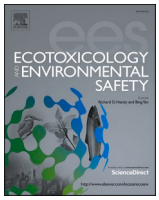
Ecotoxicology and Environmental Safety 302 (2025) 118574

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

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



Review

Endocrine disrupting chemicals exposure and health: An umbrella review

Junhao Chen [a,1], Pan Song [b,1], Chao Li [d], Hengjia Liu [d], Lei Zhang [c], Yi Zhou [a], Zhien Zhou [a,*], Weigang Yan [a,*]

[a] Department of Urology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China
[b] Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
[c] The First Clinical Medical College of Lanzhou University, Lanzhou 730000, China
[d] The Second Clinical Medical College of Lanzhou University, Lanzhou 730000, China

ARTICLE INFO

Edited by Professor Bing Yan

Keywords:
Endocrine disrupting chemicals
Meta-analysis
Health outcomes
Systematic review
Umbrella review

ABSTRACT

The aim of this umbrella review was to evaluate the quality, potential biases, and validity of the existing evidence on the relationship between endocrine disrupting chemicals (EDCs) exposure and health outcomes, through a comprehensive review of available meta-analyses. The included meta-analyses were searched across multiple databases, including PubMed, Embase, and Web of Science. This umbrella review included systematic reviews and meta-analyses of randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies that assessed the impact of EDCs exposure on various health outcomes in humans. The search resulted in the identification of 67 meta-analyses and 109 health outcomes from 7552 unique articles. All of these 109 health outcomes were derived from meta-analyses of observational studies. EDCs exposure included pesticides (n = 30), BPA (n = 13), PAHs (n = 18), PFAS (n = 10), and heavy metals (n = 38). Sixty-nine harmful associations were found to be statistically significant, along with one beneficial association. The remaining 39 outcomes were either harmful or beneficial but did not reach statistical significance. Significant harmful associations between EDCs exposure and 22 cancer outcomes, 21 neonatal/infant/child-related outcomes, 18 metabolic disorder outcomes, 17 cardiovascular disease outcomes, 11 pregnancy-related outcomes, and 20 other outcomes (renal, neuropsychiatric, respiratory, and hematologic) were detected. Exposure to environmental EDCs is closely linked to a wide range of adverse health outcomes. Given the widespread exposure to these pollutants globally, precautionary policies may be warranted to reduce population-level exposure and mitigate potential health risks associated with environmental chemicals.

1. Introduction

Endocrine disrupting chemicals (EDCs) have become an increasingly serious public health issue globally. With the acceleration of human activities and modern industrialization, these chemical pollutants are increasing in the environment and spreading through the food chain, posing a significant threat to human health (Thompson and Darwish, 2019). EDCs can mimic, block, or interfere with hormones in the human endocrine system, disrupting their normal function and leading to a range of physiological and health problems (Lauretta et al., 2019). These endocrine disruptors include polycyclic aromatic hydrocarbons (PAHs), polyfluoroalkyl substance (PFAS), bisphenol A (BPA), pesticides, and heavy metals (Metcalfe et al., 2022). Despite their varying chemical properties and mechanisms of action, they all possess significant endocrine-disrupting characteristics that can have profound effects on the human endocrine system (Zoeller et al., 2012).

Humans are continuously exposed to these pollutants through various pathways, such as the environment, food, and consumer products. Notably, these substances tend to have high persistence and accumulation, enabling them to remain in organisms for extended periods, leading to chronic exposure (Yilmaz et al., 2020). Therefore, studying the comprehensive effects of these pollutants on human health is not only of significant academic value but also of great practical importance for the development of effective public health policies and environmental management strategies. In 2009, the International Endocrine Society issued its first scientific statement, highlighting the

* Correspondence to: Department of Urology, Surgical Building of Peking, Union Medical College Hospital, No.1 Shuaifuyuan, Wangfujing, Dong Cheng District, Beijing 100730, China.
E-mail addresses: zhouzhien@163.com (Z. Zhou), pumchywg@sina.com (W. Yan).
[1] Contributed equally.

https://doi.org/10.1016/j.ecoenv.2025.118574
Received 2 June 2025; Received in revised form 23 June 2025; Accepted 23 June 2025
Available online 24 June 2025

potential harm of endocrine disruptors to human health, marking the beginning of widespread attention in this field (Gore et al., 2015). Since then, more and more studies have focused on the impact of these substances on human health and revealed their associations with various chronic diseases, such as metabolic disorders, reproductive health issues, and certain types of cancer (Kahn et al., 2020).

