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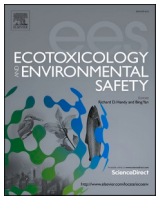

# The association between endocrine disrupting chemicals and MAFLD: Evidence from NHANES survey

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ABSTRACT

Previous studies on the association of endocrine-disrupting chemicals (EDCs) with metabolic dysfunction-associated fatty liver disease (MAFLD) are very limited. This study analyzed the association of EDCs exposure with MAFLD among 5073 American adults from the 2017–2018 National Health and Nutrition Examination Survey. The results showed that increased exposure to 3 EDCs metabolites (namely As, DiNP and PFOA) were significantly associated with MAFLD, the odds ratio of which were 1.819 (95% CI: 1.224, 2.702), 1.959 (95% CI: 1.224, 3.136) and 2.148 (95% CI: 1.036, 4.456), respectively. Further, the bayesian kernel machine regression model also revealed that phthalates exposure was strongly connected with the MAFLD, particularly in females and the elderly over 65. Moderating effect analysis suggested that higher body mass index (BMI) and inflammatory diet habit (indicated by dietary inflammatory index) strengthened the association between EDCs and MAFLD, whereas population with higher level of insulin sensitivity showed lower risk. In conclusion, our results suggest that either single or combined exposure to EDCs metabolites is link to MAFLD. Our findings also encourage people to sustain a healthy diet, normal levels of insulin sensitivity and BMI, which may help to alleviate the association of MAFLD risk in exposure to EDCs. These results also help us to better understand the association of EDCs and MAFLD and provide effective evidences for preventing MAFLD from the EDCs exposure aspect.

## 1. Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) has risen to be a global health issue. A recent worldwide expert consensus statement suggested the classification of MAFLD, which could be diagnosed independent of disease status if there was an indication of hepatic steatosis linked with metabolic dysfunction (Eslam et al., 2020; Tilg et al., 2020). It is estimated that MAFLD affects more than one-third of the worldwide population (Chan et al., 2022). And people with MAFLD show a high risk of liver cirrhosis and hepatocellular carcinoma (Lee et al., 2022), which caused around 21.1 million disability-adjusted life years in 2016 (Collaboration, 2018).

Among these environmental factors related to MAFLD, endocrine-disrupting chemicals (EDCs) exposure is acknowledged connecting with the emergence and progression of MAFLD (Cano et al., 2021; Praveena et al., 2018). Heavy metals, phthalates (PAEs), and per- and poly-fluoroalkyl substances (PFASs) are all typical EDCs that can compromise the hormonal transmission, cause oxidative stress, and subsequently mediate metabolic problems (Cano et al., 2021). Moreover, EDCs is widely found in the environment, such as soil and air (Wang et al., 2022). Besides, EDCs is widely used in the production of daily household products, such as PAEs in cosmetics and plastic products (Net et al., 2015) and PFASs in textiles, surfactants and food packaging (Sunderland et al., 2019). Researches have confirmed that EDCs exposure caused harm to liver health, leading to non-alcoholic fatty liver disease (NAFLD), etc. (Cano et al., 2021; Net et al., 2015; Sunderland et al., 2019).

EDCs exposure causes an immunological response and oxidative stress, which often contribute to MAFLD (Praveena et al., 2018; Yang et al., 2014; Zhang et al., 2019). Animal experiment has found that perfluorooctanoic acid (PFOA) exposure causes severe hepatocyte damage and significant invasive inflammatory cells (Yang et al., 2014). Continuous exposure to PAEs in humans has also been linked to the suppression of liver detoxifying enzymes, which leads to liver disease (Praveena et al., 2018). Teschke concluded that cadmium (Cd) may form Cd metallothionenin (Cd-MT) complex in the liver, causing

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mitochondrial dysfunction leading to MAFLD (Teschke, 2022). However, he also indicated that PAEs entered the human body and reached the liver for metabolism, but there was no evidence to support that PAEs causing liver damage (Teschke and Xuan, 2022). This is not consistent with the results of other study (Yu et al., 2021). In addition, most studies on MAFLD were devoted to exploring the association of MAFLD with diseases like cardiovascular disease (Lee et al., 2022), rarely focused on the factors that influenced the occurrence and development of MAFLD. What's more, epidemiological evidence for the association between EDCs and MAFLD is very limited, making it difficult for us to understand the effect of EDCs on MAFLD.

Since EDCs can impair hepatocyte function and contribute to MAFLD, we conceptualized this research to investigate the association between EDCs and MAFLD with the National Health and Nutrition Examination Survey (NHANES) population. To identify potentially susceptible sub-populations, subgroup analysis separated by socioeconomic and life behavior characteristics were performed. Besides, we also evaluated the different modification effects of different body mass index (BMI), dietary inflammatory index (DII), physical activity and insulin sensitivity (HOMA-IS) intensities. By doing these analyses, we hope to learn more about the association between EDCs and MAFLD, and the effects of DII, BMI and HOMA-IS on the relationships of MAFLD with EDCs.

## 2. Materials and methods

### 2.1. Study design and population

Based on the availability of information on the MAFLD and EDCs metabolites, one cycle of NHANES data from 2017 to 2018 (aged 18 years and older) was included in this analysis. After screening for (1) complete MAFLD information and (2) complete BMI information. Finally, a total of 5073 participants including 2507 men and 2566 women, were included for analysis. All participants provided written informed consent, and the study methods were approved by the National Center for Health Statistics' Research Ethics Review Board and the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

### 2.2. EDCs metabolites

In spot urine/serum samples provided by a randomly selected subsample of subjects, a total of 3 urinary metals [arsenic (As), Cd, and mercury (Hg)], 19 urinary PAEs metabolites, and 9 serum PFASs metabolites were assessed. Before being sent to the National Center for Environmental Health, Center for Disease Control and Prevention for processing, samples were gathered at a mobile examination center and stored at − 30 °C (CDC, 2008). The specific methods of EDCs detection can be found in the supplementary materials. An imputed fill value was provided in the analyte results box for analytes with results below the low limit of detection (LLOD), which was calculated by dividing the LLOD by the square root of 2 (LLOD/$\sqrt{2}$).

### 2.3. Definition of MAFLD

In this study, MAFLD was defined based on hepatic steatosis (Siddiqui et al., 2019; Younossi, et al., 2022) and any of the three elements listed below: obesity, type 2 diabetes, or metabolic abnormalities (Fig. 1) (Eslam et al., 2020).

### 2.4. Covariates

Through the questionnaire, physical examination, and laboratory tests, we obtained information on age, gender, race, educational attainment, family income-to-poverty ratio (PIR), body mass index (BMI, kg/m$^2$), marital status, alcohol consumption, cotinine, dietary inflammatory index (DII), hepatitis, hypertension, physical activity, sleep, creatinine, and insulin sensitivity (HOMA-IS).

