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The relationship between metabolic syndrome and environmental endocrine disruptors: A systematic review and meta-analysis

Graphical abstract

Highlights

- An association between EEDs and MetS was revealed
- EEDs increase the risk of MetS in exposed population
- PFASs and PAEs exposure induced a higher prevalence of MetS in women than in men

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In brief

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Article

The relationship between metabolic syndrome and environmental endocrine disruptors: A systematic review and meta-analysis

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SUMMARY

Metabolic syndrome (MetS) is considered to be an important factor leading to an increased risk of chronic non-communicable diseases. Studies have found that exposure to environmental endocrine disruptors (EEDs) is associated with MetS, but the relationship between the two is unclear. In order to clarify the relationship between the two, a systematic review and meta-analysis were conducted to investigate their association. We searched Web of Science databases, Embase, and PubMed. We then utilized I^2 statistics to assess the literature heterogeneity and pooled the data using both fixed-effects model (I^2 < 50%) and the random effects model (I^2 > 50%) in accordance with the PRISMA guidelines. The results showed that exposure to perfluoroalkyl substances (PFASs) was associated to specific components of MetS, such as PFNA and "high waist circumference" (OR = 1.23, 95% CI: 1.10–1.38), and PFOA and "elevated blood pressure" (OR = 1.05, 95% CI: 1.01–1.08). Exposure to phthalates (PAEs) increases the risk of MetS, with MECPP (OR = 1.16, 95% CI: 1.04–1.29) being an example. Moreover, polychlorinated biphenyls (PCBs) (OR = 1.47, 95% CI: 1.13–1.93) and organochlorine pesticides (OCPs) (OR = 1.97, 95% CI: 1.33–2.90) showed a positive association with the MetS. This study reveals that EEDs are a risk factor for MetS, which provides new evidence for the relationship between population EEDs exposure and MetS.

INTRODUCTION

Nowadays, many infectious diseases have been effectively controlled, and chronic non-communicable diseases (NCDs) have become a major threat to human health. Metabolic syndrome (MetS) is an important risk factor for chronic non-communicable diseases such as cardiovascular disease and diabetes.[1] MetS refers to abnormalities in related cardiac metabolic indicators, such as dyslipidemia and elevated blood pressure,[2] which increases the risk of chronic diseases in patients with MetS.[3] Studies have reported that about 20%–30% of the general population in the world has MetS,[4] with the adult prevalence rate in China being 33.9%.[5] Moreover, in the United States, the prevalence of MetS in adults has increased from 25.3% to 34.3% in just a few decades.[6] Many factors are associated with MetS, including excessive caloric intake, unhealthy living habits (such as lack of physical activity and sedentary behavior), composition of the gut microbiota, and genetic factors.[7] In addition, environmental endocrine disruptors (EEDs) are an important trigger for MetS.[8]

EEDs are defined as "exogenous substances or mixtures that alter the function of the endocrine system and cause adverse health effects on intact organisms or their offspring or (sub) populations."[9] EEDs are abundant, including polychlorinated biphenyls (PCBs), bisphenol A, nonylphenol, phthalates (PAEs), perfluoroalkyl substances (PFASs), organochlorine pesticides (OCPs), herbicides (such as atrazine), and fungicides.[10–14] Humans can contact EEDs such as the digestive tract through a variety of ways, due to the lipophilicity of EEDs, they can accumulate in human tissues for a long time, causing great harm to human health outcomes.[15] And some EEDs can be detected in indoor dust, revealing a high risk of human exposure.[16]

Previous studies have shown that EEDs exposure is associated with MetS.[17] For example, exposure to bisphenol A during pregnancy and lactation in Wistar rats can lead to weight gain, elevated serum insulin, impaired glucose tolerance, and susceptibility to metabolic syndrome in offspring.[18] Additionally, Di-(2-ethylhexyl) phthalate exposure can lead to abnormal blood glucose and lipid metabolism in adult mice and hepatocytes, and cause intestinal microbial disorders.[19] Moreover, another study also found that low-dose exposure to 3,3 ′, 4,4 ′, 5-pentachlorobiphenyl (PCB126) caused lipid and glucose metabolism disorders in mice.[20] However, population studies have also found a similar association. Mustieles et al. found that exposure to persistent organic pollutants is associated with an increased risk of metabolic disorders.[21] Additionally, a cross-sectional study involving 331 individuals revealed a positive association between dioxin-like and non-dioxin-like PCBs

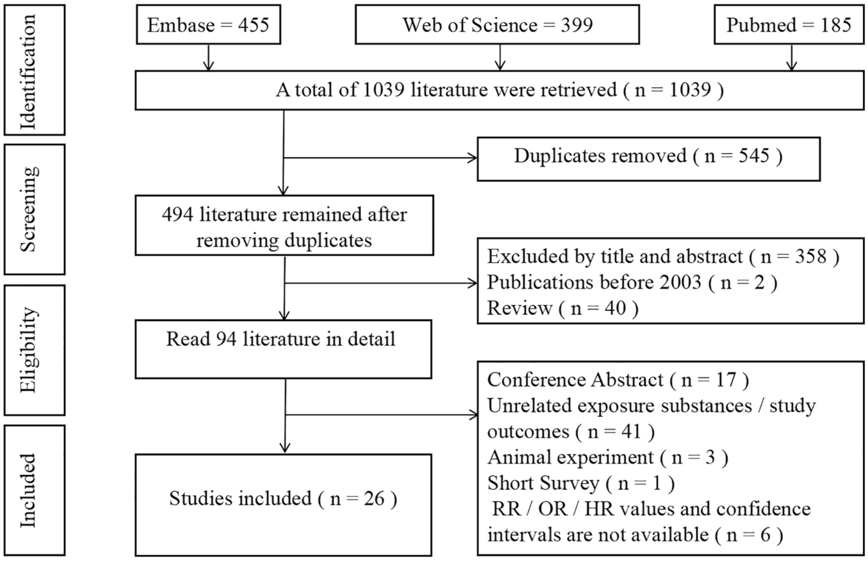

Figure 1. Flow chart of literature screening under PRISMA guidelines

and MetS.[22] Similarly, people with high urinary phthalate metabolites also had the same outcome.[23]

In summary, exposure to EEDs may increase the risk of MetS. However, the conclusions between different studies are inconsistent. In addition, the association between the two has not been systematically summarized. Therefore, we conducted a meta-analysis to summarize the relationship between the two to provide the latest epidemiological evidence on EEDs and MetS.

RESULTS

Results of the literature search

Among the 1039 articles, 458 articles were initially screened using EndNoteX9 software, and then 87 articles were manually excluded, including 2 articles published before 2003 and 40 reviews. After carefully reading the title and abstract, 358 articles were excluded, and the remaining 94 articles were read in detail. Among them, 17 were conference abstracts, 6 lacked available/calculable OR/RR/HR and confidence intervals, 41 had nothing to do with exposed substances/research results, 3 were animal experiments, and 1 was a short survey. Finally, 26 studies were included for detailed reading and data extraction, all in English. Figure 1 shows the detailed process of literature selection.

Characteristics of literature and quality assessment

The research encompassed 26 investigations, involving a cumulative sample size of 51,884, which all demonstrated the link between EEDs and "MetS/MetS components." Among these studies, there were 1 nested case-control study, 2 cohort studies, and 23 cross-sectional studies. The research were conducted across multiple continents, including Europe, North America and Asia, including Croatia, the United States, Canada, China, Italy, South Korea, Sweden, Spain, India, and Mexico. The main sample types used were serum, plasma, adipose tissue, and urine. The exposure substances examined were mainly PCBs, PFASs, PAEs, and OCPs. The included literature's basic characteristics are exhibited in Table S6. The average score of the literature quality evaluation was 7.35 ($\geq$6), thereby signifying that the studies were of high quality. Further details of the NOS scoring table can be found in Tables S2 and S3.

Meta-analysis

The summary of the association between the four EEDs and the "MetS/MetS components" is presented in Table S4.

