0.21, 95 %CI: 0.08–0.58) exhibited a significant negative correlation with DKD. In addition, the association between n-PFOA and DKD differed significantly between age groups (P for interaction as 0.028). In the subgroup of participants aged < 60, a significant negative correlation was observed between each of the five PFASs included and DKD. Additionally, PFHxS, PFNA, n-PFOS, and Sm-PFOS presented significant interactions in the BMI subgroups (P for interaction as 0.013, 0.007, 0.011, 0.010). In participants with BMI ≥ 30 kg/m^2, five individual PFASs were considered to exhibit significant negative correlations with DKD. Additionally, HOMA-IR might be a potential modifier for the relationship between PFHxS , PFNA, and DKD (P for interaction as 0.016 and 0.010, respectively). A significant inverse association between these two PFASs and DKD was observed among participants with HOMA-IR≥ 3, whereas a positive association was noted in the subgroup with HOMA-IR < 3. The ORs between PFASs and DKD were lower in groups with higher HOMA-IR values.

The correlation between metals and metalloid exposure and DKD among age, gender, BMI, HbA1c, and HOMA-IR groups was not significantly different.

3.4. WQS regression model to assess the association between co-exposure to EDCs and DKD

As shown in Supplementary Table S5, after adjusting for confounding factors, the WQS index for co-exposure to metals and metalloid + mVOCs (OR: 2.34, 95 % CI: 1.04–5.28) and co-exposure to blood metals and metalloid (OR: 1.59, 95 % CI: 1.12–2.14) indicated significantly positive associations with DKD, while the WQS index for co-exposure to PFASs (OR: 0.66, 95 % CI: 0.44–0.98) demonstrated significantly negative associations with DKD. Only co-exposure to mVOCs (OR: 1.77, 95 % CI: 0.96–3.24) showed a positive but not statistically s