Race was classified as Non-Hispanic White, Non-Hispanic Black, Mexican American, and other races (including Other Hispanic and Multi-Racial). Educational attainment was divided into three categories: less than high school graduate, high school graduate or equivalent, and above high school graduate. PIR was categorized as quartile 1 (Q1, <1.18), quartile 2 (Q2, 1.18–2.09), quartile 3 (Q3, 2.09–4.07) and quartile 4 (Q4, ≥4.07) based on quartiles. BMI was computed as dividing body mass in kilograms by height in meters squared. Marital status was categorized as married/conhabity, never, and widowed/divorced/

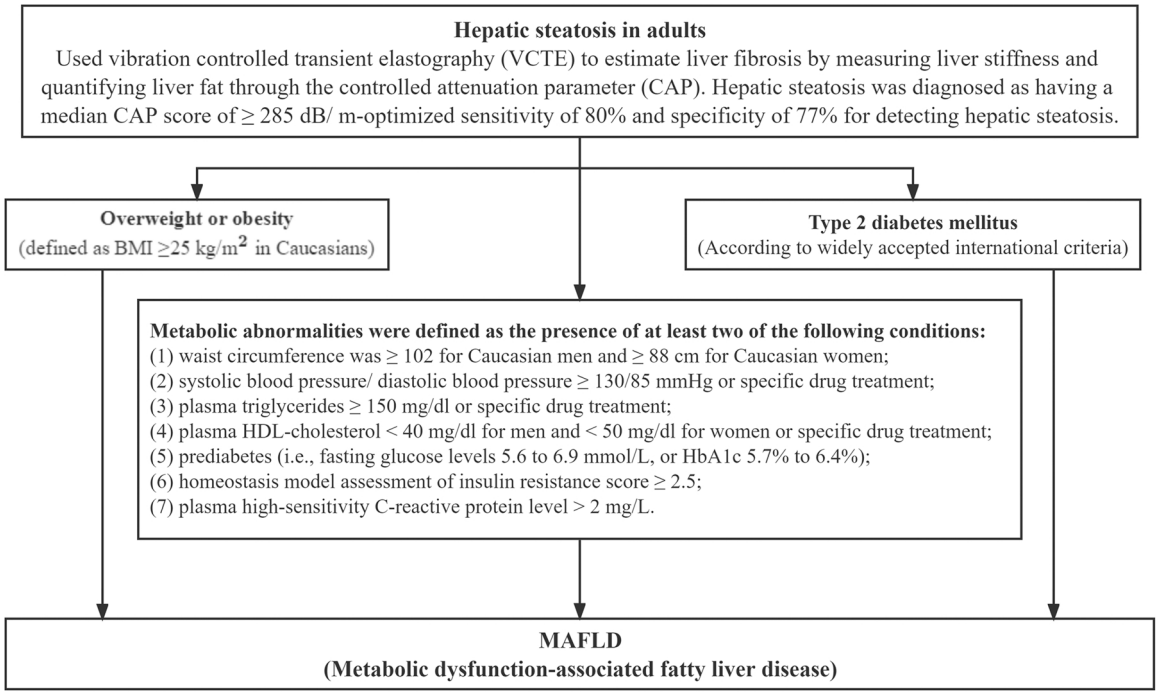


**Fig. 1.** Definition of MAFLD.

separated. "Had at least 12 alcohol drinks/ 1 year?" was used to assess alcohol intake, with the value of current drinking or none. Cotinine concentration was used to assess individual tobacco exposure. Hepatitis was defined as one participant had at least one type of hepatitis A, B, C, D, or E. Raised systolic blood pressure $\geq$ 140 mmHg, elevated diastolic blood pressure $\geq$ 90 mmHg, physician-diagnosed hypertension, or usage of antihypertensive medicines were used to diagnose hypertension. The homeostasis model assessment for insulin sensitivity (HOMA-IS) index was calculated as 1/ [(fasting insulin concentration*fasting glucose concentration)/22.5] (Matthews et al., 1985).

The DII was a composite indicator for the inflammatory diet habit (Shivappa et al., 2014). A higher positive value indicated a stronger pro-inflammatory effect and a higher negative value indicated a stronger anti-inflammatory effect. The specific calculation of DII scores has been previously reported (Zhao et al., 2022). The information on dietary intake for the nutrients and food items was extracted from the NHANES 24-h recall data for each participant's DII, which comprised 27 food characteristics. DII was classified into quartiles in this study, with the highest quartile (Q4) representing the most proinflammatory potentiality.

The metabolic equivalent (MET) was used to determine physical activity, which represented the level of oxygen necessary to sustain resting metabolism. It is a typical indication to describe the relative energy metabolism level throughout varied activities based on energy consumption in a calm and seated position. The formula of computation was physical activity (MET-h/week) = MET*weekly frequency*duration of each physical activity. Participant with physical activity = 0 was considered as inactive, < 30 MET-h/week was defined as low activity, 30–60 MET-h/week was defined as medium activity, and $\geq$ 60 MET-h/week was defined as high activity (CDC, 2008). Demographic covariates with missing values were used predictive mean based on multiple imputations.

### 2.5. Statistical analysis

In the descriptive analysis for baseline characteristics of the participants, T-test was performed to assess differences in continuous variables between MAFLD and non-MAFLD participants. Furthermore, chi-square test was utilized to evaluate categorical population characteristics. EDCs concentration was classified into quartiles (Q1: $P_{0–25}$, Q2: $P_{25–50}$, Q3: $P_{50–75}$, Q4: $P_{75–100}$). Logistic regression model was used to evaluate the association between log-transformed EDCs metabolites and MAFLD, and the strength of the association was determined with the odds ratio (OR) and confidence interval (CI). We also fitted 3 models to test the model's robustness: model 1 only adjusted for creatinine. Model 2 based on model 1 and adjusted for age, gender, race, educational attainment, PIR, BMI, and marital status. Model 3 based on model 2 and further adjusted for alcohol consumption, cotinine, DII, hepatitis, hypertension, physical activity, sleep, and HOMA-IS. In order to further analyze the impact of several EDCs metabolites together affecting MAFLD, we employed the bayesian kernel machine regression (BKMR) model was carried out to examine the association of 3 heavy metals, 10 PAEs, 7 PFASs, and simultaneous exposure to 10 PAEs and 7 PFASs on MAFLD. Moreover, we also conducted subgroup analysis by gender, age, and hepatitis. At the same time, the product interaction term of EDCs metabolites and subgroup factors was included in the model to detect their interaction with MAFLD. Finally, we also carried out analyzing the moderating effect of BMI, DII, physical activity and HOMA-IS on the association between EDCs metabolites and MAFLD. $P < 0.05$ (two-tailed) was defined as statistical significance for all statistical analysis done with R software (R Development Core Team; http://R-project.org).

## 3. Results

### 3.1. Baseline characteristics of MAFLD and EDCs metabolites

Table 1 shows the baseline characteristics of the subjects. Participants with MAFLD were mostly male, older, and had a higher BMI than Non-MAFLD. We also found a higher prevalence of type 2 diabetes mellitus and hypertension in MAFLD participants. In comparison to those with MAFLD, individuals without MAFLD were more likely to be physically active ($P = 0.007$). Compared with the non-MAFLD group, the MAFLD group had a higher DII level ($P = 0.015$) and a lower HOMA-IS level ($P < 0.001$).

The characteristics of 22 EDCs metabolites are shown in Table S1. The detection rates of the heavy metals in urinary samples ranged from 50.48% to 100%, the detection rates of the PAEs metabolites in urinary samples ranged from 58.97% to 99.88%. The detection rates of the PFASs metabolites in serum samples ranged from 58.63% to 99.75%. Among all tested heavy metals, the As had the highest average level with a mean concentration of 19.84 μg/L. Diethyl phthalate (DEP) had the highest mean concentration, followed by Di-2-ethylhexyl terephthalate (DEHTP) and Di-(2-ethyl-hexyl) phthalate (DEHP), with mean concentrations of 185.52 ng/mL, 112.15 ng/mL, and 26.09 ng/mL, respectively. Among PFASs, the highest exposure was found in perfluorooctane sulfonic acid (PFOS), with a concentration of 6.99 ng/mL.