PAHs are typical environmental pollutants generated primarily from the incomplete combustion or pyrolysis of organic materials, especially in industrial activities and household cooking. These compounds are not only genotoxic but are also closely related to the development of several types of cancer (Barbosa et al., 2023; Wang et al., 2022a). PFAS, due to their strong chemical stability and long-lasting nature, are often referred to as "forever chemicals." They are widely used in stain-resistant fabrics, fast-food containers, and fire-suppressing foams, resulting in widespread environmental pollution, and have been found to pose potential risks to the immune, endocrine, and reproductive systems of humans (Evich et al., 2022).

Pesticides, as important tools for increasing agricultural yields, help protect crops from pests. However, their overuse and misuse cause environmental pollution, and long-term exposure to pesticide residues in the food chain can lead to endocrine system disruptions, immune suppression, and other health issues (Kaur et al., 2024). Similarly, BPA, a xenoestrogen, is widely used in plastics and food packaging materials, making it a common pollutant in daily human exposure. The endocrine-disrupting effects of BPA have been widely studied, particularly regarding its potential harm to reproductive health and neurodevelopment (Costa and Cairrao, 2024).

Heavy metals, such as cadmium (Cd), lead (Pb), and mercury (Hg), constitute another category of common EDCs. While metals like zinc and copper are essential trace elements for human health, excessive concentrations can become toxic. Unlike these essential metals, heavy metals such as cadmium, lead, and mercury accumulate in the body over time and not only fail to serve any physiological purpose but also cause severe damage to the endocrine system, leading to a variety of health problems, such as neurological damage, kidney injury, and cardiovascular diseases (Balali-Mood et al., 2021; Rehman et al., 2018).

Although numerous meta-analyses of observational studies examining the relationship between EDCs and various health outcomes have been published in recent decades, drawing definitive conclusions remains challenging. This is due to limitations in study designs, differences in exposure measurement methods, inconsistencies in findings, and variations in how exposure is defined. Consequently, a thorough evaluation of the quality of the existing evidence on the links between EDC exposure and health outcomes is essential before establishing detailed exposure limit policies. To assess the quality, potential bias, and validity of the evidence from all studies about EDCs and their health effects, we conducted an umbrella review of the relevant meta-analyses.

2. Methods

2.1. Umbrella review methods

This study is an umbrella review, aiming to comprehensively summarize high-level evidence on the associations between exposure to EDCs and health outcomes. We conducted a systematic search, extraction, and analysis of extensive data from published systematic reviews and meta-analyses examining the relationships between EDCs exposure (pesticides, BPA, PAHs, PFAS, and heavy metals) and various health outcomes. These meta-analyses were included because they had typically completed literature screening, quality appraisal, and data synthesis, providing more interpretable and integrated findings across diverse health endpoints and populations (Papatheodorou, 2019). Typically, exposure to EDCs was assessed through concentrations in blood or urine, types of occupational exposure, or questionnaires, and the data were subsequently synthesized through meta-analyses. Moreover, we didn't include systematic reviews that lacked meta-analyses. This umbrella review has been prospectively registered in the PROSPERO database (CRD420251077493) (https://www.crd.york.ac.uk/prospero/).

2.2. Literature search

We searched databases such as PubMed, Embase, and Web of Science for systematic reviews and meta-analyses of randomized controlled trials (RCTs) and observational studies from inception through January 2025. We searched the relevant databases by combining subject terms, keywords, and variations of text words related to EDCs: (pesticides OR pesticide) OR (bisphenol A OR BPA) OR (polycyclic aromatic hydrocarbons OR PAHs) OR (polyfluoroalkyl substances OR PFAS) OR (metals OR metal) AND (systematic review OR meta-analysis). The study selection process followed the PRISMA 2020 guidelines. Records identified through database searches were imported into EndNote and duplicates were removed. After removing duplicates, two authors (JHC and PS) independently screened the titles and abstracts to identify potentially relevant meta-analyses. The full texts of the remaining articles were then retrieved and assessed independently by the same two reviewers to identify meta-analyses that met the inclusion criteria. Any discrepancies between the two reviewers during the screening process were resolved by a third author (CL). Additionally, we manually searched the reference lists of all included articles for meta-analyses and reviews to ensure no relevant studies were missed.