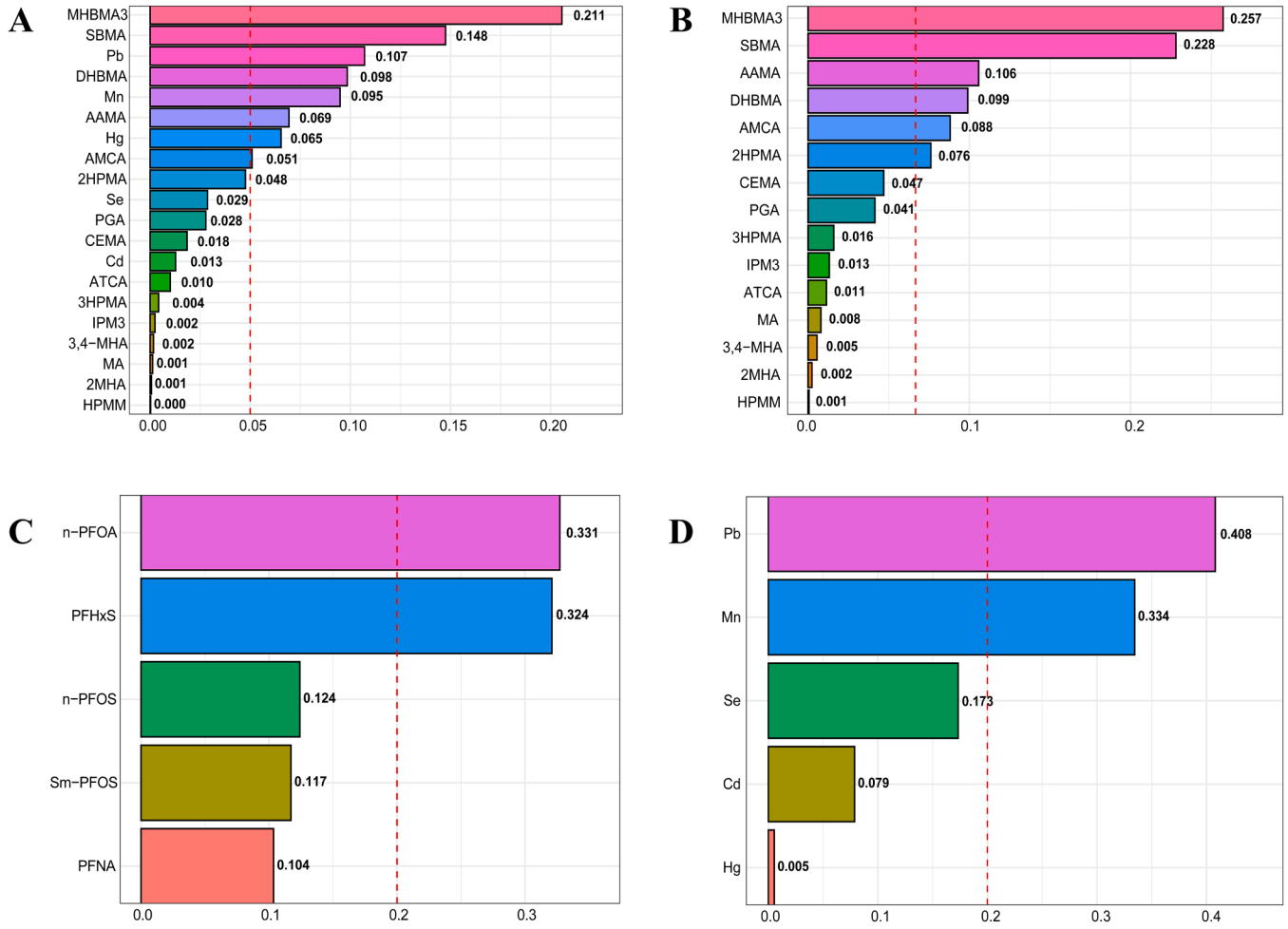

Fig. 3. WQS model regression index weights in the model of co-exposure to metals and metalloid + mVOCs (A) , co-exposure to mVOCs (B) , co-exposure to PFASs (C) , and co-exposure to metals and metalloid (D). The urine mVOCs were initially corrected by urinary creatinine and then log-transformed to achieve a normal distribution. The serum PFASs, as well as blood metals and metalloid, were all log-transformed to achieve a normal distribution. All models were adjusted for age, sex, race, education level, marital status, poverty-income ratio, body mass index, hypertension, hyperlipidemia, smoking status, alcohol intake, physical activity, homeostatic model assessment of insulin resistance, hemoglobin A1c, high-sensitivity C-reactive protein, serum creatinine, serum uric acid, blood urea nitrogen, systemic immune-inflammation index, systemic inflammation response index.

The estimated EDCs metabolite weights in each WQS index are shown in Supplementary Table S6 and Fig. 3. The chemicals with the highest weights in the co-exposure to metals and metalloid + mVOCs model were, in order, MHBMA3, SBMA, Pb, DHBMA, Mn, AAMA, Hg, and AMCA (weights as 0.211, 0.148, 0.107, 0.098, 0.095, 0.069, 0.065, and 0.051, respectively). The weights of these chemicals all exceed the threshold parameter, as shown by the red dotted line in the figure. The threshold parameter is generally defined as the reciprocal number of elements in the co-exposure (Carrico et al., 2015). In the co-exposure to metals and metalloid model, the metals with weights above the threshold parameter are Pb (0.408) and Mn (0.334). In the co-exposure to PFASs model, the weights of n-PFOA (0.331) and PFHxS (0.324) were higher, while the weights of n-PFOS, Sm-PFOS, and PFNA were 0.124, 0.117, and 0.104, respectively. MHBMA3 (0.257), SBMA (0.228), AAMA (0.106), DHBMA (0.099), AMCA (0.088), and 2HPMA (0.076) had higher weights in the co-exposure to mVOCs model.

3.5. The BKMR model to assess the association between co-exposure to EDCs and DKD

3.5.1. Correlations between chemicals

Considering the collinearity among EDC metabolites, we calculated the Pearson correlation coefficients for log-transformed chemicals in four models: co-exposure to metals and metalloid + mVOCs, co-exposure to mVOCs, co-exposure to PFASs, and co-exposure to metals and metalloid. The results revealed strong correlations between 2MHA and 3,4-MHA, 3HPMA and HPMM, IPM3 and MHBMA3, IPM3 and HPMM, HPMM and MHBMA3 in co-exposure to mVOCs (Supplementary Fig. 2B). In contrast, the correlation between metals and metalloid + mVOCs was weak (Supplementary Fig. 2A). The correlations among all five PFASs were statistically significant ($P < 0.001$), with Sm-PFOS and n-PFOS showing the strongest correlation ($r = 0.88$), and high correlations among the other chemicals (Supplementary Fig. 2 C, ranging from 0.56 to 0.88). In addition, the correlations between metals