Association between perfluoroalkyl substances and "MetS/MetS components"

Studies of the association between PFASs and "MetS/MetS components" have been conducted using 11 sources of literature.[24–34] Our results suggest that there is no association between PFASs exposure and MetS in the population (Figure 2). However, PFNA exposure is positively associated to "high waist circumference" (OR = 1.23, 95% CI: 1.10–1.38) and negatively associated with PFOA (OR = 0.79, 95% CI: 0.64–0.97) (Figure S19); PFOA (OR = 1.09, 95% CI: 1.04–1.15) and PFHxS (OR = 1.03, 95% CI: 1.00–1.06) exposure are positively associated to "Elevated Triglycerides" (Figure S20); and PFOS (OR = 1.09, 95% CI: 1.03–1.16), PFOA (OR = 1.05, 95% CI: 1.01–1.08), PFHxS (OR = 1.05, 95% CI: 1.02–1.09), PFNA (OR = 1.11, 95% CI: 1.02–1.20) exposure are associated with "elevated blood pressure" in the population (Figure S22). There is no association between population PFOS, PFOA, PFHxS, PFNA exposure and "reduced High-density lipoprotein (HDL) cholesterol (HDL-C)" (Figure S21) or "Fasting blood glucose" (FBG) (Figure S23). In addition, we studied the relationship between PFOA, PFNA, PFHxS exposure and MetS by gender stratification, and found no significant association between them. However, the overall pooled results suggest that exposure to these three PFASs may increase MetS risk in women (OR = 2.24, 95% CI: 1.15–4.38), this phenomenon was not seen in the male subgroup (Figures S24 and S25). We observed Statistically significant heterogeneity ($I^2 \geq 50\%$ or $p \leq 0.05$) in the pooled results. For the results with significant heterogeneity ($I^2 > 50\%$), we conducted a subgroup analysis to explore the possible sources of heterogeneity. The results showed that "study area," "sample type," "sample size," and "country type" were the main reasons for the heterogeneity of most results (Table 1).

Association between phthalates exposure and "MetS/MetS components"

Seven articles studied the association between PAEs and "MetS/MetS components,"[35–41] the results showed that a positive association between MECPP (OR = 1.16, 95% CI: 1.04–1.29), MCPP (OR = 1.10, 95% CI: 1.00–1.22), MEHHP (OR = 1.19, 95% CI: 1.05–1.34) (Figure 3). MEOHP (OR = 1.14, 95%

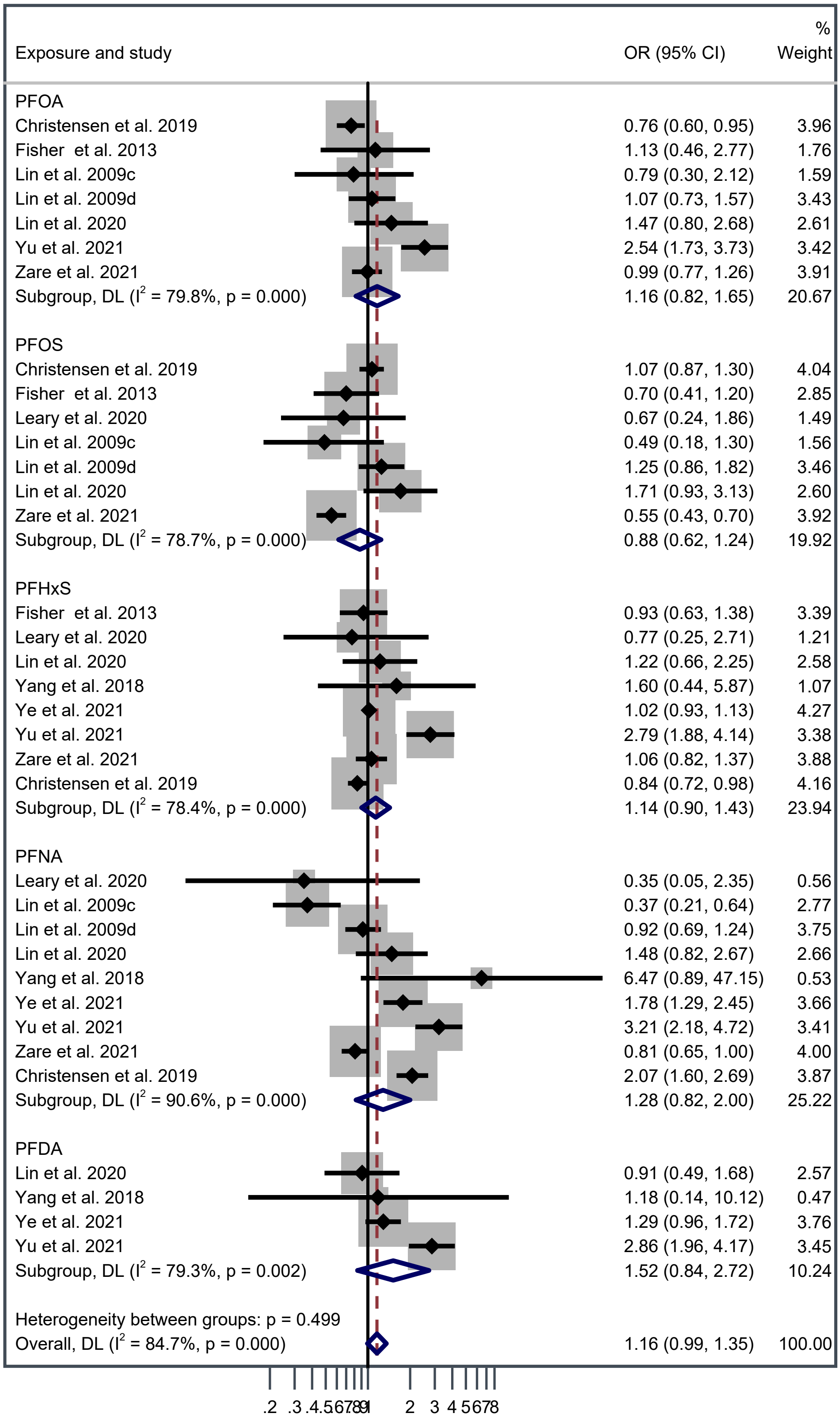

Figure 2. Forest plot of the relationship between Metabolic syndrome and perfluoroalkyl substances exposure, ORs (95% CI). c: Adolescent; d: Adult

Table 1. Subgroup analysis explored possible sources of heterogeneity in the meta-analysis results

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
MetS (PFOA)				
Study region				
Asia	2	**2.04 (1.20–3.44)**	55.4	0.134
North America	4	0.84 (0.70–1.02)	**0.0**	0.441
Europe	1	0.99 (0.77–1.27)	/	/
Sample type				
Serum	6	1.17 (0.80–1.70)	83.1	0.000
Plasma	1	1.13 (0.46–2.77)	/	/
Urine	0	**/**	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	6	1.13 (0.77–1.65)	82.4	0.000
≤500	1	1.47 (0.80–2.49)	/	/
Country type				
Developed country	5	0.89 (0.77–1.04)	**0.0**	0.441
Developing country	2	**2.04 (1.20–3.44)**	55.4	0.134
MetS (PFOS)				
Study region				
Asia	1	1.71 (0.93–3.14)	/	/
North America	5	0.97 (0.75–1.25)	**33.3**	0.200
Europe	1	**0.55 (0.43–0.70)**	/	/
Sample type				
Serum	6	0.91 (0.61–1.35)	81.8	0.000
Plasma	1	0.70 (0.41–1.20)	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	5	0.81 (0.55–1.19)	82.7	0.000
≤500	2	1.18 (0.48–2.89)	58	0.123
Country type				
Developed country	6	0.79 (0.56–1.14)	78.5	0.000
Developing country	1	1.71 (0.93–3.14)	/	/
MetS (PFHxS)				
Study region				
Asia	4	1.52 (0.82–2.82)	87.5	0.000
North America	3	**0.85 (0.74–0.98)**	**0.0**	0.882
Europe	1	1.06 (0.82–1.37)	/	/
Sample type				
Serum	7	1.18 (0.91–1.53)	81.3	0.000
Plasma	1	0.93 (0.63–1.38)	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	5	1.14 (0.88–1.48)	87.2	0.000
≤500	3	1.17 (0.71–1.94)	**0.0**	0.699
Country type				
Developed country	4	0.90 (0.79–1.01)	**0.0**	0.490
Developing country	4	1.52 (0.82–2.82)	87.5	0.000