2.3. Eligibility criteria

We included systematic reviews and meta-analyses that assessed the impact of EDCs on human health. During our literature search, our goal was to include studies with various research designs, including RCTs, cohort studies, case-control studies, and cross-sectional studies. However, we were unable to find any RCTs that met the inclusion criteria during the final screening. Meta-analyses were eligible for inclusion if they compared the effects of EDCs exposure on the health outcomes using relative risk (RR), odds ratio (OR), or hazard ratio (HR). The exposures considered in the meta-analyses included pesticides, BPA, PAHs, PFAS, Hg, Cd and Pd. If a study reported multiple health outcomes, we extracted data for each outcome separately. In cases where multiple systematic reviews or meta-analyses examined the same exposure–outcome association, we included only one meta-analysis per specific exposure–outcome pair. We prioritized the most recent study with the largest sample size. When a single meta-analysis reported on multiple outcomes, each outcome was treated as an independent unit of analysis. To reduce the risk of duplication or bias due to overlapping primary studies across reviews, we did not combine or pool estimates across different meta-analyses. The exclusion criteria for this umbrella review included meta-analyses that evaluated the effects of EDCs exposure on health outcomes in specific disease populations, studies with data that could not be extracted, non-English studies, and animal or cell culture studies.

2.4. Data extraction

Two reviewers (JHC and PS) independently collected the following data from each eligible study: the first author's name, year of publication, type of EDCs exposure, method of exposure measurement, health outcomes, the number of studies included, study design, comparison groups (high vs. low, higher vs. lower, highest vs. lowest, exposed vs. non-exposed), the number of cases and total participants, and the estimated summary effect (RR, OR, or HR) with 95 % confidence intervals (CI). In addition, we extracted the effect models, heterogeneity assessments, and publication bias evaluations. The effect models included random effect models and fixed effect models; heterogeneity was assessed using the I^2 statistic and Cochran's Q test P value; and publication bias was assessed by calculating the P-value of Egger's test or by

observing the symmetry of the funnel plot. Any disagreements were resolved by a third author (CL).

2.5. Quality assessment of methods and evidence

Two reviewers (JHC and PS) assessed the methodological quality of the included studies using AMSTAR, a reliable and widely accepted tool for evaluating the quality of systematic reviews and meta-analyses (Huang et al., 2023; Shea et al., 2007). Additionally, we applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to evaluate the strength of evidence for each health outcome, categorizing it as "high," "moderate," "low," or "very low" quality to inform our conclusions (Guyatt et al., 2011). Furthermore, we classified the evidence into four levels based on established criteria: class I (convincing evidence), class II (strongly suggestive evidence), class III (suggestive evidence), class IV (weak evidence), and NS (non-significant) (Huang et al., 2023; Wallace et al., 2020) (Table 1). In interpreting results, we primarily relied on the GRADE to determine the strength of conclusions. Outcomes with moderate or high quality were interpreted with more confidence, while those with low or very low quality were discussed cautiously and considered as suggestive evidence. We also noted that the evidence classification criteria offer an algorithm-based evaluation, while GRADE includes some subjective judgments, and any inconsistency between the two was handled with appropriate caution in the narrative synthesis.

2.6. Data analysis

To meet the standardized criteria required for evidence classification, we reanalyzed the summary effect estimates from the included meta-analyses. On one hand, all included meta-analyses only reported threshold p-values (e.g., $p < 0.05$ or $p < 0.01$), which made it impossible to determine whether they met criteria such as $p < 10^{-6}$. On the other hand, to evaluate whether the 95 % confidence interval of the largest study excluded the null value, we calculated the standard error to identify the corresponding study and extracted its data. Reanalyses were conducted using the same model type (fixed-effect or random-effects) as reported in the original studies. Detailed results are provided in Supplementary File 2. Additionally, we extracted the number of cases and total participants from the original studies included in each meta-analysis (Theodoratou et al., 2014). We did not extract data on dose-response relationships, as only a small number of the included studies performed such analyses. Furthermore, if the included meta-analysis did not incorporate original studies enrolled in other meta-analyses, we merged the data from all relevant studies and conducted a reanalysis. If reanalysis from a meta-analysis was not possible, we extracted the summary data and, to the extent feasible, assessed heterogeneity and publication bias based on the available information from the meta-analysis. For the heterogeneity tests, we considered a $P < 0.10$ as statistically significant (Higgins and Thompson, 2002). For all other tests, a $P < 0.05$ was regarded as significant. We employed Review Manager version 5.3 and Stata version 15.1 to conduct the evidence synthesis, perform Egger's test, and carry out the small study effects.