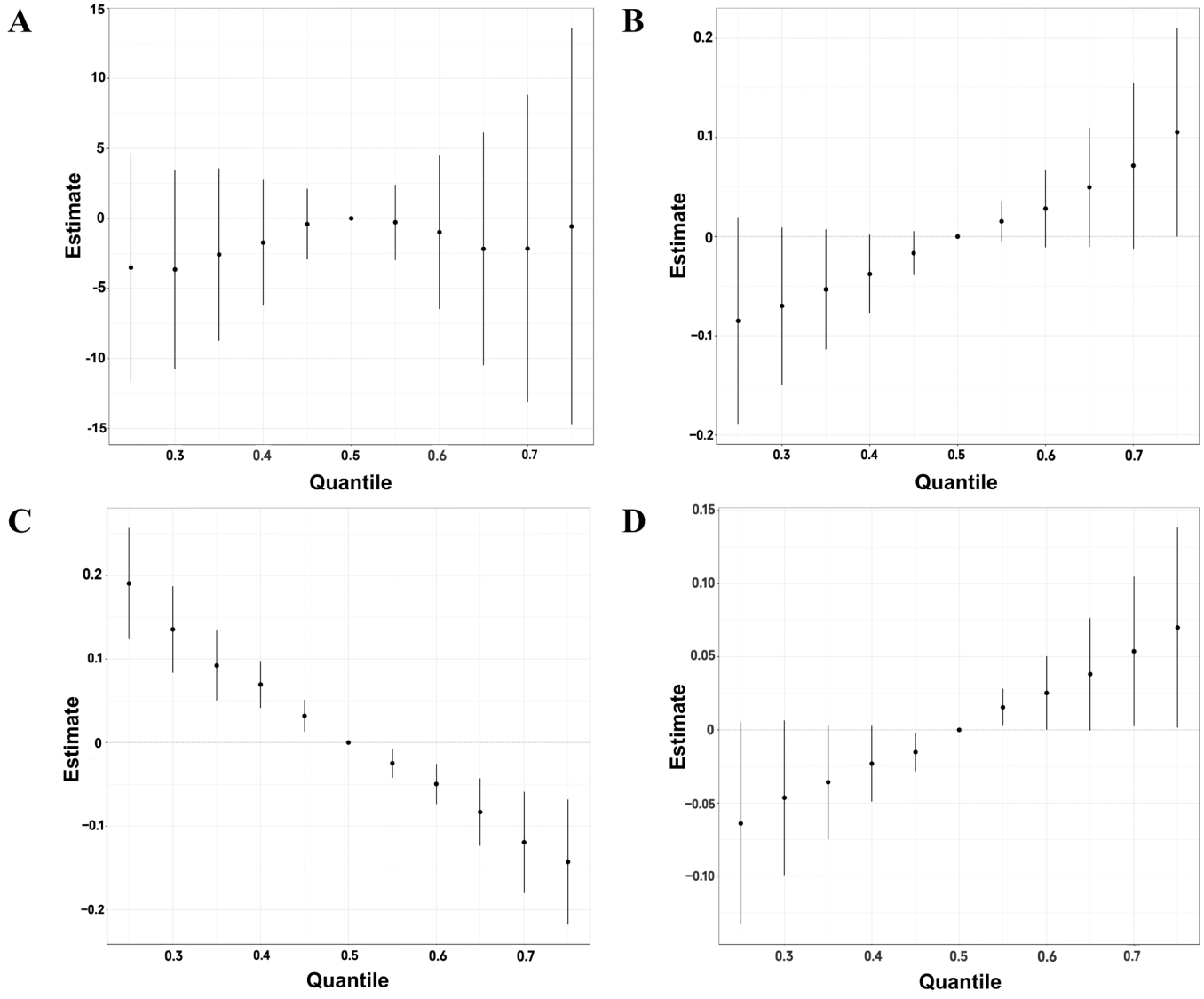

Fig. 4. Overall effect (95 % CI) of the patterns for co-exposure to metals and metalloid + mVOCs (A), co-exposure to mVOCs (B) , co-exposure to PFASs (C) , and co-exposure to metals and metalloid (D) on DKD by BKMR model when all the chemicals at particular percentiles were compared to all the chemicals at their 50th percentile. The urine mVOCs were initially corrected by urinary creatinine and then log-transformed to achieve a normal distribution. The serum PFASs, as well as blood metals and metalloid, were all log-transformed to achieve a normal distribution. All models were adjusted for age, sex, race, education level, marital status, poverty-income ratio, body mass index, hypertension, hyperlipidemia, smoking status, alcohol intake, physical activity, homeostatic model assessment of insulin resistance, hemoglobin A1c, high-sensitivity C-reactive protein, serum creatinine, serum uric acid, blood urea nitrogen, systemic immune-inflammation index, systemic inflammation response index.

and metalloid were relatively weak (Supplementary Fig. 2D), with relatively high correlations between Pb and Cd. These chemicals were grouped based on their correlation coefficients and similar exposure sources.