(*Continued on next page*)

Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
MetS (PFNA)				
Study region				
Asia	4	**2.20 (1.41–3.42)**	63.4	0.042
North America	4	0.82 (0.37–1.83)	92.2	0.000
Europe	1	0.81 (0.65–1.00)	/	/
Sample type				
Serum	9	1.28 (0.82–2.00)	90.6	0.000
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	6	1.24 (0.75–2.06)	93.8	0.000
≤500	3	1.47 (0.44–4.97)	53.2	0.118
Country type				
Developed country	5	0.85 (0.48–1.48)	91.5	0.000
Developing country	4	**2.20 (1.41–3.42)**	63.4	0.042
MetS (PFDA)				
Study region				
Asia	4	1.52 (0.84–2.27)	79.3	0.002
North America	0	/	/	/
Europe	0	/	/	/
Sample type				
Serum	4	1.52 (0.84–2.27)	79.3	0.002
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	2	1.90 (0.87–4.15)	90.7	0.001
≤500	2	0.93 (0.51–1.68)	**0.0**	0.819
Country type				
Developed country	0	/	/	/
Developing country	4	1.52 (0.84–2.27)	79.3	0.002
High waist circumference (PFOS)				
Study region				
Asia	0	/	/	/
North America	3	0.82 (0.51–1.31)	67.2	0.048
Europe	1	1.76 (0.97–3.19)	/	/
Sample type				
Serum	3	0.82 (0.51–1.31)	67.2	0.048
Plasma	1	1.76 (0.97–3.19)	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	3	0.82 (0.51–1.31)	67.2	0.048
≤500	1	1.76 (0.97–3.19)	/	/
Country type				
Developed country	3	0.82 (0.51–1.31)	67.2	0.048
Developing country	1	1.76 (0.97–3.19)	/	/

(*Continued on next page*)

Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
Elevated Triglycerides (PFNA)				
Study region				
Asia	1	1.23 (1.07–1.41)	/	/
North America	3	1.13 (0.70–1.80)	82.1	0.004
Europe	2	1.23 (0.74–2.06)	**46.4**	0.172
Sample type				
Serum	5	1.15 (0.96–1.37)	70.0	0.010
Plasma	1	1.95 (0.82–4.62)	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	5	1.15 (0.96–1.37)	70.0	0.010
≤500	1	1.95 (0.82–4.62)	/	/
Country type				
Developed country	4	1.12 (0.87–1.44)	73.6	0.010
Developing country	2	**1.26 (1.03–1.55)**	**6.5**	0.301
Reduced High-density lipoprotein (HDL) cholesterol (PFOS)				
Study region				
Asia	0	/	/	/
North America	4	**1.25 (1.05–1.49)**	**4.7**	0.370
Europe	2	0.93 (0.57–1.54)	58.6	0.120
Sample type				
Serum	4	1.13 (0.77–1.66)	86.4	0.000
Plasma	2	1.18 (0.90–1.54)	**0.0**	0.637
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	5	1.13 (0.83–1.54)	84.7	0.000
≤500	1	1.38 (0.69–2.77)	/	/
Country type				
Developed country	5	1.13 (0.83–1.54)	84.7	0.000
Developing country	1	1.38 (0.69–2.77)	/	/
Reduced High-density lipoprotein (HDL) cholesterol (PFOA)				
Study region				
Asia	0	/	/	/
North America	5	**1.23 (1.03–1.46)**	**0.0**	0.573
Europe	2	0.96 (0.76–1.21)	**11.9**	0.287
Sample type				
Serum	5	1.13 (0.90–1.42)	58.4	0.447
Plasma	2	1.25 (0.93–1.68)	**0.0**	0.646
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	6	1.14 (0.93–1.39)	59.0	0.032
≤500	1	1.53 (0.61–3.82)	/	/
Country type				
Developed country	6	1.14 (0.93–1.39)	59.0	0.032
Developing country	1	1.53 (0.61–3.82)	/	/

(*Continued on next page*)

Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
Reduced High-density lipoprotein (HDL) cholesterol (PFHxS)				
Study region				
Asia	2	0.59 (0.13–2.65)	70.1	0.067
North America	2	0.98 (0.58–1.64)	95.5	0.000
Europe	2	**0.94 (0.89–0.99)**	**0.0**	0.974
Sample type				
Serum	4	0.92 (0.81–1.04)	85.4	0.000
Plasma	2	**1.25 (1.10–1.43)**	**0.0**	0.386
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	4	0.99 (0.87–1.13)	90.2	0.000
≤500	2	0.56 (0.13–2.29)	61.7	0.106
Country type				
Developed country	3	0.97 (0.76–1.23)	92.1	0.000
Developing country	3	0.93 (0.61–1.42)	**41.6**	0.181
Reduced High-density lipoprotein (HDL) cholesterol (PFNA)				
Study region				
Asia	2	0.60 (0.11–3.28)	64.4	0.094
North America	3	0.94 (0.60–1.48)	83.5	0.002
Europe	2	1.12 (0.46–2.77)	72.8	0.055
Sample type				
Serum	6	0.92 (0.73–1.15)	79.7	0.000
Plasma	1	2.05 (0.78–5.38)	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	5	0.93 (0.74–1.17)	82.1	0.000
≤500	2	0.72 (0.06–8.00)	76.4	0.040
Country type				
Developed country	4	0.89 (0.68–1.16)	78.0	0.003
Developing country	3	1.09 (0.51–2.35)	55.2	0.107
Fasting blood glucose (PFNA)				
Study region				
Asia	2	0.94 (0.28–3.17)	**46.3**	0.172
North America	3	1.50 (0.80–2.84)	86.3	0.001
Europe	1	1.22 (0.45–3.30)	/	/
Sample type				
Serum	5	1.32 (0.93–1.89)	76.9	0.002
Plasma	1	1.22 (0.45–3.30)	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	4	1.37 (0.97–1.95)	80.8	0.001
≤500	2	0.85 (0.26–2.78)	**26.0**	0.245
Country type				
Developed country	3	1.50 (0.80–2.84)	86.3	0.001
Developing country	3	**1.32 (1.13–1.54)**	**0.0**	0.389

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Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
MetS (male-PFNA)				
Study region				
Asia	2	1.75 (0.79–3.85)	**45.3**	0.176
North America	1	0.35 (0.05–2.40)	/	/
Europe	1	**0.76 (0.59–0.97)**	/	/
Sample type				
Serum	4	0.88 (0.71–1.09)	68.6	0.023
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	2	0.96 (0.56–1.65)	73.8	0.051
≤500	2	1.21 (0.14–10.32)	73.0	0.054
Country type				
Developed country	2	**0.75 (0.59–0.96)**	**0.0**	0.434
Developing country	2	1.75 (0.79–3.85)	**45.3**	0.176
MetS (female-PFOA)				
Study region				
Asia	2	2.58 (0.55–11.98)	90.4	0.001
North America	0	/	/	/
Europe	1	0.87 (0.52–1.45)	/	/
Sample type				
Serum	3	1.78 (0.55–5.76)	91	0.000
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	2	2.18 (0.35–13.48)	95.2	0.000
≤500	1	1.16 (0.56–2.41)	/	/
Country type				
Developed country	1	0.87 (0.52–1.45)	/	/
Developing country	2	2.58 (0.55–11.98)	90.4	0.001
MetS (female-PFNA)				
Study region				
Asia	2	3.88 (0.49–30.93)	94.5	0.000
North America	0	/	/	/
Europe	1	0.92 (0.61–1.39)	/	/
Sample type				
Serum	3	2.37 (0.51–10.95)	95.1	0.000
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	2	3.16 (0.27–36.34)	97.5	0.000
≤500	1	1.34 (0.65–2.76)	/	/
Country type				
Developed country	1	0.92 (0.61–1.39)	/	/
Developing country	2	3.88 (0.49–30.93)	94.5	0.000