Table 1
Evidence classification criteria (Huang et al., 2023; Wallace et al., 2020).

Evidence class	Description
Class I: convincing evidence	> 1000 cases (or >20000 participants for continuous outcomes); statistical significance at $P < 10^{-6}$ (random effects); no evidence of small study effects and excess significance bias; 95 % prediction interval excluded null value; no large heterogeneity (I^2<50 %)
Class II: highly suggestive evidence	> 1000 cases (or >20000 participants for continuous outcomes), statistical significance at $P < 10^{-6}$ (random effects), and largest study with 95 % confidence interval excluding null value
Class III: suggestive evidence	> 1000 cases (or >20000 participants for continuous outcomes) and statistical significance at $P < 0.001$
Class IV: weak evidence	Remaining significant associations with $P < 0.05$
NS: non-significant	$P > 0.05$

2.7. Patient and public involvement

This study primarily involved the reanalysis of existing secondary data, and therefore, the study subjects were not involved in any stage of the research implementation. Additionally, no patients were consulted in the interpretation of the results or the preparation of the manuscript.

3. Results

3.1. Characteristics of meta-analyses

Fig. 1 presents the flowchart illustrating the process of literature search and selection. Following a comprehensive search of the literature, we identified a total of 7552 unique articles. By applying the inclusion criteria, we ultimately included 109 health outcomes from 67 meta-analyses. Most of the included meta-analyses focused on the associations between EDCs exposure and cancer (n = 22), followed by neonatal/infant/child related outcomes (n = 21), metabolic disorders (n = 18), cardiovascular disease (CVD) (17), pregnancy-related outcomes (n = 11), and other diseases (n = 20) (Fig. 2). EDCs exposure included pesticides (n = 30), BPA (n = 13), PAHs (n = 18), PFAS (n = 10), and heavy metals (n = 38). Significance was reached for 69 harmful associations and one beneficial association. The other 39 outcomes did not reach significance. After quality assessment of evidence through GRADE and evidence classification criteria, most of the 109 meta-analyses were classified as "low" or "very low" quality and III, IV, or NS evidence class. Only three (3 %) meta-analyses were classified as "moderate" quality. Eight (7 %) meta-analyses were graded as class II, including one cancer outcome, one cardiovascular disease, and two metabolic disorders, three neonatal/infant/child related outcomes and one other outcome. No "high" quality or class I evidence was found in this umbrella review.

3.2. Cancer

3.2.1. Low and moderate quality evidence

A meta-analysis of 17 case-control and cross-sectional studies revealed a significant association between high pesticide exposure and an increased risk of prostate cancer (OR 1.33, 95 % CI 1.02–1.63) with low-quality evidence (GRADE class III) (Lewis-Mikhael et al., 2016). Additionally, both occupational and environmental exposure to PAHs was linked to a higher risk of breast cancer (OR 1.21, 95 % CI 1.11–1.33), also with low-quality evidence (GRADE class III) (Gamboa-Loira et al., 2022). Furthermore, a comparison of the highest versus lowest levels of Cd exposure showed a 32 % increased risk of cancer mortality in the general population associated with higher urinary or blood Cd levels (HR 1.32, 95 % CI 1.15–1.51), with low-quality evidence (GRADE class II) (Guo et al., 2022) (Fig. 3).

3.2.2. Very low quality evidence

A meta-analysis involving 3955 cases and 9948 controls revealed that occupational pesticide exposure significantly increased the risk of acute myeloid leukemia (AML) (OR 1.51, 95 % CI 1.10–2.08) (Foucault et al., 2021). Similarly, high pesticide exposure was associated with a greater risk of non-Hodgkin lymphoma (RR 1.41, 95 % CI 1.13–1.75) than low pesticide exposure was (Zhang et al., 2019). Additionally, pesticide exposure was linked to a 65 % increased risk of bladder cancer (OR 1.65, 95 % CI 1.22–2.22) and a 10 % increased risk of kidney cancer (OR 1.10, 95 % CI 1.01–1.19) compared with no exposure (Liang et al., 2016; Xie et al., 2016). Occupational exposure to PAHs, including among aluminum production workers and iron and steel foundry