3.5.2. Overall co-exposure effect

Fig. 4 illustrates BKMR estimated effect values of the overall effect of different EDCs exposure patterns on DKD. We initially fixed all chemical concentrations at their median and then compared the estimated effect values for DKD when the metabolite concentrations of these EDCs were at different percentiles (ranging from 0 % to 100 %). After adjusting for all covariates, we observed a significant positive correlation between DKD (odds of DKD) and having all blood metals and metalloid overall concentrations at the 75th percentile or above, compared to the 50th percentile (Fig. 4D). PFASs co-exposure showed a significant negative correlation with DKD compared to the median concentration (Fig. 4C). Although no statistically significant relationship was found between mVOC co-exposure and DKD, an overall upward trend was observed (Fig. 4B). However, no overall effect of mVOC, metals, and metalloid co-exposure on DKD was observed (Fig. 4A).

3.5.3. Univariate dose-responses curves

Supplementary Fig. 3 illustrates the univariate dose-response curves associated with the outcome (DKD) when metabolite levels of other EDCs are fixed at the 50th percentile. In the case of co-exposure to mVOCs, the prevalence of DKD increased with higher concentrations of 3HPMA, 2HPMA, MHBMA3, PGA, and DHBMA. At the same time, it decreased with higher levels of IPM3 and CEMA (Supplementary Fig. 3B). In co-exposure to PFASs, a negative correlation was observed between PFHxS, n-PFOA, and Sm-PFOS and the prevalence of DKD (Supplementary Fig. 3C). Furthermore, DKD prevalence continued to increase with rising serum concentrations of Pb, Cd, and Mn. In contrast, Hg negatively correlated with DKD (Supplementary Fig. 3D).

3.5.4. Bivariate exposure-response curves

To investigate potential interactions between co-exposed EDC metabolites, we plotted bivariate exposure-response curves (Supplementary Fig. 4). BKMR interaction analysis revealed interactions among 2HPMA, 2MHA, 3HPMA, AAMA, AMCA, ATCA, Cd, Hg, IPM3, MHBMA3, and SBMA in the co-exposure to metals and metalloid + mVOCs model when one of each pair was fixed at the 10th, 50th, and 90th percentiles (while the rest were fixed at their medians) (Supplementary Fig. 4A). In contrast, no potential interaction between any two chemicals and DKD was observed in other co-exposure models (mVOCs, PFASs, metals and metalloid) (Supplementary Fig. 4B-4D).

3.5.5. The groupPIP and condPIP for co-exposure

The groupPIP and condPIP for different exposure patterns generated by the BKMR model are shown in Table S7. Among metals and metalloid + mVOCs, the groupPIP was higher than 0.5 for both mVOCs (group 1) and metals and metalloid (group 2). Additionally, the contribution of MHBMA3 to DKD was highest in group 1 (condPIP = 0.41), whereas Pb was the greatest contributor in group 2 (condPIP = 0.40). For co-exposure to mVOCs, group 1 (MHBMA3, 3HPMA, HPMM, IPM3) had the highest groupPIP (0.68), with MHBMA3 contributing most significantly (condPIP = 0.62). The groupPIPs for group 2 and group 3 were 0.49 and 0.39, respectively, with PGA (condPIP = 0.39) and CEMA (condPIP = 0.40) being the most significant contributors in group 2 and group 3, respectively. In co-exposure to PFASs, group 1 (Sm-PFOS, n-PFOS) had a groupPIP of 0.77, primarily contributed by Sm-PFOS (condPIP = 0.88). Meanwhile, group 2 (PFHxS, n-PFOA, PFNA) had a groupPIP of 0.68, with PFHxS making the largest contribution (condPIP = 0.42). The results indicated that in the co-exposure metals and metalloid model, group 1 exhibited a higher groupPIP (0.99), with Pb playing the most prominent role (condPIP = 0.99).