### 3.2. Association between EDCs metabolites exposure and MAFLD

Table 2 summarizes the association between EDCs metabolites exposure and MAFLD. We found that exposure to EDCs metabolites were significantly associated with MAFLD (Tables 2 and S2). The urinary PAEs metabolites showed the greatest correlation with MAFLD, with OR ranging from 0.805 to 2.354. For example, log-transformed Di-iso-nonyl phthalate (DiNP) metabolites was positively associated with MAFLD in model 3 ($OR_{Log10}$: 1.959, 95% CI: 1.224, 3.136) . Compared to the Q1, the OR of the Q4 for DEHP, DiNP, DEHTP and PAEs on MAFLD were 2.002 (95% CI: 1.045, 3.834), 2.354 (95% CI: 1.240, 4.465), 2.199 (95% CI: 1.254, 3.856) and 1.859 (95% CI: 1.013, 3.412), respectively.

Heavy metals were also found to be significantly linked to MAFLD. For example, log-transformed As was positively associated with MAFLD in model 3 ($OR_{Log10}$: 1.819, 95% CI: 1.224, 2.702). Logistic regression revealed that log-transformed As exposure was positively associated with MAFLD in the Q4 group (OR: 2.299, 95% CI: 1.267, 4.170), but not Cd and Hg.

As for serum PFASs metabolites, there were statistically significant association between them and MAFLD. For example, log-transformed PFOA metabolites was positively associated with MAFLD in model 3 ($OR_{Log10}$: 2.148, 95% CI: 1.036, 4.456). There was a greater reported OR for MAFLD in the Q4 group of log-transformed PFOA metabolites than in the Q1 group (1.803 95% CI: 1.029, 3.160).

Fig. 2 describes the correlation of the EDCs metabolites with MAFLD in the BKMR model. Increased concentrations of PAEs metabolites were positively correlated with MAFLD compared to median concentration. The other EDCs metabolites (heavy metals, PFASs, and PAEs+PFASs) were positively correlated with MAFLD, but none was statistically significant.

### 3.3. Stratified analysis

Our results reported that the association of EDCs metabolites exposure with MAFLD was altered with age (Fig. 3 and Table S3). The OR of MAFLD was 1.368 (95% CI: 0.560, 3.343) in log-transformed PAEs metabolites among people who were < 45 years, which were 1.093 (95% CI: 0.458, 2.609) and 4.014 (95% CI: 1.377, 11.702) for aged 45–65 group and above 65 years group, respectively. Additionally, we also found that the association between serum 2-(N-methylperfluorooctanesulfonamido) acetic acid (PFOSA) metabolite exposure and

**Table 1**
Characteristics of the included participants from NHANES 2017–2018 [n (%) or mean±SD].

| Characteristics | | Non-MAFLD (n = 3202) | MAFLD (n = 1871) | Total (n = 5073) | P[a] |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age | | 47.50 ± 19.05 | 52.89 ± 16.65 | 49.49 ± 18.39 | < 0.001 |
| Gender | Male | 1451 (45.32) | 1056 (56.44) | 2507 (49.42) | < 0.001 |
| | Female | 1751 (54.68) | 815 (43.56) | 2566 (50.58) | |
| Race | Non-Hispanic White | 1059 (33.07) | 670 (35.81) | 1729 (34.08) | < 0.001 |
| | Non-Hispanic Black | 827 (25.83) | 345 (18.44) | 1172 (23.10) | |
| | Mexican American | 345 (10.77) | 354 (18.92) | 699 (13.78) | |
| | Other Race | 971 (30.32) | 502 (26.83) | 1473 (29.04) | |
| PIR | Q1 (<1.18) | 820 (25.61) | 447 (23.89) | 1267 (24.98) | 0.429 |
| | Q2 (1.18–2.09) | 789 (24.64) | 478 (25.55) | 1267 (24.98) | |
| | Q3 (2.09–4.07) | 782 (24.42) | 482 (25.76) | 1264 (24.92) | |
| | Q4 (≥4.07) | 811 (25.33) | 464 (24.80) | 1275 (25.13) | |
| Educational attainment | Less than high school graduate | 629 (19.64) | 371 (19.83) | 1000 (19.71) | 0.529 |
| | High school graduate or equivalent | 792 (24.73) | 487 (26.03) | 1279 (25.21) | |
| | Above high school | 1781 (55.62) | 1013 (54.14) | 2794 (55.08) | |
| Marital status | Marry/Conhabity | 1789 (55.87) | 1199 (64.08) | 2988 (58.90) | < 0.001 |
| | Widowed/Divorced/Separated | 731 (22.83) | 415 (22.18) | 1146 (22.59) | |
| | Never | 682 (21.30) | 257 (13.74) | 939 (18.51) | |
| Lifestyle behaviors | | | | | |
| Alcohol consumption | None | 699 (21.83) | 486 (25.98) | 1185 (23.36) | 0.001 |
| | Current | 2503 (78.17) | 1385 (74.02) | 3888 (76.64) | |
| Cotinine (ng/mL) | | -0.58 ± 1.69 | -0.73 ± 1.64 | -0.64 ± 1.68 | 0.001 |
| DII | Q1 (<−0.11) | 824 (25.73) | 448 (23.94) | 1272 (25.07) | 0.015 |
| | Q2 (−0.11–0.98) | 790 (24.67) | 473 (25.28) | 1263 (24.90) | |
| | Q3 (0.98–2.28) | 758 (23.67) | 510 (27.26) | 1268 (25.00) | |
| | Q4 (≥2.28) | 830 (25.92) | 440 (23.52) | 1270 (25.03) | |
| Physical activity | Inactive | 747 (23.33) | 516 (27.58) | 1263 (24.90) | 0.007 |
| | Low activity | 1505 (47.00) | 849 (45.38) | 2354 (46.40) | |
| | Medium activity | 387 (12.09) | 201 (10.74) | 588 (11.59) | |
| | High activity | 563 (17.58) | 305 (16.30) | 868 (17.11) | |
| Sleep (h/day) | | 7.83 ± 1.53 | 7.66 ± 1.47 | 7.77 ± 1.51 | < 0.001 |
| Comorbidities | | | | | |
| BMI | | 27.0 ± 6.0 | 33.9 ± 7.3 | 29.58 ± 7.34 | < 0.001 |
| Hepatitis[b] | No | 1277 (42.05) | 766 (42.58) | 2043 (42.25) | 0.718 |
| | Yes | 1760 (57.95) | 1033 (57.42) | 2793 (57.75) | |
| Hypertension | No | 2054 (64.15) | 826 (44.15) | 2880 (56.77) | < 0.001 |
| | Yes | 1148 (35.85) | 1045 (55.85) | 2193 (43.23) | |
| HOMA-IS | | 0.64 ± 0.62 | 0.29 ± 0.32 | 0.51 ± 0.55 | < 0.001 |
| MAFLD conditions | | | | | |
| Overweight or obesity | No | 1296 (40.47) | 97 (05.18) | 1393 (27.46) | < 0.001 |
| | Yes | 1906 (59.53) | 1774 (94.82) | 3680 (72.54) | |
| Type 2 diabetes mellitus | No | 2803 (87.54) | 1244 (66.49) | 4047 (79.78) | < 0.001 |
| | Yes | 399 (12.46) | 627 (33.51) | 1026 (20.22) | |
| Metabolic dysregulation | Waist circumference (cm)[c] | 93.06 ± 14.39 | 111.51 ± 15.21 | 99.89 ± 17.19 | < 0.001 |
| | Blood pressure (mmHg)[d] | < 0.001 | | | |
| | No | 1811 (58.44) | 645 (35.52) | 2456 (49.97) | |
| | Yes | 1288 (41.56) | 1171 (64.48) | 2459 (50.03) | |
| | Triglyceride (mg/dL)[e] | 94.15 ± 89.35 | 145.49 ± 120.89 | 112.97 ± 104.97 | < 0.001 |
| | HDL-cholesterol (mg/dL)[f] | 56.28 ± 15.56 | 47.48 ± 13.26 | 53.00 ± 15.34 | < 0.001 |
| | Prediabetes[g] | < 0.001 | | | |
| | No | 1912 (62.22) | 943 (52.07) | 2855 (58.46) | |
| | Yes | 1161 (37.78) | 868 (47.93) | 2029 (41.54) | |
| | Insulin resistance[h] | < 0.001 | | | |
| | No | 915 (62.67) | 180 (21.20) | 1095 (47.42) | |
| | Yes | 545 (37.33) | 669 (78.80) | 1214 (52.58) | |
| | hs CRP (mg/L)[i] | 3.24 ± 6.85 | 5.31 ± 8.74 | 4.01 ± 7.67 | < 0.001 |