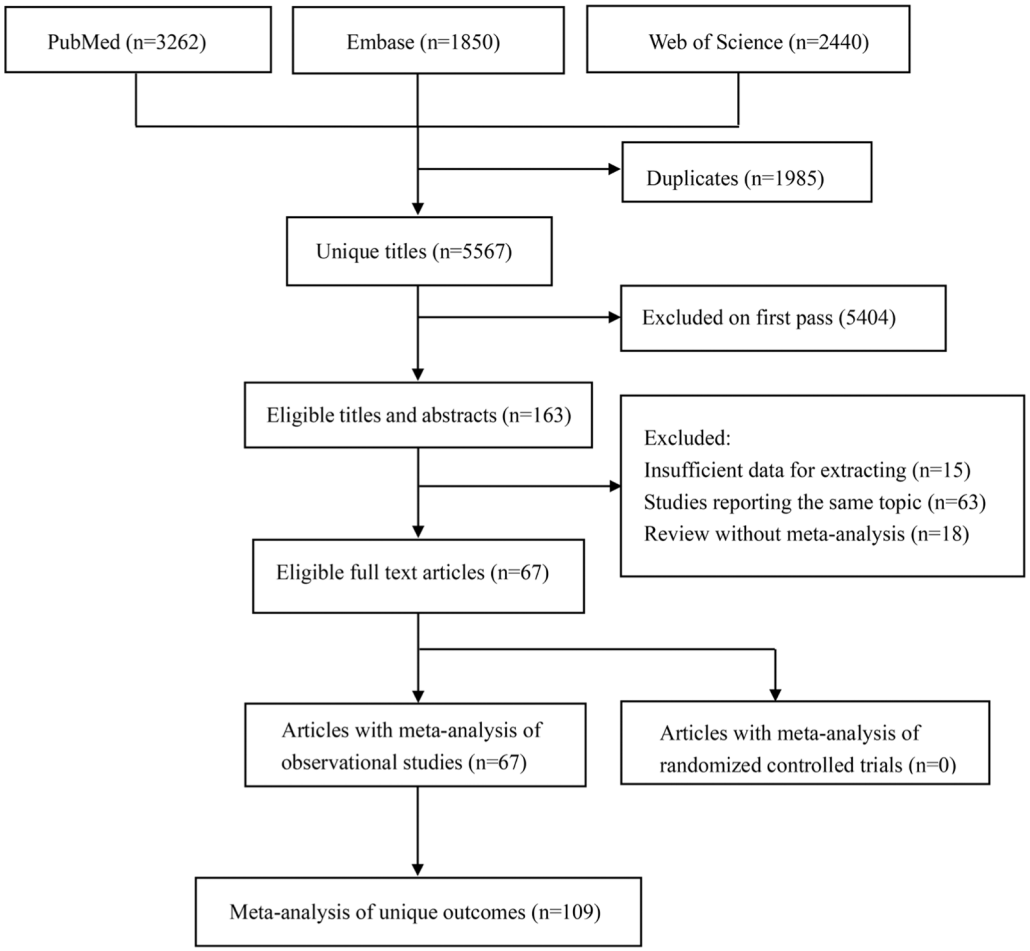


Fig. 1. Flowchart of systematic search and selection process.

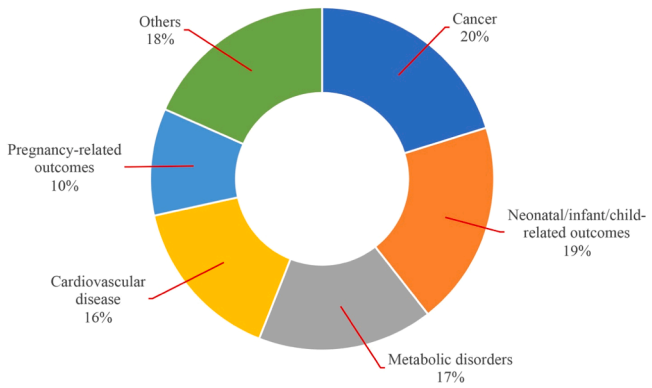


Fig. 2. Map of health outcomes associated with EDCs exposure.