3.6. Mediation analysis

Based on Table S8, we further evaluated whether serum globulin levels and oxidative stress products (serum bilirubin, gamma-glutamyl transferase) mediated the positive correlation between blood Pb and DKD. Table S8 and Fig. 5 show that serum globulins significantly mediated the association between Pb and DKD, accounting for 7.25 % of the mediation.

4. Discussion

In this study based on NHANES 2015–2018, we applied several statistical methods to examine the relationship between individual EDC metabolites and diverse co-exposure models and DKD. Here are several novel findings from our study:

Firstly, both individual metals/metalloid and co-exposure to metals and metalloid models consistently emphasize Pb as a significant risk factor for DKD. In the WQS regression and BKMR models, co-exposure to metals and metalloid models showed a significant positive correlation with DKD. Additionally, globulin has been identified as a mediator of the positive association between Pb and DKD. According to previous research, declines in kidney function among middle-aged and elderly diabetic patients are associated with blood lead levels (Tsaih et al., 2004). Previous studies conducted among 4234 adult diabetic patients in Chinese communities have shown a significant positive correlation between high lead levels and DKD prevalence (Wan et al., 2021). Several prospective studies among type 2 diabetic patients have observed that environmental lead exposure accelerates the decline in the glomerular filtration rate (Huang et al., 2013; Lin et al., 2006). A British study showed that renal biopsies from occupationally lead-exposed populations exhibited ultrastructural alterations in proximal tubules, sometimes accompanied by the formation of intranuclear inclusion bodies (Cramer et al., 1974). Renal tubule injury is one of the important markers of DKD, and it is a pathway related to glomerular dysfunction and the development of proteinuria and CKD (Thomas et al., 2005). In animal experimental models, Pb induced reactive oxygen species (ROS) production and weakened cellular antioxidant capacity in experimental rats (Liu et al., 2012). In addition, Simoes et al. proposed that Pb promotes oxidative stress and inflammation by activating ROS and COX-2 through the MAPK signaling pathway and increases vascular reactivity (Simões et al., 2015). Microvascular damage plays a crucial role in the

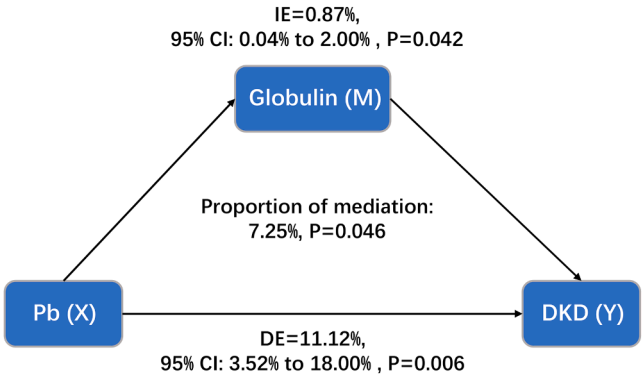

Fig. 5. Estimated proportion of the association between blood Pb and DKD mediated by serum globulins. The blood Pb had been log-transformed to achieve a normal distribution. Covariates included age, sex, race, education level, marital status, poverty-income ratio, body mass index, hypertension, hyperlipidemia, smoking status, alcohol intake, physical activity, homeostatic model assessment of insulin resistance, hemoglobin A1c, high-sensitivity C-reactive protein, serum creatinine, serum uric acid, blood urea nitrogen, systemic immune-inflammation index, systemic inflammation response index. Abbreviations: IE, the estimate of the indirect effect; DE, the estimate of the direct effect; Proportion of mediation = IE/DE + IE.

occurrence and progression of kidney disease in diabetic patients (Thomas et al., 2015). It is worth noting that metals and metalloids always co-exist and interact in the environment. A nationally representative NHANES study indicated that blood lead, blood cadmium, and urinary cadmium were positively associated with DKD risk in diabetic patients and that there may be dose-response relationships and interactions in the associations of Cd, Pb with DKD (Zhang et al., 2024). Furthermore, for any metals or metalloids, no significant interactions were observed in subgroups stratified by age, gender, BMI, HbA1c, and HOMA-IR. In this study, two models of WQS and BKMR were used, and all found that the co-exposure to five blood metals and metalloid (Pb, Mn, Cd, Hg, Se) were significantly associated with a higher prevalence of DKD, further suggesting that metal exposure may promote the progression of DKD.