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; SD, standard deviation; PIR, family income-to-poverty ratio; DII, dietary inflammatory index; BMI, body mass index; HOMA-IS, insulin sensitivity; hs CRP, high-sensitivity C-reactive protein.

[a] P for comparison between non-MAFLD and MAFLD.

[b] Hepatitis caused by a virus is divided into five types according to the virus series: A, B, C, D and E.

[c] Caucasian men/women of waist circumference ≥ 102/88 cm.

[d] Blood pressure ≥ 130/85 mmHg or particular medication therapy.

[e] Plasma triglycerides ≥ 150 mg/dl or particular medication therapy.

[f] Plasma HDL-cholesterol < 40 mg/dl to men and < 50 mg/dl to women or particular medication therapy.

[g] Prediabetes (i.e., HbA1c 5.7–6.4%, or fasting glucose levels 5.6–6.9 mmol/L).

[h] Homeostasis model insulin resistance evaluation score ≥ 2.5.

[i] hs CRP (Plasma high-sensitivity C-reactive protein) level > 2 mg/L.

**Table 2**
Odds ratio (95% confidence interval) of MAFLD relationship of endocrine-disrupting chemicals metabolites, NHANES 2017–2018.

| | | Model 1 (OR 95% CI) | P | Model 2 (OR 95% CI) | P | Model 3 (OR 95% CI) | P |
|---|---|---|---|---|---|---|---|
| As (μg/L) | Q1 | Ref. | 0.279 | Ref. | **0.048** | Ref. | **0.006** |
| | Q2 | 1.294 (0.961, 1.741) | | 1.248 (0.874, 1.781) | | 1.378 (0.774, 2.452) | |
| | Q3 | **1.403 (1.032, 1.909)** | | 1.232 (0.850, 1.786) | | 1.490 (0.824, 2.693) | |
| | Q4 | 1.196 (0.883, 1.621) | | **1.503 (1.033, 2.187)** | | **2.299 (1.267, 4.170)** | |
| | Log10 | 1.126 (0.920, 1.378) | | **1.356 (1.052, 1.748)** | | **1.819 (1.224, 2.702)** | |
| DEP (ng/mL) | Q1 | Ref. | 0.976 | Ref. | 0.490 | Ref. | 0.646 |
| | Q2 | 1.279 (0.958, 1.708) | | 1.215 (0.862, 1.712) | | **1.916 (1.110, 3.307)** | |
| | Q3 | 1.065 (0.791, 1.435) | | 1.155 (0.807, 1.654) | | 1.574 (0.891, 2.781) | |
| | Q4 | 1.071 (0.788, 1.456) | | 1.180 (0.810, 1.719) | | 1.339 (0.723, 2.480) | |
| | Log10 | 0.976 (0.823, 1.157) | | 1.005 (0.814, 1.241) | | 0.871 (0.619, 1.224) | |
| DEHP (ng/mL) | Q1 | Ref. | **0.012** | Ref. | 0.337 | Ref. | **0.013** |
| | Q2 | 1.287 (0.957, 1.730) | | 0.905 (0.634, 1.291) | | 1.274 (0.718, 2.261) | |
| | Q3 | 1.367 (0.997, 1.875) | | 1.056 (0.726, 1.537) | | **2.037 (1.135, 3.653)** | |
| | Q4 | **1.558 (1.116, 2.175)** | | 1.152 (0.771, 1.719) | | **2.002 (1.045, 3.834)** | |
| | Log10 | **1.376 (1.036, 1.827)** | | 1.082 (0.770, 1.520) | | 1.455 (0.838, 2.527) | |
| DiNP (ng/mL) | Q1 | Ref. | **0.002** | Ref. | **0.038** | Ref. | **0.003** |
| | Q2 | **1.623 (1.202, 2.191)** | | 1.355 (0.948, 1.937) | | 1.206 (0.670, 2.169) | |
| | Q3 | **1.730 (1.254, 2.386)** | | **1.507 (1.029, 2.206)** | | **1.869 (1.018, 3.433)** | |
| | Q4 | **1.760 (1.264, 2.452)** | | **1.552 (1.040, 2.315)** | | **2.354 (1.240, 4.465)** | |
| | Log10 | **1.459 (1.128, 1.885)** | | **1.375 (1.011, 1.871)** | | **1.959 (1.224, 3.136)** | |
| DiDP (ng/mL) | Q1 | Ref. | **0.002** | Ref. | 0.443 | Ref. | 0.092 |
| | Q2 | 1.299 (0.955, 1.768) | | 0.983 (0.685, 1.411) | | 1.258 (0.706, 2.241) | |
| | Q3 | **1.373 (1.016, 1.856)** | | 0.957 (0.667, 1.373) | | 1.371 (0.768, 2.449) | |
| | Q4 | **1.658 (1.208, 2.277)** | | 1.174 (0.803, 1.716) | | 1.670 (0.924, 3.018) | |
| | Log10 | **1.301 (1.005, 1.684)** | | 1.093 (0.798, 1.497) | | 1.418 (0.879, 2.287) | |
| DEHTP (ng/mL) | Q1 | Ref. | 0.897 | Ref. | **0.022** | Ref. | **0.006** |
| | Q2 | 0.971 (0.729, 1.292) | | 1.119 (0.798, 1.568) | | 1.256 (0.739, 2.133) | |
| | Q3 | 0.972 (0.727, 1.301) | | 1.089 (0.770, 1.540) | | 1.380 (0.791, 2.408) | |
| | Q4 | 1.020 (0.755, 1.377) | | **1.592 (1.106, 2.292)** | | **2.199 (1.254, 3.856)** | |
| | Log10 | 1.007 (0.860, 1.181) | | **1.261 (1.040, 1.530)** | | **1.571 (1.163, 2.122)** | |
| PAEs (ng/mL) | Q1 | Ref. | 0.482 | Ref. | **0.045** | Ref. | **0.014** |
| | Q2 | 1.067 (0.795, 1.432) | | 1.098 (0.774, 1.557) | | 1.198 (0.684, 2.097) | |
| | Q3 | 1.252 (0.916, 1.711) | | **1.460 (1.007, 2.117)** | | **2.178 (1.226, 3.868)** | |