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Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
MetS (female-PFHxS)				
Study region				
Asia	2	4.31 (0.46–40.41)	94.9	0.000
North America	0	/	/	/
Europe	1	1.12 (0.80–1.57)	/	/
Sample type				
Serum	3	2.71 (0.60–12.29)	95.1	0.000
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	2	3.81 (0.33–43.48)	97.5	0.000
≤500	1	1.37 (0.65–2.88)	/	/
Country type				
Developed country	1	1.12 (0.80–1.57)	/	/
Developing country	2	4.31 (0.46–40.41)	94.9	0.000
MetS (MEHP)				
Study region				
Asia	1	0.72 (0.36–1.43)	/	/
North America	2	0.85 (0.62–1.16)	78.6	0.031
Europe	0	/	/	/
Sample type				
Serum	0	/	/	/
Plasma	0	/	/	/
Urine	3	0.89 (0.78–1.01)	60.3	0.081
Adipose tissue	0	/	/	/
Sample size				
≥500	3	0.89 (0.78–1.01)	60.3	0.081
≤500	0	/	/	/
Country type				
Developed country	2	0.85 (0.62–1.16)	78.6	0.031
Developing country	1	0.72 (0.36–1.43)	/	/
MetS (∑DEHP)				
Study region				
Asia	1	0.69 (0.40–1.19)	/	/
North America	3	1.32 (0.73–2.37)	59.9	0.083
Europe	0	/	/	/
Sample type				
Serum	0	/	/	/
Plasma	0	/	/	/
Urine	4	**1.30 (1.00–1.69)**	74.7	0.008
Adipose tissue	0	/	/	/
Sample size				
≥500	3	0.99 (0.41–2.37)	82.9	0.003
≤500	1	1.16 (0.65–2.08)	/	/
Country type				
Developed country	2	1.18 (0.34–4.12)	71.5	0.061
Developing country	2	0.88 (0.53–1.47)	**39.2**	0.200

(*Continued on next page*)

Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
Elevated Blood Pressure (∑DEHP)				
Study region				
Asia	1	0.69 (0.41–1.16)	/	/
North America	3	**1.48 (1.12–1.96)**	**0.0**	0.425
Europe	0	/	/	/
Sample type				
Serum	0	/	/	/
Plasma	0	/	/	/
Urine	4	1.13 (0.68–1.86)	63.4	0.042
Adipose tissue	0	/	/	/
Sample size				
≥500	3	1.03 (0.57–1.85)	73.9	0.022
≤500	1	1.84 (0.63–5.36)	/	/
Country type				
Developed country	2	1.35 (0.84–2.18)	**35.1**	0.214
Developing country	2	1.00 (0.39–2.55)	61.8	0.105
Elevated Triglycerides (∑DEHP)				
Study region				
Asia	1	0.59 (0.37–0.93)	/	/
North America	3	**1.44 (1.11–1.85)**	**0.0**	0.502
Europe	0	/	/	/
Sample type				
Serum	0	/	/	/
Plasma	0	/	/	/
Urine	4	1.12 (0.68–1.83)	76.1	0.006
Adipose tissue	0	/	/	/
Sample size				
≥500	3	0.99 (0.54–1.81)	81.8	0.004
≤500	1	1.72 (0.89–3.31)	/	/
Country type				
Developed country	2	**1.39 (1.04–1.84)**	**3.2**	0.309
Developing country	2	0.98 (0.34–2.79)	85.6	0.008
Reduced High-density lipoprotein (HDL) cholesterol (MBzP)				
Study region				
Asia	1	0.65 (0.41–1.02)	/	/
North America	3	1.34 (0.98–1.83)	**0.0**	0.905
Europe	0	/	/	/
Sample type				
Serum	0	/	/	/
Plasma	0	/	/	/
Urine	4	1.10 (0.73–1.66)	56.5	0.075
Adipose tissue	0	/	/	/
Sample size				
≥500	3	1.03 (0.63–1.69)	66.6	0.050
≤500	1	1.51 (0.70–3.26)	/	/
Country type				
Developed country	2	1.31 (0.93–1.84)	**0.0**	0.767
Developing country	2	0.93 (0.41–2.11)	70.9	0.064

(*Continued on next page*)

Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
Fasting blood glucose (∑DEHP)				
Study region				
Asia	1	1.11 (0.69–1.79)	/	/
North America	3	0.89 (0.32–2.48)	71.4	0.030
Europe	0	/	/	/
Sample type				
Serum	0	/	/	/
Plasma	0	/	/	/
Urine	4	1.06 (0.62–1.81)	60.6	0.055
Adipose tissue	0	/	/	/
Sample size				
≥500	3	1.39 (0.99–1.95)	**17.9**	0.296
≤500	1	0.46 (0.18–1.17)	/	/
Country type				
Developed country	2	**1.62 (1.15–2.27)**	**0.0**	0.355
Developing country	2	0.79 (0.34–1.83)	62.9	0.101
MetS (PCB153)				
Study region				
Asia	2	**2.31 (1.54–3.45)**	**0.0**	0.937
North America	1	1.00 (0.48–2.10)	/	/
Europe	1	1.12 (0.84–1.50)	/	/
Sample type				
Serum	3	**1.78 (1.02–3.12)**	**47**	0.152
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	1	1.12 (0.84–1.50)	/	/
Sample size				
≥500	1	1.00 (0.48–2.10)	/	/
≤500	3	1.69 (0.94–3.05)	75.4	0.017
Country type				
Developed country	3	1.16 (0.89–1.50)	**0.0**	0.375
Developing country	1	**2.29 (1.48–3.54)**	/	/
MetS (p,p′-DDE)				
Study region				
Asia	4	1.49 (0.57–3.91)	91.8	0.000
North America	2	1.30 (0.83–2.04)	**4.3**	0.307
Europe	1	0.86 (0.70–1.06)	/	/
Sample type				
Serum	6	1.43 (0.77–2.66)	86.6	0.000
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	1	0.86 (0.70–1.06)	/	/
Sample size				
≥500	2	1.30 (0.83–2.04)	**4.3**	0.307
≤500	5	1.34 (0.74–2.42)	91.2	0.000
Country type				
Developed country	5	0.99 (0.76–1.29)	**18.6**	0.296
Developing country	2	2.11 (0.49–9.19)	97.1	0.000

(*Continued on next page*)

Table 1. *Continued*

Groups	No. of Literature	OR (95% CI)	I^2 (%)	*P*
MetS (β-HCH)				
Study region				
Asia	4	**1.81 (1.10–2.97)**	65.2	0.035
North America	2	**2.36 (1.43–3.91)**	**0.0**	0.357
Europe	0	/	/	/
Sample type				
Serum	6	**1.97 (1.33–2.90)**	60.8	0.026
Plasma	0	/	/	/
Urine	0	/	/	/
Adipose tissue	0	/	/	/
Sample size				
≥500	2	**2.36 (1.43–3.91)**	**0.0**	0.357
≤500	4	**1.81 (1.10–2.97)**	65.2	0.035
Country type				
Developed country	4	**2.18 (1.41–3.37)**	**0.0**	0.743
Developing country	2	1.87 (0.91–3.84)	88.2	0.004
MetS (HCB)				
Study region				
Asia	2	1.36 (0.30–6.14)	70.2	0.067
North America	1	**6.15 (1.66–22.83)**	/	/
Europe	2	**1.37 (1.13–1.66)**	**0.0**	0.942
Sample type				
Serum	3	2.19 (0.62–7.68)	69.3	0.039
Plasma	1	**1.38 (1.03–1.85)**	/	/
Urine	0	/	/	/
Adipose tissue	1	**1.36 (1.05–1.76)**	/	/
Sample size				
≥500	1	**2.36 (1.43–3.91)**	**0.0**	0.357
≤500	5	**1.38 (1.11–1.72)**	**12.6**	0.330
Country type				
Developed country	5	**1.53 (1.07–2.21)**	**52.0**	0.080
Developing country	0	/	/	/

Note: "/": no value; PFDA: Perfluorodecanoic acid; PFHxS: Perfluorohexane sulfonic acid; PFNA: Perfluorononanoic acid; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctane sulfonate; ∑DEHP: Molar sum of di-2-ethylhexyl phthalate metabolites; HCB: Hexachlorobenzene; MBzP: Monobenzyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; p,p-DDE: p,p′-dichlorodiphenyldichloroethylene; PCB153: 2,2′,4,4′,5,5′-hexachlorobiphenyl; β-HCH: β-hexachlorocyclohexane.