More and more studies have shown that inflammatory response and abnormal activation of the immune system play an important role in the pathophysiology of DKD. Globulin (GLB) is a type of serum protein, both a product of immune response and one of the common inflammatory factors, including α-globulin, β-globulin, and γ-globulin. Some epidemiological studies have shown a positive correlation between GLB and diabetes (Lindsay et al., 2001). A study based on the American population suggested a correlation between high levels of GLB and a high prevalence of DKD (Wang et al., 2022). Currently, the potential mechanisms of GLB and diabetic nephropathy are not precise. An animal experimental model indicated that GLB could promote the expression of TNF-α and IL-6, participating in the process of kidney damage (Khater et al., 2021). Advanced glycation end products (AGEs) are essential regulators in the progression of DKD (Sourris and Forbes, 2009), and Kostov et al. reported that anti-AGE EL IgG antibodies and anti-AGE EL IgM antibodies could be used as biomarkers of vascular injury in Type 2 Diabetes (Kostov et al., 2022). In addition, recent studies have found that in response to Pb exposure and related diseases, the organism's inflammatory response is increased, and the immune system is activated (Kalahasthi et al., 2022). Lead exposure promotes inflammation by inducing ROS production, inhibiting antioxidant enzymes, and activating MAPK regulatory pathways (Jing et al., 2020). Lutz et al. investigated and found that IgE levels increased significantly with increasing blood lead concentrations in 279 children (Lutz et al., 1999). With a common pathogenesis in mind, we hypothesized whether Pb exposure would increase the risk of DKD via serum globulin. The study's results indicated that GLB significantly mediated the association between Pb and DKD, with the mediation proportion being 7.25 %. Thus, we conjectured that excessive Pb exposure increases the prevalence of DKD by promoting inflammatory response and immune response.

Secondly, Table S9 shows that acrylamide, toluene, xylene, acrolein, 1,3-butadiene, ethylbenzene, styrene, propylene oxide, N,N-dimethylformamide, cyanide, isoprene, and crotonaldehyde, among others, are the parent chemicals of 15 urine metabolites of volatile organic compounds (mVOCs) included in this study (Li et al., 2021). In the logistic regression model, elevated exposures to N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA), N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine (MHBMA3), and Phenylglyoxylic acid (PGA) were associated with an increased prevalence of DKD. MHBMA3 was considered the most essential chemical in both the WQS and the BKMR models for co-exposure models (mVOCs + metals and metalloid, mVOCs), with higher mVOCs concentrations associated with increased prevalence of DKD. N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA) and MHBMA3 are urinary biomarkers of 1,3-butadiene (BD), with environmental tobacco smoke (ETS) being a significant source of BD (Nieto et al., 2021). It has been shown that MHBMA3 is a highly sensitive biomarker of BD in smoking populations (Chen and Zhang, 2022). A prospective study in Korea found an association between increased smoking duration and decreased eGFR (Lee et al., 2021), while Ito et al. found a significant positive correlation between smoking and proteinuria (Ito et al., 2020). An animal study demonstrated that diabetic rats exposed to tobacco smoke exhibit higher levels of creatinine and urea, with a higher risk of DKD (Napierala et al., 2019). Additionally, in a cross-sectional study conducted on a US population, BD exposure was associated with an increased risk of insulin resistance and diabetes incidence (Liang et al., 2023). Increased insulin resistance was recognized as a significant indicator of renal failure (Spoto et al., 2016). Smoking has also been reported to exacerbate oxidative stress and inflammatory responses in diabetic nephropathy (Agarwal, 2005). Many studies have indicated that tobacco smoke may promote the production of oxidative free radicals or elevate inflammatory factors such as renal interleukin (IL), tumor necrosis factor α (TNF-α), C-reactive protein (CRP), renal monocyte chemotactic protein-1, and neutrophils (Agarwal, 2005; Al Hariri et al., 2016; Kayama et al., 2015; Rafacho et al., 2011), and even increase renal fibrosis significantly by upregulating transforming growth factor beta (TGF-β) and fibronectin (Mayyas and Alzoubi, 2019; Obert et al., 2011). Oxidative stress, inflammatory responses, and renal fibrosis collectively accelerate structural and functional damage to the kidneys in diabetic patients. Furthermore, an animal experiment found that ethylbenzene, as a precursor chemical of mandelic acid (MA) and phenyl glyoxylic acid (PGA), could induce apoptosis of renal tubular cells in experimental rats through the mitochondrial pathway (Zhang et al., 2010). There are also studies showing that certain VOCs (e.g., bromodichloromethane and dibromochloromethane) cause impaired renal function (Thornton-Manning et al., 1994) and that people chronically exposed to benzene, toluene, and xylenes (BTX) have higher levels of urea and creatinine (Neghab et al., 2015). In the RCS analyses, we found inverted U-shaped and S-shaped associations between 2HPMA, MHBMA3, and DKD. As endocrine disruptors, mVOCs can influence various receptor-mediated responses, and these responses tend to increase and then decrease with increasing doses. This non-monotonic dose-response curve results from the combined influence of several factors, including receptor occupancy, differences in gene expression, and nonlinear pharmacokinetics(Pan et al., 2024; Welshons et al., 2003). The current research primarily focuses on the impact of individual chemicals on organisms, with more studies on volatile organic compounds (VOCs) related to proteinuria and eGFR in chronic kidney disease, while there is limited research on their association with DKD. Our study assessed the correlation between 15 individual mVOCs, their co-exposure, and DKD. Although no statistically significant difference was observed between co-exposure to mVOCs and DKD, a positive correlation was still evident. This study may provide a new perspective on the prevention of DKD and help fill the gaps in this area of research.