| | Q4 | 1.089 (0.785, 1.513) | | 1.408 (0.949, 2.087) | | **1.859 (1.013, 3.412)** | |
| | Log10 | 1.014 (0.792, 1.298) | | 1.203 (0.892, 1.622) | | 1.361 (0.851, 2.179) | |
| PFDeA (ng/mL) | Q1 | Ref. | **0.001** | Ref. | **0.050** | Ref. | 0.891 |
| | Q2 | 0.763 (0.520, 1.118) | | **0.591 (0.368, 0.949)** | | 0.554 (0.274, 1.121) | |
| | Q3 | 0.717 (0.510, 1.008) | | **0.615 (0.401, 0.941)** | | 0.829 (0.440, 1.562) | |
| | Q4 | **0.486 (0.325, 0.727)** | | **0.539 (0.326, 0.889)** | | 0.762 (0.365, 1.591) | |
| | Log10 | **0.572 (0.410, 0.796)** | | 0.726 (0.482, 1.092) | | 1.130 (0.621, 2.056) | |
| PFHxS (ng/mL) | Q1 | Ref. | 0.154 | Ref. | 0.763 | Ref. | 0.678 |
| | Q2 | **1.691 (1.242, 2.303)** | | **1.487 (1.015, 2.178)** | | **1.851 (1.036, 3.309)** | |
| | Q3 | **1.411 (1.066, 1.868)** | | 1.175 (0.810, 1.705) | | 1.214 (0.693, 2.125) | |
| | Q4 | 1.295 (0.963, 1.740) | | 1.168 (0.785, 1.738) | | 1.346 (0.732, 2.477) | |
| | Log10 | 1.165 (0.891, 1.523) | | 1.041 (0.722, 1.501) | | 1.363 (0.766, 2.423) | |
| PFOA (ng/mL) | Q1 | Ref. | 0.301 | Ref. | 0.062 | Ref. | **0.029** |
| | Q2 | 1.264 (0.941, 1.699) | | 1.161 (0.808, 1.668) | | 1.437 (0.821, 2.516) | |
| | Q3 | 1.180 (0.889, 1.565) | | 1.358 (0.956, 1.928) | | **1.760 (1.027, 3.014)** | |
| | Q4 | 1.180 (0.889, 1.567) | | 1.374 (0.952, 1.983) | | **1.803 (1.029, 3.160)** | |
| | Log10 | 1.093 (0.766, 1.560) | | 1.311 (0.824, 2.085) | | **2.148 (1.036, 4.456)** | |
| PFOS (ng/mL) | Q1 | Ref. | 0.061 | Ref. | 0.454 | Ref. | 0.202 |
| | Q2 | **1.397 (1.039, 1.880)** | | 1.322 (0.919, 1.900) | | 1.625 (0.935, 2.824) | |
| | Q3 | **1.411 (1.050, 1.895)** | | 1.302 (0.890, 1.905) | | 1.609 (0.896, 2.889) | |
| | Q4 | **1.347 (1.002, 1.809)** | | 1.200 (0.799, 1.803) | | 1.575 (0.848, 2.923) | |
| | Log10 | 1.119 (0.860, 1.456) | | 0.995 (0.691, 1.433) | | 1.318 (0.761, 2.283) | |
| PFASs (ng/mL) | Q1 | Ref. | 0.293 | Ref. | 0.788 | Ref. | 0.313 |
| | Q2 | 1.308 (0.974, 1.758) | | 1.195 (0.832, 1.716) | | 1.098 (0.635, 1.900) | |
| | Q3 | 1.221 (0.913, 1.634) | | 1.106 (0.760, 1.610) | | 1.204 (0.688, 2.109) | |
| | Q4 | 1.207 (0.900, 1.620) | | 1.091 (0.734, 1.619) | | 1.346 (0.745, 2.432) | |
| | Log10 | 1.107 (0.809, 1.514) | | 1.053 (0.682, 1.627) | | 1.489 (0.774, 2.864) | |

All results of endocrine-disrupting chemicals metabolites had been log-transformed. Model 1: only adjusted for creatinine. Model 2: based on model 1 and adjusted for age, gender, race, educational attainment, family income-to-poverty ratio, body mass index and marital. Model 3: based on model 2 and adjusted for alcohol consumption, cotinine, dietary inflammatory index, hepatitis, hypertension, physical activity, sleep and insulin sensitivity. This analysis was carried out in a logistic regression model. The first, second, third, and fourth quartiles of log-transformed endocrine-disrupting chemical concentration were denoted by Q1($P_{0-25}$), Q2($P_{25-50}$), Q3($P_{50-75}$) and Q4($P_{75-100}$). Log10 represented the metabolite concentration had been log-transformed for analysis. The statistically significant indices were marked in bold ($P < 0.05$). P indicated P for trend. Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval.

MAFLD was modified by gender, showing apparent effect of PFOSA metabolite on MAFLD among females. Conversely, no significant changes in "EDCs metabolites-MAFLD" correlation was seen across participants with varied hepatitis status. Furthermore, we found apparent affects of the Q4 group of EDCs metabolites on MAFLD among males and older (≥ 45), which was also true for participants with hepatitis, especially in PAEs metabolites (Table S4). However, for females, EDCs showed a negative correlation on MAFLD even at low exposure level. For example, the OR of MAFLD was 3.974 (95% CI: 1.586, 9.961) at the Q2 with log-transformed DEP metabolite in females, although the OR was 1.210 (95% CI: 0.577, 2.538) in males.