CI: 1.00–1.29), MBzP (OR = 1.19, 95% CI: 1.07–1.32) and ΣDEHP (OR = 1.30, 95% CI: 1.00–1.69) (Figure S26) were positively associated with MetS. The relationship between PAEs exposure and MetS was studied by gender stratification. Only MCPP (OR = 1.25, 95% CI: 1.00–1.56) exposure was positively associated with MetS in women, the overall combined results suggested that women's exposure to PAEs increased the risk of MetS (OR = 1.12, 95% CI: 1.01–1.25) (Figure S28), this phenomenon was not observed in men (Figure S27). After analyzing the relationship between PAEs exposure and the "MetS component," we found that only MEP exposure (OR = 1.60, 95% CI: 1.05–2.46) was positively associated to "FBG," whereas no other components showed a significant association (Figures S29–S32). Subgroup analysis was carried out to pinpoint causes of heterogeneity ($I^2 \geq 50\%$). The results showed that "study area," "sample type," "sample size," and "country type" were the main reasons for the heterogeneity of most results (Table 1).

Association between being exposed to polychlorinated biphenyls, organochlorine pesticides, and metabolic syndrome

In the study of the relationship between polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and MetS, a total of 8 articles provided available data.[42–49] Our results revealed a positive association between population PCB118 (OR = 1.47, 95% CI: 1.13–1.93), PCB153 (OR = 1.39, 95% CI: 1.11–1.73), PCB180 (OR = 1.26, 95% CI: 1.02–1.55), β-HCH (OR = 1.97, 95% CI: 1.33–2.90), Oxychlordane (OR = 1.69, 95%

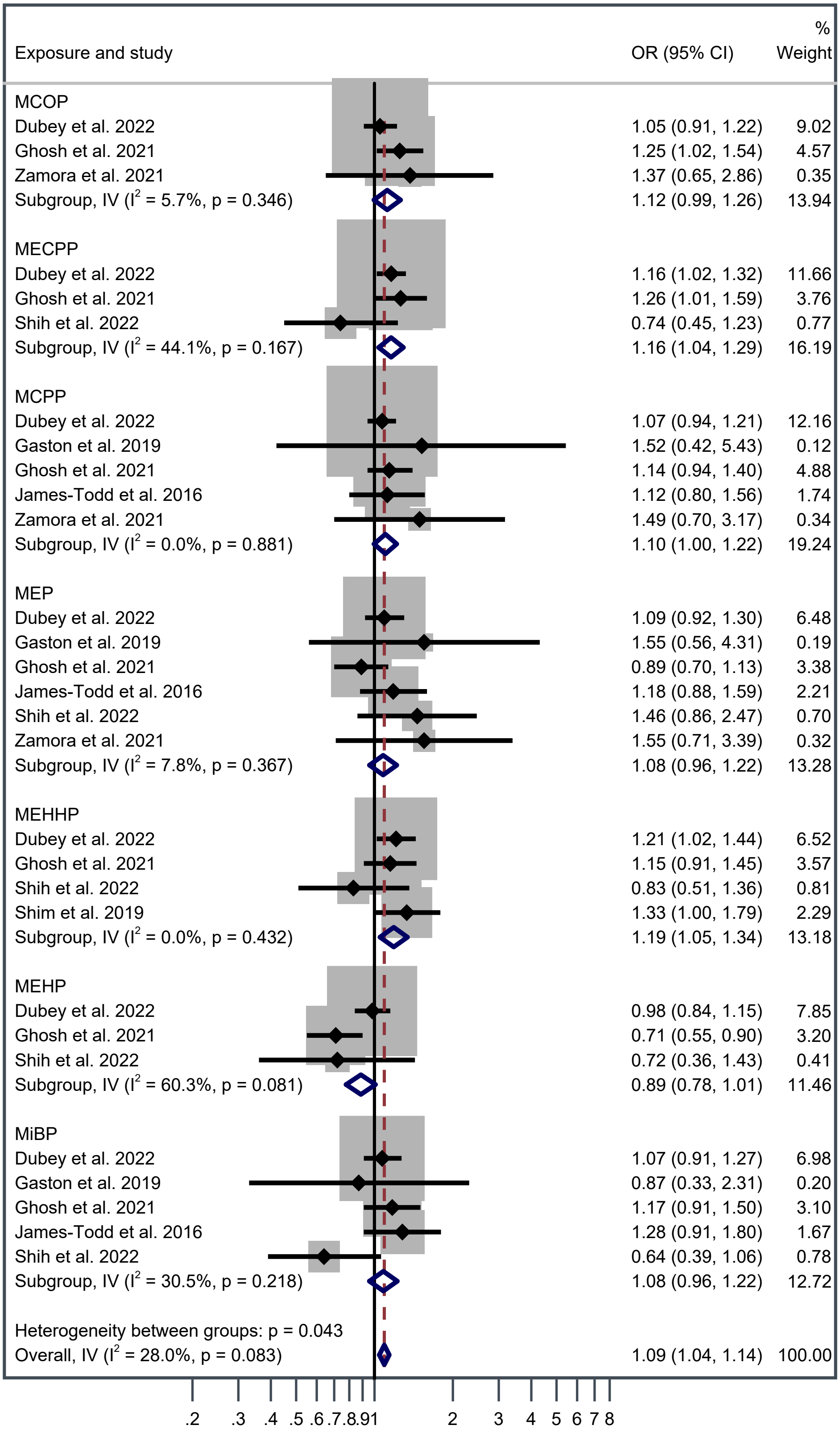

Figure 3. Forest plot of the relationship between Metabolic syndrome and PAEs exposure, ORs (95% CI)

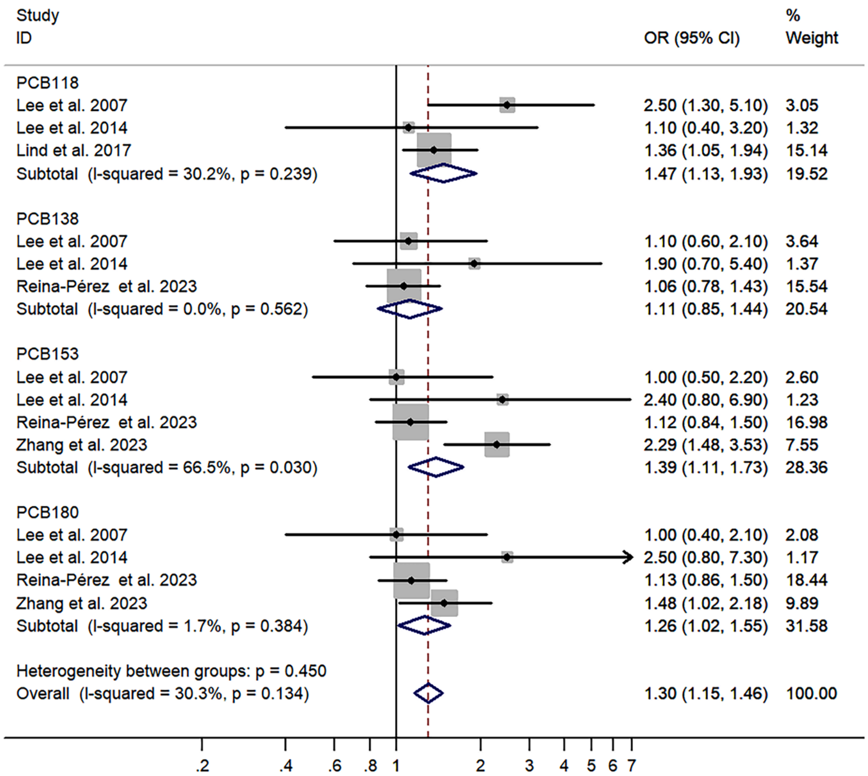

Figure 4. Forest plot of the relationship between Polychlorinated biphenyls exposure and Metabolic syndrome, ORs (95% CI)

CI: 1.08–2.65) (Figures 4 and 5), HCB (OR = 1.42, 95% CI: 1.18–1.71) exposure and MetS (Figure S33). For the pooled results with high heterogeneity ($I^2 \geq 50\%$), we performed a subgroup analysis to identify the source of heterogeneity. The outcomes showed that "study area," "sample type," "sample size," and "country type" were the main reasons for the heterogeneity of most results (Table 1).