workers, was also associated with a 27 % higher risk of bladder cancer (RR 1.27, 95 % CI 1.18–1.37) (Rota et al., 2014). Furthermore, another pooled analysis showed that individuals with pesticide exposure had a 48 % higher risk of thyroid cancer compared to those without exposure (OR 1.48, 95 % CI 1.15–1.91) (Han et al., 2019). The most recent meta-analysis found that occupational PAHs exposure increased the risk of lung cancer (OR 1.23, 95 % CI 1.08–1.41), particularly among workers in the coal/coke and iron/steel industries (Singh et al., 2018). Additionally, occupational exposure to PAHs was significantly associated with an increased risk of laryngeal cancer (OR 1.29, 95 % CI 1.10–1.52) (Paget-Bailly et al., 2012). Moreover, a meta-analysis of 399191 participants and 24017 incident cases of breast cancer identified a positive association between higher Cd exposure and the risk of developing breast cancer (OR 1.13, 95 % CI 1.00–1.28) (Fig. 3).

No significant associations were found between pesticide exposure and hepatocellular carcinoma (Lu et al., 2022), cutaneous melanoma (Stanganelli et al., 2020), or breast cancer (Park et al., 2014). Similarly, no significant links were observed between PAHs exposure and Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, or multiple myeloma (Alicandro et al., 2016). Furthermore, BPA exposure was not significantly associated with breast cancer (Liu et al., 2021), nor was PFAS exposure linked to breast cancer (Liu et al., 2023)or cancer mortality related to Pb exposure (Guo et al., 2022).

3.3. Cardiovascular disease

3.3.1. Low and moderate quality evidence

Recent studies have shown a positive association between pesticide exposure and an increased risk of hypertension (OR 1.21, 95 % CI 1.07–1.38) (low; IV) (Hernández-Mariano et al., 2022) and CVD (OR 1.12, 95 % CI 1.00–1.24) (low; IV) (Fu et al., 2020). A comprehensive analysis of 37 studies involving 348,259 non-overlapping participants revealed that exposure to Pb and Cd increased the risk of CVD by 43 % (RR 1.43, 95 % CI 1.16–1.76) (low; III) and 33 % (RR 1.33, 95 % CI 1.09–1.64) (low; IV), respectively, when comparing the highest and lowest thirds of baseline exposure levels (Chowdhury et al., 2018). Additionally, this study found that Pb exposure was significantly associated with an increased risk of coronary heart disease (CHD) (RR 1.85, 95 % CI 1.27–2.69) (low; IV) (Chowdhury et al., 2018). Extreme category analysis further indicated that the highest versus lowest Pb (RR 1.07, 95 % CI 1.00–1.14) (low; IV) and Cd (RR 1.30, 95 % CI 1.13–1.48)

Outcome	Category	No of cases /total	Risk estimate (95% CI)	Risk estimate (95% CI)	No of studies (T/R/C/P)	I^2 (%)	Egger test P value	AMSTAR	GRADE	Evidence class
AML	Pesticides	3955/9948		1.51 (1.10 to 2.08)	14/0/0/14	76.0	0.950	9	very low	IV
Bladder cancer	Pesticides	NA/NA		1.65 (1.22 to 2.22)	9/0/2/7	80.6	0.358	8	very low	IV
Bladder cancer	PAHs	427/121133		1.27 (1.18 to 1.37)	19/0/19/0	0.0	>0.05	9	very low	IV
Thyroid cancer	Pesticides	675/651689		1.48 (1.15 to 1.91)	8/0/7/1	48.0	NA	5	very low	IV
Non-Hodgkin lymphoma	Pesticides	245/65000		1.41 (1.13 to 1.75)	6/0/1/5	NA	NA	7	very low	IV
Prostate cancer	Pesticides	8403/23257		1.33 (1.02 to 1.63)	17/0/0/17	44.8	0.072	9	low	III
Kidney cancer	Pesticides	3340/247379		1.10 (1.01 to 1.19)	11/0/7/4	69.0	>0.05	8	very low	IV
Lung cancer	PAHs	2571/296810		1.23 (1.08 to 1.41)	24/0/24/0	78.6	NA	5	very low	II
Larynx cancer	PAHs	NA/NA		1.29 (1.10 to 1.52)	29/0/22/7	26.0	0.300	5	very low	IV
Breast cancer	PAHs	17480/50059		1.21 (1.11 to 1.33)	17/0/0/17	44.1	0.065	7	low	III
Breast cancer	Cd	24017/399191		1.13 (1.00 to 1.28)	17/0/9/8	77.0	NA	8	very low	IV
Cancer mortality	Cd	NA/52628		1.32 (1.15 to 1.51)	7/0/7/0	27.6	0.287	9	low	IV