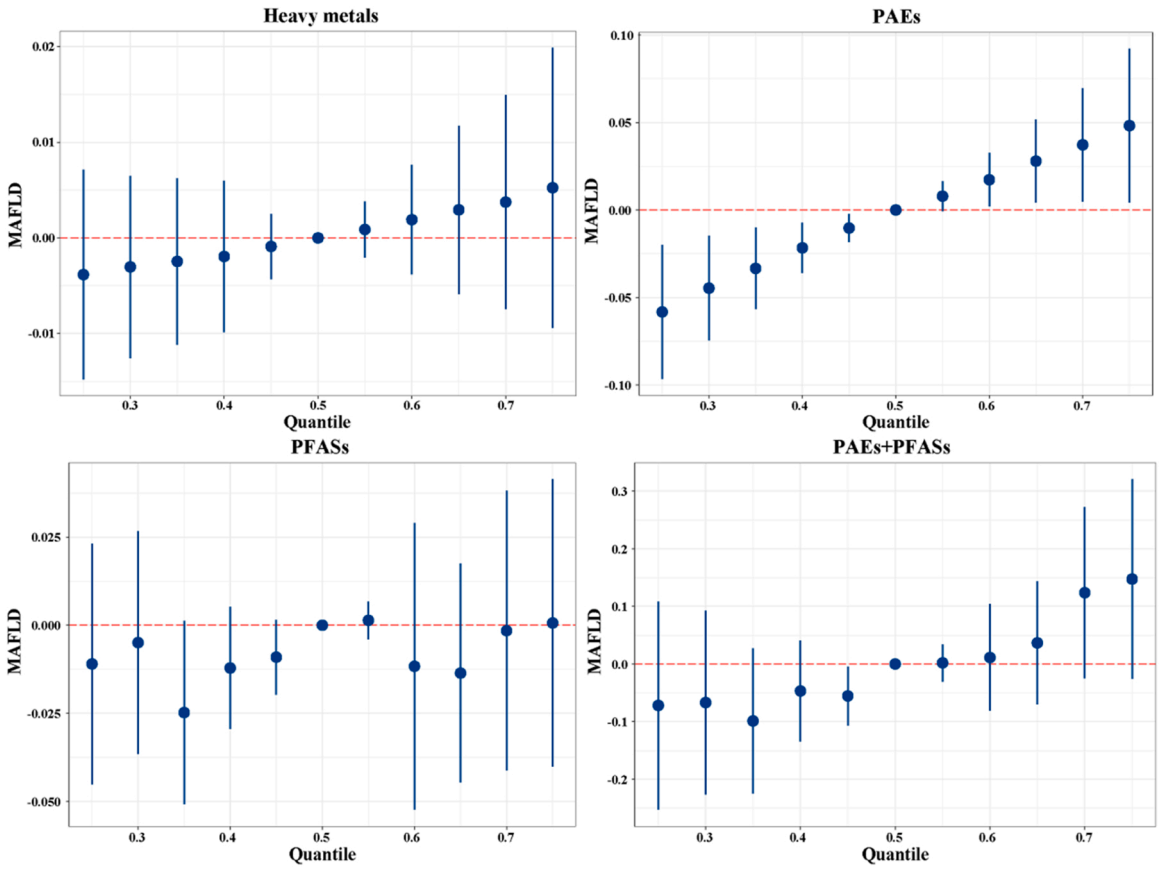


**Fig. 2.** Dose-response association (odds ratio and confidence interval) between endocrine-disrupting chemicals metabolites co-exposure and MAFLD. All results of endocrine-disrupting chemicals metabolites had been log-transformed. This analysis was carried out in the BKMR model. Heavy metals included As, Cd and Hg. PAEs included DEP, DiBP, DnBP, BBzP, DEHP, DnOP, DiNP, DiDP, DEHTP and DINCH. PFASs included PFDeA, PFHxS, PFOSA, PFNA, PFUA, PFOA and PFOS. Covariates included creatinine, age, gender, race, educational attainment, family income-to-poverty ratio, body mass index and marital, alcohol consumption, cotinine, dietary inflammatory index, hepatitis, hypertension, physical activity, sleep and insulin sensitivity. Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; PAEs, phthalates; PFASs, per- and poly-fluoroalkyl substances.

### *3.4. Moderating effect analysis*

BMI, DII, physical activity, and HOMA-IS were found that have moderating effect on the association between EDCs metabolites exposure and MAFLD (Fig. 4 and Table S5). In particular, the higher BMI group showed strengthened the association of EDCs metabolites with MAFLD. Similar modification effect was also observed at higher level of DII. The higher DII score indicated a stronger pro-inflammatory effect, which would positively strengthen the relationship of EDCs metabolites on MAFLD. For example, when DII was in the Q3 group, DII positively regulated the relationship between perfluorohexane sulfonic acid (PFHxS) metabolite and MAFLD ($\beta = 1.327$, $P = 0.027$).

Meanwhile, we found substantial changes in "EDCs metabolites-MAFLD" correlation across adults with varying levels of physical activity. We found a stronger association of EDCs metabolites with MAFLD in the Q1 and Q2 groups of physical activity. Furthermore, our results suggested that physical activity helped to alleviate the MAFLD risk of DiBP, which was apparent in the Q4 physical activity group ($\beta = -1.180$, $P = 0.130$). This was also true for HOMA-IS score, since the higher HOMA-IS score showed lower MAFLD risk in exposure to DEP, particular in the Q3 group ($\beta = -0.646$, $P = 0.018$).

## 4. Discussion

This study initially analyzed the association of EDCs metabolites with MAFLD based on NHANES 2017–2018. Our results provide strong evidence to support the speculation that the certain exposure to EDCs was associated with MAFLD, especially PAEs. These findings were more noticeable in females, hepatitis subjects, and people over the age of 65. Additionally, increased BMI and DII may increase the risk of EDCs on MAFLD, whereas increased insulin sensitivity may decrease the risk. These findings may advance our understanding on the association of EDCs with MAFLD.

Even though the specific causes of the "EDCs-MAFLD" association remains unknown, the current study's findings may be generally interpreted by the findings of past researches (Costello et al., 2022; Zhang et al., 2019). Firstly, EDCs exposure triggers oxidative stress and inflammatory response that lead to abnormal liver function (Yang et al., 2014; Zhang et al., 2019). For example, a vitro experiment showed that Mono-2-ethylhexyl phthalate (MEHP) promoted lipid accumulation via JAK2/STAT5 in liver cells and further contributed to NAFLD (Zhang et al., 2019). Moreover, heavy metals usually trigger the overproduction of reactive oxygen species (ROS) in hepatocytes, and mechanical steps cause experimental liver injury, leading to the breakdown of antioxidant defense systems and the formation of lipid peroxidation (Teschke, 2022). Secondly, exposure to EDCs reduces RACK1 expression so as to induce immunosuppression, which in turn makes the organism more susceptible to adverse effects (DeWitt et al., 2019; Masi et al., 2022). Thirdly, in a review of PFASs and markers of liver injury by Costello et al., the positive correlations were observed among PFOA, PFOS, and PFNA and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in humans. Complementary evidence from experimental rodent study provides biological plausibility that these associations may be reasonable. PFASs are positively correlated with ALT levels in