Publication bias and sensitivity analysis

The robustness of the combined results was detected by the leave-one-out method. The results showed that most of the combined results were stable, but we did have some statistically significant changes in the results, such as "Heptachlor epoxide-MetS." The results of sensitivity analysis are shown in Table S4. The sensitivity analysis is shown in Figures S1–S18. The results of Egger test and Begg test showed that only a very small part of the combined results had publication bias ($p < 0.05$), and no significant publication bias was found in the rest (Table S5).

DISCUSSION

In our systematic review and meta-analysis, three databases (Web of Science, Embase, and PubMed) were searched in detail and 26 newly published epidemiological surveys in the last 20 years were identified. The results of meta-analysis showed that exposure to four common EEDs (PFASs, PCBs, OCPs and PAEs) was associated with an increased risk of MetS.

PFASs are a kind of persistent organic matter and a common EEDs. They are very stable in the environment and bioaccumulative. Humans are mainly exposed through food intake. Due to industrial emissions, water pollution is serious, and human consumption of contaminated aquatic organisms and drinking water leads to increased exposure risk.[50,51] Previously, an epidemiological study found that people with higher serum PFASs were positively associated with MetS.[33] Additionally, higher serum PFOA concentration in women before pregnancy will increase the risk of gestational diabetes.[52] An animal experiment found that exposure to PFOS during pregnancy and lactation in pregnant rats can lead to signs of pre-diabetes and impaired glucose tolerance in offspring in adulthood.[53] These findings suggest that PFASs exposure could rise the risk of MetS. Our results also demonstrate a favorable association between PFASs exposure and "MetS components," such as "High waist circumference," "Elevated Triglycerides," and "Elevated blood pressure," especially between PFASs exposure and "Elevated blood pressure," which is in agreement with the meta-analysis results of Pan et al.,[54] which suggests that PFASs exposure can increase blood pressure. Our findings did not reveal a significant correlation between PFASs exposure and MetS, which is in line with the meta-analysis results of Zare et al.[55] Nevertheless, based on their findings, we further demonstrated the positive association between PFASs exposure and "MetS components," thus filling the gap between PFASs and MetS. Subgroup analysis showed that "sample type," "study area," and "country type (developed/developing country) " were all important factors leading to heterogeneity sources, and the results of "PFASs exposure and MetS/MetS components" showed statistically significant changes. The possible reason for this phenomenon may be due to the different levels of PFASs pollution between different regions. For example, the median concentration of PFOA detected in breast milk of Chinese mothers was 34.5 pg/mL,[56] while the median concentration of PFOA detected in breast milk of American mothers was 13.9 pg/mL.[57] Secondly, it may be due to the economic gap between developed and developing countries. High-income groups have a higher frequency of aquatic organisms such as seafood intake than low-income groups,[58] Because aquatic organisms are more likely to be polluted by PFASs,[51] the potential health risks of high-income groups may be higher than those of low-income groups. Previous studies have also found that although the concentrations of PFASs detected from different blood samples (serum, plasma, and whole blood) are roughly the same, the concentration of PFASs in blood samples generally follows the following

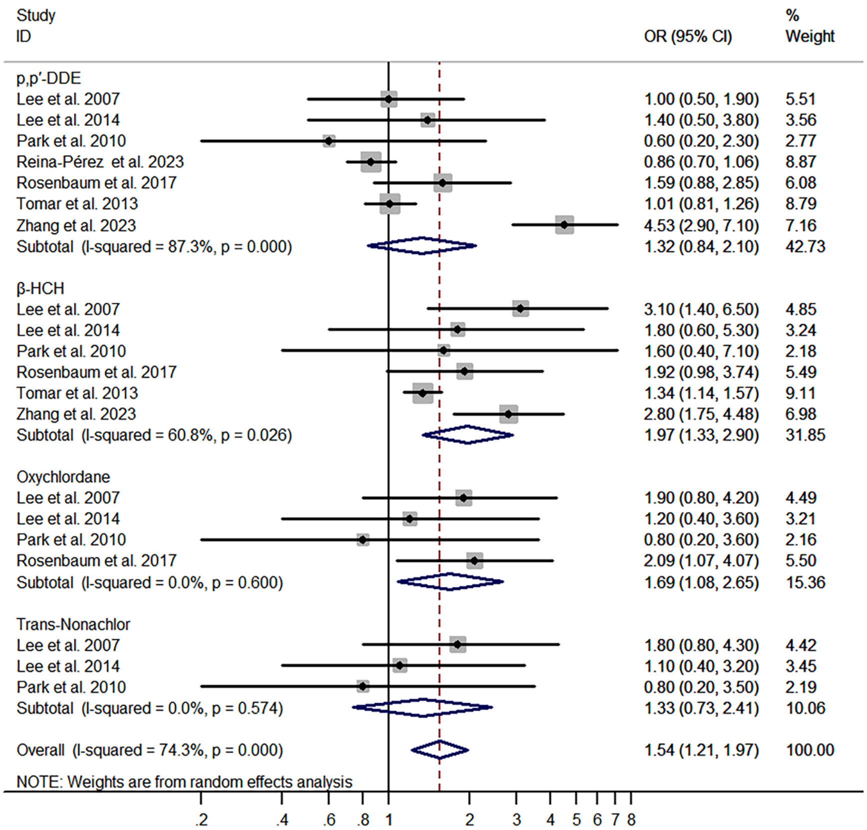

Figure 5. Forest plot of the relationship between Organochlorine pesticides exposure and Metabolic syndrome, ORs (95% CI)

order: serum > plasma > whole blood.[59] Due to the inconsistency of the "blood sample types" included in the study, heterogeneity is inevitable. In addition, studies have shown that PFASs in the blood are age-related,[59] and different age populations may be the source of the high heterogeneity. As the literature does not limit the age of the population, the age distribution within the investigations is uneven, and thus subgroup analysis of age factors has not been conducted. To further explore the relationship between PFASs and MetS/MetS components, future research should take into account the influence of age factors.

Like PFASs, PAEs are also typical EEDs, which can be found in medical devices (such as intravenous bags and drugs).[60] PAEs can affect the normal function of endocrine glands, resulting in reproductive abnormalities, immune system disorders, metabolic diseases and energy homeostasis imbalance.[61] For example, exposure to PAEs can lead to elevated liver transaminases, increased risk of liver dysfunction and cardiac metabolic adverse events, and increased risk of insulin resistance in healthy normal-weight men.[62] Furthermore, PAEs can affect lipid and glucose homeostasis, induce insulin resistance and increase the risk of diabetes.[63] In order to confirm whether exposure to PAEs in the population can induce the risk of cardiac metabolic adverse events, metabolic diseases and insulin resistance, we pooled the latest epidemiological evidence. The results confirmed that exposure to PAEs metabolites in the population increased the risk of MetS, and the overall combined results were relatively stable and less heterogeneous ($I^2 \leq 50\%$), indicating that our results were stable and reliable. In particular, MEP exposure was observed to be positively associated to Fasting Blood Glucose (FBG), indicating that the exposed population has an elevated risk of MetS and thus amplifies the diabetic risks, which is in accordance with prior research and the results of Zhang et al.'s meta-analysis.[64] In addition, we also found that the risk of MetS in the exposed population was studied by gender stratification. The overall combined results showed that female PAEs exposure was positively associated with MetS, which was consistent with the results of PFASs, while this phenomenon was not observed in the male exposed population. The possible reason for this phenomenon is that personal care products and cosmetics contain PAEs, and the female group is the main consumer, which may lead to higher PAEs concentration in the body than men,[65,66] resulting in a higher risk of MetS than men, but the specific mechanism of action is still unclear. In the future, *in vivo* experiments can be carried out to study the mechanism of EEDs leading to MetS from gender differences. In addition, subgroup analysis found that "sample size, study area, and country type" are sources of heterogeneity. Due to the small sample size of some studies, studies with larger data statistical capabilities are relatively insufficient. Secondly, there are racial differences and dietary differences among people in different "study areas," and many studies do not adjust the covariate-economic factors (such as poverty income ratio). Because there are differences in living standards and living environment among people in different countries, these factors may have a potential impact on the results.