However, when investigating the correlation between co-exposure to mVOCs + metals and metalloid and DKD, we found that the overall co-exposure showed a significant positive correlation in the WQS model, while there was no correlation between the overall co-exposure and DKD in the BKMR model. Additionally, various chemicals such as 2HPMA, 2MHA, 3HPMA, AAMA, AMCA, ATCA, Cd, Hg, IPM3, MHBMA3, and SBMA may exhibit potential interactions in DKD. The WQS model is more suitable than the individual chemicals analysis for identifying the main risk factors contributing to the overall body burden. In contrast, the BKMR model is more relevant for identifying nonlinear effects and interactions between chemicals (Zhang et al., 2019). In the co-exposure to mVOCs + metals and metalloid model, we found that more than half of the univariate dose-responses curves of chemicals showed a nonlinear trend. For example, an inverted 'U' shape was found between Cd, AAMA, AMCA, and DKD. Hg, 2MHA, and IPM3 presented the "M" trend. So far, more and more studies have demonstrated that (non-) noble metal-based oxidation catalysts can degrade VOCs (Wu et al., 2021). Additionally, mercury can react with xylene or toluene and may form some organic mercury compounds such as methylmercury and phenylmercury (Clarkson and Magos, 2006). A study suggested that the kidney may take up Hg^{2+} through organic anion transporter proteins on the basal lateral plasma membrane of proximal tubule epithelial cells, or amino acid transporter proteins, or in the form of Hg^{2+}-albumin complexes (Bridges and Zalups, 2005). We speculated that there may be

interactions, such as competitive binding and binding reactions between VOCs and metals. Further research is required to explore the interaction of metals and VOCs in DKD.

At the end of this study, we observed a significant negative correlation between PFASs and DKD, whether a individual chemical was analyzed in logistic regression models or co-exposure to PFASs was assessed using WQS and BKMR models. Several epidemiological studies suggested that exposure to PFASs may be associated with decreased renal function (Blake et al., 2018; Jain and Ducatman, 2019b). However, a C8 Health Project involving 53,650 Americans (including 5210 individuals with diabetes) revealed a significant positive correlation between PFASs and eGFR, which was more pronounced in the diabetic population (Conway et al., 2018). Previous cross-sectional and longitudinal studies from China also observed a correlation between high PFAS exposure and low DKD prevalence (Li et al., 2022). The specific mechanism behind the negative association between PFASs and DKD remains unclear but may involve the following hypotheses: The hyperglycemic environment in diabetic patients may cause various metabolic abnormalities, leading to pathophysiological structural changes in renal units, which in turn result in renal tissue hypoxia (Alicic et al., 2017). Additionally, renal hypoxia exacerbates the progression of DKD (Friederich-Persson et al., 2013). Perfluorocarbons could function as effective oxygen carriers, with an oxygen transport capacity even exceeding that of hemoglobin, and can mitigate hypoxia-induced organ damage, playing a crucial role in organ transplantation (Hosgood and Nicholson, 2010; Riess, 2006; Spahn, 1999). Beyond these mechanisms, the complex and delayed excretion of PFASs in the human body may also contribute. This complex relationship is further supported by the inverted U-shaped trend between eGFR stages and PFASs proposed by Jain et al. PFASs are secreted into the urine via OAT1 transporter proteins in the renal tubules, where long-chain PFASs can be reabsorbed from the urine by OAT4 transporter proteins in the renal tubules. The balance between reabsorption and secretion is altered in the kidneys with DKD, as renal disease progression reduces the contribution of OAT4-mediated PFAS reabsorption compared to healthy kidneys (Conway et al., 2018; Jain and Ducatman, 2019a; Nakagawa et al., 2009). An increasing body of research suggests that declining kidney function may involve potential reverse causation. However, further large-scale prospective studies and animal experiments are needed to explore the relationship between PFASs and DKD in more depth. The subgroup analyses revealed that the association between exposure to PFASs and the prevalence of DKD differed significantly across BMI groups. The negative correlation between PFASs and DKD was especially pronounced in individuals with a BMI of $\geq$ 30 kg/m^2. If the hypothesis of chronic hypoxia theory holds, PFASs have been shown to exhibit certain antioxidant effects (Hosgood and Nicholson, 2010; Riess, 2006; Spahn, 1999). These antioxidant effects are more pronounced in obese individuals, who experience higher levels of oxidative stress than those with normal weight (Furukawa et al., 2017). The association between PFASs and DKD varies across different HOMA-IR groups. PFASs show a significant negative correlation with DKD in individuals with stronger insulin resistance. Several studies have demonstrated a negative correlation between PFASs and HOMA-IR (Tian et al., 2024; Yan et al., 2023). Animal studies suggested that PFASs may have an affinity for PPAR-α and PPAR-γ receptors, acting as agonists to activate them, which regulates fatty acid metabolism and transcription of various insulin-related genes, thereby enhancing insulin sensitivity and reducing HOMA-IR (Ojo et al., 2020; Wolf et al., 2008).