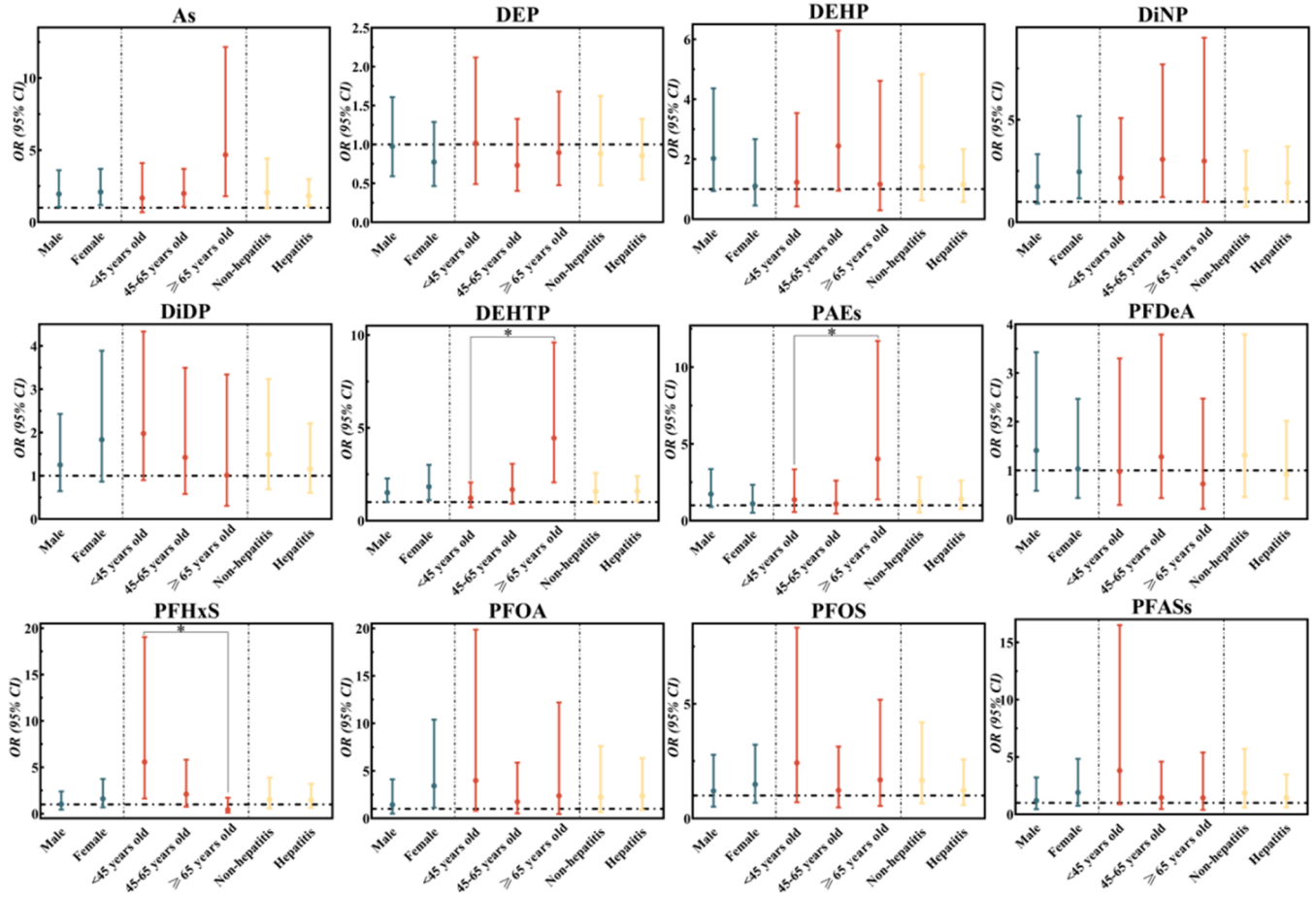


**Fig. 3.** Interactive effect of gender, age, hepatitis and endocrine-disrupting chemicals metabolites on MALFD. All results of endocrine-disrupting chemicals metabolites had been log-transformed. This analysis was carried out in a logistic regression model. Covariates included creatinine, age, gender, race, educational attainment, family income-to-poverty ratio, body mass index and marital, alcohol consumption, cotinine, dietary inflammatory index, hepatitis, hypertension, physical activity, sleep and insulin sensitivity. Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; CI, confidence interval. *P < 0.05 indicates that the interaction is significant.

humans, suggesting that PFASs exposure may contribute to the prevalence of MAFLD (Costello et al., 2022). Fourthly, as exposure may cause liver fibrosis, lead to fatty liver, and may also lead to hepatocyte necrosis and apoptosis, which has been both confirmed in human and animal experiments (Teschke and Xuan, 2022). Finally, EDCs exposure impairs hepatic glucose/lipid metabolism and leads to metabolic disorders, then triggering the occurrence and development of MAFLD (Rahman et al., 2022; Sui et al., 2021). Indeed, the dicyclohexyl phthalate (DCHP) was identified as a potent pregnane X receptor-selective agonist that triggered higher plasma cholesterol level in wild-type mice (Sui et al., 2021). In this study, we suggested that the adversary affects of EDCs on MAFLD, the impact of EDCs may play an important role in the occurrence and development of MAFLD through the above pathways. But further toxicological studies and epidemiological studies are also needed to elucidate the biological role of EDCs in the development of MAFLD.

Furthermore, the finding of the subgroup analysis suggested that senior individuals (≥ 65 years old) may be more likely to enhance the association of EDCs with MAFLD than young people (< 45 years old). This may be explained in two ways. On the one hand, older people have progressively dysregulated and weakened immune systems, leading to a persistent inflammatory response, which may explain why older individuals are more sensitive to EDCs exposure (Shaw et al., 2013). On the other hand, aging itself enhances hepatic steatosis, which would impair fatty acid oxidation and increase hepatic de novo lipogenesis (Gong et al., 2017). This has been previously studied and confirmed in NAFLD (Bertolotti et al., 2014), but there are fewer related studies on MAFLD, indicating that more researches are urgently needed to confirm these speculations. Besides, we also found there were gender differences in relationship of exposure to EDCs and MAFLD, particularly the MAFLD risk was greater on males than females at high level of EDCs exposure. Since there was strong antioxidant impact of estrogen (Borrás et al., 2003; Torres et al., 2018), we hypothesized that the lower EDCs exposure might increase oxidative stress to stimulate estrogenic effects or exert estrogenic effects, which could be protective at higher exposure (Bhatia et al., 2014). A zebrafish experiment proposed that the main histopathological changes caused by PFOS exposure were lipid droplet accumulation, most prominent in the liver of males (Du et al., 2009). As expected, the presence of hepatitis strengthened the association of EDCs exposure with MAFLD. Particularly, people with hepatitis are more likely to develop MAFLD when combined with metabolic disorders (Huang et al., 2022). However, few studies have investigated the influence of EDCs on MAFLD, which is one key strength of this study.

Many current evidences supported that bad living practices may exacerbate the link between EDCs and MAFLD (Dallio et al., 2021; Molina-Molina et al., 2022). In this investigation, physical activity did not appear to change the association between EDCs and MAFLD. This is consistent with the finding of Guo et al. (2022), but they have merely focused on the relationship between air pollution and MAFLD. Nevertheless, our findings may have some useful implications to certain degree for MAFLD prevention. We suggest that further larger sample populations are encouraged to explore whether physical activity could mitigate the deleterious affects of EDCs. However, we did find some