Studies have shown that the ingestion of PCBs and OCPs can lead to impaired insulin function, abdominal obesity, liver steatosis, and an increased risk of metabolic disorder in Sprague-Dawley rats.[67] Moreover, C57B/6 mice exposed to PCB mixtures have been found to experience carbohydrate metabolism disruption, hyperinsulinemia, and exacerbated insulin resistance in obese mice.[68] Furthermore, Wistar female rats exposed to Malathion before pregnancy have been observed to have glucose intolerance in both the female rats and their offspring. Additionally, there is an augmented diabetic risk and pre-diabetes during pregnancy.[69] These findings suggest that PCBs and OCPs are risk factors for metabolic diseases, including type 2 diabetes and MetS. Our results are consistent with previous studies, indicating that PCBs and OCPs are associated with MetS, which can increase the risk of metabolic diseases. The sensitivity analysis showed stable results, and the heterogeneity results were relatively low, increasing the confidence in the results. For the results with high heterogeneity, we conducted subgroup analysis and found that the results showed a statistically significant change. Because the included studies were conducted in different regions, and the use of pesticides in different countries was different (such as the use of pesticides in developing countries may be higher than that in developing countries), different races, inconsistent sample types, different research designs and statistical methods, and different sample sizes, these factors will inevitably affect the stability of the results. Therefore, when classified into the same subgroup, there may be a statistically significant change in the results.

Epidemiological research has preliminarily established that exposure to EEDs in the population increases the risk of developing MetS. However, the exact mechanism of how EEDs cause MetS is yet to be fully understood. Studies have found that the PFOA treatment of a mouse pancreas β Cell line can activate Endoplasmic reticulum stress and damage β Cells through the ATF4/CHOP/TRIB3 pathway, which inhibits insulin secretion.[70] Additionally, chlorinated polyfluorinated ether sulfonates (Cl-PFAESs) have been observed to enhance adipogenesis of 3T3-L1 cells through peroxisome proliferator-activated receptors (PPARs) signaling pathways.[71] Long-term chronic exposure to diethyl phthalate (DEP) in adult male Swiss albino mice has been seen to induce excessive activation of NADPH oxidase 2, leading to continuous oxidative stress, which then damages insulin signals of liver cells and fat cells, causing insulin resistance and heightens the risk of type 2 diabetes and MetS.[72] Wu et al. discovered that PCB 153 intervention in C57 mice could decrease the expression of hepatocyte nuclear factor 1b (HNF1b) and glutathione peroxidase 1 (GPx1) in liver cells, increase ROS levels, and intensify NF-κB-mediated inflammatory responses, thereby leading to lipid accumulation and abnormal glucose metabolism.[73] In addition, BPA, as a common EEDs, is also a risk factor for MetS, and numerous existing studies have confirmed that BPA is an obesogenic factor, indirectly suggesting its potential role as a risk factor for MetS. Research has also revealed that BPA and its substitutes, such as bisphenol S (BPS), are associated with obesity. Specifically, the transcription factor PPARγ, a key regulator of adipogenesis, controls the expression of multiple genes involved in fat cell formation. BPA and its substitutes, including BPS, can activate and interact with PPARγ, contributing to obesity development. For instance, cell experiments have demonstrated that BPS exposure leads to intracellular triglyceride accumulation and upregulates adipogenic genes such as PLIN1, PPARγ, and ap2. Additionally, growing evidence highlights the role of estrogen receptors (ERs) in regulating metabolism and energy utilization. Reduced estrogen levels or the knockout of estrogen receptors result in increased abdominal fat, elevated cholesterol, insulin resistance, and glucose intolerance. BPA can interact with ERs to enhance the differentiation of human adipose stem cells into mature adipocytes. These mechanisms by which BPA promotes obesity have been comprehensively summarized in the review by Varghese et al.[74] These evidences suggest that EEDs may lead to insulin resistance and increase the risk of metabolic diseases by activating endoplasmic reticulum stress to cause β-cell damage, activating PPARγ signaling pathway to affect cell adipogenesis, inducing oxidative stress to cause mitochondrial dysfunction, mediating inflammatory response to cause lipid accumulation and abnormal glucose metabolism.

In addition, this article finds that exposure to EEDs leads to gender differences in MetS, what might be the cause of this outcome? Previous studies have indicated that MetS exhibits different prevalence trends between men and women, with estrogen potentially playing a significant regulatory role. Presently, ovariectomized animal models, with reduced circulating endogenous estradiol levels, are widely used to investigate the effects of estradiol on metabolic homeostasis. A study reported that ovariectomized mice experienced increased food intake, loss of pancreatic β-cell function, and cell death, leading to increased fat mass, insulin resistance, glucose intolerance, dyslipidemia, ectopic fat deposition, and other glucose and lipid metabolism disorders. Notably, estradiol supplementation could partially reverse these pathological changes.[75] Estrogen in pancreatic β--cells regulates insulin secretion, nutrient homeostasis, and cell survival; hence, its deficiency can promote metabolic dysfunction, increasing the risk of obesity, MetS, and type 2 diabetes.[76] Researchers have developed agonists for estrogen-related receptor (ERR) α, β, and γ nuclear receptors-SLU-PP-332. Injecting SLU-PP-332 into obese model mice increases energy expenditure and fatty acid oxidation while reducing fat accumulation. In MetS models, ERR agonists have been shown to effectively mitigate obesity and improve insulin sensitivity, showing their therapeutic potential for MetS treatment.[77] The regulatory effects of estrogen are primarily mediated through its binding to various receptors, including nuclear and extranuclear estrogen receptor (ER)α and ERβ, along with the G protein-coupled ER. Altogether, these studies highlight the critical role of estrogen in regulating metabolic diseases, including MetS. Additionally, they suggest that differences in physiological estrogen concentrations and normal estrogen function between sexes may be key factors contributing to sex-associated differences in the prevalence of MetS. Previous studies have shown that EED exposure can affect estrogen levels. For instance, blood mercury levels were reported to affect estrogen concentrations in Cambodian residents.[78] Moreover, in females experiencing early miscarriage, estradiol levels have been positively correlated with urinary mercury concentrations.[79] Both Bisphenol A (BPA) and per- and polyfluoroalkyl substances have been associated with reduced estrogen levels.[80,81] Similarly, Polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls have been shown to significantly alter estrogen metabolism in pregnant females.[82] These findings suggest that EEDs exposure can disrupt estrogen balance and impair its normal functions, contributing to gender differences in the incidence of metabolic diseases such as MetS.