This study has the following strengths. Firstly, it evaluated the relationship between multiple EDCs (both individual and co-exposure chemicals) and DKD. Secondly, we applied numerous statistical methods and adjusted for potential confounding variables to ensure model stability and the reliability of the results. Lastly, all the data used in this study came from NHANES, a database that employs a rigorous multi-stage randomized sampling design with strict research procedures and quality assurance checks. Nevertheless, there are some limitations to this study. First, due to the cross-sectional design, causality between EDCs and DKD cannot be inferred. Second, although we considered several important factors, it was not possible to completely exclude the effects of other unaccounted-for confounding factors. Third, the concentrations of EDCs were measured only at a single time point, which requires a repeated measurement design to more accurately reflect individual exposure levels. Fourth, although we considered the combined exposure effects on participants, the limited sample size prevented us from assessing the association between simultaneous exposure to three EDC metabolites (mVOCs, metals and metalloid, and PFASs) and DKD. The Weighted Quantile Sum (WQS) regression model has limitations, as it considers individual effects in only one direction and cannot simultaneously account for both positive and negative individual effects. The complementary use of the Bayesian Kernel Machine Regression (BKMR) model helps address this limitation. Given the current study's limitations, further prospective research is needed to support our findings.

5. Conclusion

In summary, after considering the results from the three regression models, we concluded that there was a significant positive correlation between metals and metalloid co-exposure and the prevalence of DKD, with Pb being the most important contributor. It was determined that serum globulin played a partial mediating role in the positive association between Pb exposure and DKD. Persistent exposure and accumulation of 2HPMA, MHBMA3, and PGA were significantly associated with an increased risk of DKD. Nonlinear positive associations between 2HPMA, MHBMA3, and DKD were observed, with MHBMA3 showing an inverted U-shape and 2HPMA exhibiting S-shaped dose-response curves. Moreover, in co-exposure to metals, metalloid, and mVOCs, the BKMR model revealed potential interactions among 2HPMA, 2MHA, 3HPMA, AAMA, AMCA, ATCA, Cd, Hg, IPM3, MHBMA3, and SBMA in their association with DKD. Finally, individual or co-exposure to PFASs was significantly negatively associated with DKD, especially in obese individuals (BMI $\geq$ 30 kg/m^2). Given the cross-sectional design of this study and the complexity of the relationship between renal function and endocrine-disrupting chemicals (EDCs) in serum or urine, these findings should be interpreted with caution, and further research is needed to elucidate the potential mechanisms underlying these observations.

Ethics statement

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the NCHS Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

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CRediT authorship contribution statement

Chen Hongyu: Validation, Supervision, Resources, Funding acquisition. **Xu Luhuan:** Supervision, Project administration, Methodology, Investigation, Formal analysis. **Ye Xiaoang:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation. **Li Xinru:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation.

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118044.

Data availability

The study data are available on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes).

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