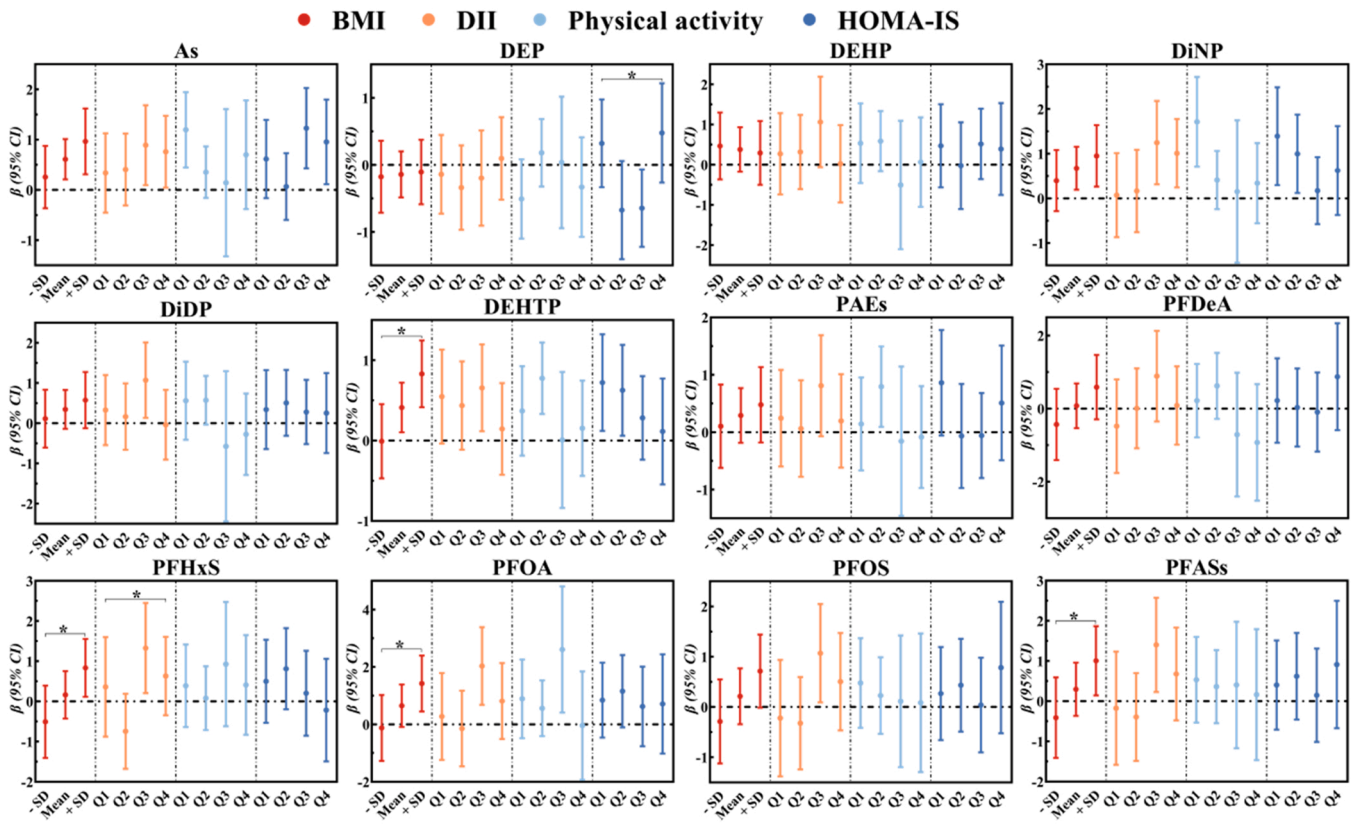


**Fig. 4.** Moderating effect of BMI, DII, Physical activity and HOMA-IS on association between endocrine-disrupting chemicals metabolites and MAFLD. All results of endocrine-disrupting chemicals metabolites had been log-transformed. This analysis was carried out in a moderation model by the "bruceR" package in R software. Covariates included creatinine, age, gender, race, educational attainment, family income-to-poverty ratio, body mass index and marital, alcohol consumption, cotinine, dietary inflammatory index, hepatitis, hypertension, physical activity, sleep and insulin sensitivity. Mean±SD represents BMI as a continuous variable divided into three dimensions by Mean±SD. The first, second, third, and fourth quartiles of DII/physical activity/HOMA-IS were denoted by Q1($P_{0–25}$), Q2($P_{25–50}$), Q3 ($P_{50–75}$) and Q4($P_{75–100}$). * Represents a moderating effect of BMI/DII/HOMA-IS in the association of "EDCs metabolites-MAFLD", $P < 0.05$ is statistically significant. Abbreviations: SD, standard deviation; CI, confidence interval; BMI, body mass index; DII, dietary inflammatory index; HOMA-IS, insulin sensitivity; MAFLD, metabolic dysfunction-associated fatty liver disease.

meaningful moderating affects. The insulin sensitivity had a modifying effect on the relationship between EDCs and MAFLD, particularly when insulin sensitivity at the Q3 level, it could negatively modulate the relationship between EDCs and MAFLD. Therefore, we speculate that the higher insulin sensitivity could lead to the modification of hormones in the body to accelerate the metabolism of EDCs and thus decrease the risk. But this still needs to be confirmed by further mechanism studies.

Furthermore, BMI was found to be a positive regulator of EDCs and MAFLD in this research. In particular, obese people were more vulnerable to the negative affects of EDCs on MAFLD. According to one study, the European Union requires €15.6 billion in yearly phthalate-attributable obesity-related societal expenses (Legler et al., 2015). This may be explained by that the PAEs induce obesity by activating nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-α) and PPAR-gamma (PPAR-γ) (Hurst et al., 2003). Obesity then increases the level of oxidative stress in the body, which is higher than in population with normal weight (D'Alessandro et al., 2022). The previous study also showed that obesity was also higher in people with MAFLD than in those without MAFLD (Guo et al., 2022). Therefore, obese individuals may be more susceptible to the adverse affects of EDCs on MAFLD. Finally, we found that DII also positively modulated the relationship between EDCs and MAFLD, because the higher DII may prompt greater oxidative stress in the organism (Barrea et al., 2018). Hence, a healthy weight, a normal pancreatic function, a healthy diet and suitable physical activity may be important to sustain a healthy liver function.

Even though this research has several strengths in comprehending the association between MAFLD and EDC exposure, some limitations should not be ignored. First, because this was a cross-sectional study, it was impossible to establish cause-and-effect between EDCs and MAFLD. Although biological explanation was presented in the discussion part, cohort designs and animal researches would be essential and required to further confirm our findings. Second, single-point EDCs evaluation did not accurately reflect individual real exposure level due to data restriction. As a result, more repeated measure design would be critical to corroborate our findings. In addition, participants will always be exposed to multiple EDCs simultaneously, and even though the BKMR model was utilized in our study to assess the association between combined EDCs exposure and MAFLD, the sample size of the population for combined exposure assessment was small and simultaneous exposure assessment of 3 EDCs could not be performed due to data limitation. This needs to be confirmed by more in-depth cohorts or panel studies. Fourth, we did not find any effects of physical activity due to the small sample size. Thus, a larger population would be important and necessary to further explore the physical activity effects on the relationship between EDCs exposure and MAFLD. Fourth, potential confounders such as extra EDCs and the normalized differential vegetation index might all contribute to the study's bias. Finally, the external exposure impact of EDCs could not be evaluated due to the lack of data on environmental EDCs exposure.

## 5. Conclusion

In conclusion, this research suggests that single or combined

exposure to EDCs metabolites (heavy metals, PAEs, and PFASs) may be linked to MAFLD. Females, participants with hepatitis, and people over the age of 65 are most vulnerable to be effected by EDCs on MAFLD. Our findings also encourage people to sustain a healthy diet, normal level of insulin sensitivity and BMI, which may help to alleviate the MAFLD risk in exposure to EDCs. These results also help us to better understand the association of EDCs and MAFLD and provide effective evidence for preventing MAFLD from the EDCs exposure aspect. Furthermore, the government should take comprehensive efforts to restrict EDCs.

## CRediT authorship contribution statement

**Ruoyi Lei:** Conceptualization, Methodology, Software, Visualization, Writing – original draft. **Baode Xue:** Data curation, Formal analysis, Validation. **Xiaoyu Tian:** Methodology, Software. **Ce Liu:** Methodology, Software. **Yanlin Li:** Visualization. **Jie Zheng:** Visualization. **Bin Luo:** Conceptualization, Writing – review & editing, Supervision.

## 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.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.114836.

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