In view of the fact that many new pollutants are defined as EEDs and the pollution in the environment is still severe, the exposure of EEDs can cause health damage to multiple systems (such as reproductive system) of the human body. Therefore, this article makes some suggestions based on previous studies: This article emphasizes the need to enhance understanding of the impact of EEDs. Given the vast diversity of EEDs, many types remain understudied and poorly understood. It is crucial to intensify both basic and clinical research, particularly to identify the minimum thresholds at which EEDs cause harm to human health and to implement regulatory restrictions. Moving forward, there is a pressing need to develop safer, low-risk alternatives to EEDs to mitigate their health hazards. Furthermore, we advocate for the formation of a global expert team with specialized knowledge of EEDs under the auspices of international scientific organizations. These experts should collaborate with researchers, clinicians, community advocates, and policymakers to contribute to reducing the risks posed by EEDs to public health. It is hoped that a more comprehensive understanding of the endocrine-disrupting mechanisms of EEDs will inform and guide regulators and policymakers in making responsible decisions.[83,84]

There are certain constraints within our research that warrant consideration when interpreting the outcomes. Firstly, the methods of EED detection and the samples tested varied across the studies, potentially leading to discrepancies in EED exposure concentrations and affecting the results. Secondly, despite extracting data from the model with the most adjusted covariates to minimize the impact of confounding variables, different literature adjusts covariates differently and cannot be unified, for the meta-results with publication bias, we need to be cautious when interpreting the results. Therefore, caution should be taken when interpreting them. Thirdly, when the literature studies the relationship between EEDs and MetS with low concentration as a reference, the effect size of high concentration EEDs was preferentially extracted, which may overestimate the relationship. Fourthly, most of the literature included cross-sectional studies, thus, causality is still lacking. Lastly, this article only included four typical EEDs, and there is insufficient epidemiological evidence on other types of EEDs, such as bisphenol A and Nonylphenol. Therefore, in the future, larger sample Case-control and Cohort studies are imperative to delve deeper into the causal link between EEDs and MetS.

Conclusion

To conclude, our findings suggest a positive correlation between population exposure to EEDs and the MetS risks and its components. This could potentially heighten the risk of cardiovascular and metabolic diseases. Moreover, the risk of MetS was higher in women exposed to PFASs and PAEs than in men, indicating gender differences. Nevertheless, the majority of the studies included were cross-sectional studies. Subsequent research, is essential to validate and solidify the causal relationship between them. Additionally, more studies are warranted to delve deeper into the relationship and underlying mechanisms between these factors.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources can be directed to and would be fulfilled by the lead contact, Jie Yu (Yujie@zmu.edu.cn).

Materials availability

This article is a meta-analysis that did not produce any new unique reagents.

Data and code availability

The data used in this article are obtained from published studies, and all the raw data used have been shown in the original forest map. This article does not use any new data and code, and does not report the original code. Any additional information required to reanalyze the data reported in this article is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Kai Pan, Jie Xu and Jie Yu: designe the study. Kai Pan, Feng Li, Huawen Yu, Ahmad Zaharin Aris, Jie He, Chengxing Wang, Yuzhu Xu, Jie Xu, Jie Yu: analyze and interprete the data. Kai Pan, Feng Li and Huawen Yu made figures and tables. Kai Pan, Jie Xu and Jie Yu: conducte the literature screening. Kai Pan and Jie Yu: participate in the statistical analysis. Jie Yu and Kai Pan: write the article. Jie Xu: revise the article. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. All the authors read and approved this article.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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  - Inclusion criteria
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  - Data extraction and quality assessment
  - Definition of MetS
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
PubMed	https://pubmed.ncbi.nlm.nih.gov/	N/A
EMBASE	https://www.embase.com/	N/A
Web of Science	https://www.webofscience.com/wos/	N/A
International prospective register of systematic reviews	https://www.crd.york.ac.uk/PROSPERO/	N/A
Software and algorithms		
Stata software Version 12.0	StataCorp	https://www.stata.com/products/
EndNote X9	Thomson Scientific	https://endnote.com/downloads/

METHOD DETAILS

Our investigation adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[85] Furthermore, it was registered in the International Prospective Register of Systematic Reviews (PROSPERO's registration number: CRD42023434251).

Literature search

We searched three English databases, Pubmed, Embase, and Web of science. In order to ensure the latest epidemiological evidence, we searched all epidemiological investigation literature on four EEDs (perfluoroalkyl substances, polychlorinated biphenyls, organochlorine pesticides, phthalates) and MetS published in the past 20 years (January 1,2003-December 31,2023). We did not limit the language type of the literature. The key words we searched were as follows: "Metabolic Syndrome" "Polychlorinated Biphenyls", "Organochlorine pesticides", "Phthalates", and "Perfluoroalkyl substances". The detailed search strategy can be found in the Table S1.

Inclusion criteria

Our inclusion and exclusion criteria follow the PECOS statement, as illustrated in Table 2. Inclusion criteria: (1) observational studies; (2) collection of biological samples (such as urine, serum, etc.) and articles with detailed EEDs laboratory testing methods; (3) the general population without age and gender restrictions; (4) studies that offer estimations quantitatively regarding the associations between exposure to EEDs and MetS outcomes, such as hazard ratio (HR), relative risk (RR), or odds ratio (OR) along with corresponding 95% confidence intervals (CIs); (5) the study outcome of the article as "MetS/MetS components" and providing diagnostic criteria for MetS. Exclusion criteria: (1) unrelated studies, such as not involving the exposed substances and research outcomes of this article; (2) Literature research design is not observational studies, such as randomized controlled trials; (3) *In vivo/in vitro* experiments, non-population epidemiological investigation; (4) Literature review or meta-analysis, conference reports, conference summaries, case reports, editorials, etc.; (5) The available OR, RR, HR values and 95% confidence intervals could not be extracted/calculated.

Table 2. PECOS statement

PECOS	Evidence
Population	People aged $\geq$18 years, exclusion of patients receiving blood glucose-lowering treatment, populations with major cardiovascular disease, and cancer.
Exposure	Exposure to 4 kinds of EEDs (perfluoroalkyl substances, polychlorinated biphenyl, phthalates, organochlorine pesticides).
Comparator	Unexposed to 4 kinds of EEDs/exposed to lower levels of 4 kinds of EEDs.
Outcomes	MetS/MetS components.
Study	Cohort study, which is a type of observational study.

Literature selection

Two researchers independently imported all the collected literature into EndNoteX9 software. Through the software's automatic duplicate checking function and manual duplicate checking, the duplicate literature was eliminated, and the literature was screened according to the predefined inclusion/exclusion criteria. The eligible literature was retained and the full text was reviewed in detail, and the included literature was finally determined. If there are differences in the screening process, they will discuss together. During the discussion, any unresolved differences were resolved by a third researcher to ensure consensus was reached during the study selection process.

Data extraction and quality assessment

During the data extraction phase, we gathered key information from the literature, including country of study, study design, the first author and publication year, sample size, sample type, EEDs laboratory testing method, exposure substance, MetS diagnostic standard, adjusted covariates, as well as values for HR, RR, OR, and their respective confidence interval (CI). The quality assessment of the cohort and case-control studies was carried out using the Newcastle Ottawa Scale (NOS), whereas the adapted NOS was utilized for evaluating the cross-sectional study, a score of $\geq$6 points was considered indicative of medium to high quality, while lower scores indicated lower quality. The detailed evaluation method is as described above.[54] Both researchers, K. Pan and J. Yu, independently conducted the quality assessment of the literature.

Definition of MetS

Commonly accepted definitions of MetS include World Health Organization 1999 (WHO 1999), National Cholesterol Education Program (NCEP) ATP III 2005 and International Diabetes Federation (IDF) 2006,[86] the diagnostic criteria of MetS were shown in Table S7.

QUANTIFICATION AND STATISTICAL ANALYSIS

Stata 12.0 software was employed to complete the statistical analysis. We stratified by four types of EEDs and reported our results by calculating the OR of MetS risk after exposure to the four types of EEDs. I^2 statistics were used to assess the heterogeneity between varying studies; if I^2 was $\geq$50% or $p < 0.05$, it indicated that the heterogeneity between different literatures was large, prompting the use of random effect models to merge effect size; when I^2 was $\leq$50% or $p > 0.05$, fixed effect models were employed to merge.[87] We carried out a subgroup analysis to explore the possible sources of heterogeneity. To control for differences in region, sample size, and economic conditions, we divided the study area, sample size ($\geq$500 or $\leq$500), and country type (developed and developing countries) into three subgroups. Furthermore, due to the different concentrations of EEDs in different biological samples, we established another subgroup called "sample type". In total, this divided the data into five subgroups: "region, sample size ($\geq$500 or $\leq$500), sample type, and country type (developed and developing countries)". To further verify the stability of the findings, a sensitivity analysis (leave-one-out method) was performed to determine the stability of the meta-results. Publication bias was assessed using the Begg test and Egger test.[88,89]