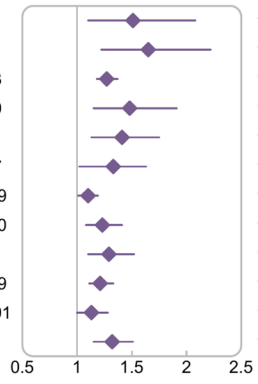


Fig. 3. Significant associations between EDCs exposure and cancer outcomes, EDCs, endocrine-disrupting chemicals; AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; T, total No. of studies; R, randomized controlled trial; C, cohort studies; P, population-based case-control and/or cross-sectional studies; AML, Acute myeloid leukemia; PAHs, polycyclic aromatic hydrocarbons; Cd, cadmium; NA, not available.

(low; III) exposures were linked to an increased risk of stroke (Bao et al., 2022). For CVD mortality, both Pb (HR 1.35, 95 % CI 1.05–1.74) (low; IV) and Cd (HR 1.45, 95 % CI 1.24–1.69) (low; IV) were associated with an elevated risk of death from CVD when the highest to lowest exposure levels were compared (Guo et al., 2022) (Fig. 4).

3.3.2. *Very low quality evidence*

High urinary levels of PAHs were found to significantly increase the risk of both hypertension and cardiovascular disease (CVD). Specifically, the risk of hypertension was elevated by 32 % (OR 1.32, 95 % CI 1.19–1.48), while the risk of CVD increased by 23 % (OR 1.23, 95 % CI 1.16–1.30) for individuals with higher PAHs exposure (Mirzababaei et al., 2022). In another meta-analysis involving 22,878 participants, after adjusting for confounding factors such as age, sex, and various cardiometabolic risk factors, a significant relationship was found between BPA exposure and an increased risk of CVD. The OR for this association was 1.13 (95 % CI 1.03–1.23) (Moon et al., 2021) (Fig. 4).

No significant associations were found between Hg exposure and the risk of CVD, CHD, or stroke in our analysis (Chowdhury et al., 2018). Similarly, we did not observe a significant link between exposure to PAHs (Mirzababaei et al., 2022) or Cd (Chowdhury et al., 2018)and the risk of CHD.

3.4. *Metabolic disorders*

3.4.1. *Low and moderate quality evidence*

A meta-analysis by Lamat and colleagues revealed that overall exposure to pesticides and their contaminants was associated with a 30 % increased risk of metabolic syndrome (MetS) (OR 1.30, 95 % CI 1.22–1.37), with low-quality evidence (GRADE class II) (Lamat et al., 2022). A more recent meta-analysis of 23 prospective studies indicated a significantly higher risk of developing type 2 diabetes mellitus (T2DM) for individuals with higher pesticide DDT exposure compared to those with lower exposure (OR 1.44, 95 % CI 1.00–2.07), with moderate-quality evidence (GRADE class IV) (Hernández-Mariano et al., 2022). Moreover, a meta-analysis conducted by Gui et al. suggested that a per ln-unit increase in the serum PFAS concentration may increase the risk of incident T2DM by 46 % (OR 1.46, 95 % CI 1.38–1.55), with

Outcome	Category	No of cases /total	Risk estimate (95% CI)	Risk estimate (95% CI)	No of studies (T/R/C/P)	I^2 (%)	Egger test P value	AMSTAR	GRADE	Evidence class
Hypertension	Pesticides	NA/2834		1.21 (1.07 to 1.38)	4/0/3/1	9.3	0.140	8	low	IV
Hypertension	PAHs	>1786/8254		1.32 (1.19 to 1.48)	3/0/2/1	62.4	0.001	8	very low	III
CVD	Pesticides	NA/10022		1.12 (1.00 to 1.24)	11/0/5/6	71.4	>0.05	8	low	IV
CVD	BPA	3691/22878		1.13 (1.03 to 1.23)	5/0/3/2	61.8	<0.01	7	very low	IV
CVD	PAHs	>2181/19026		1.23 (1.16 to 1.30)	6/0/5/1	59.7	0.158	8	very low	II
CVD	Pb	4970/110382		1.43 (1.16 to 1.76)	10/0/10/0	67.5	0.652	8	low	III
CVD	Cd	3756/50674		1.33 (1.09 to 1.64)	6/0/6/0	77.7	0.128	8	low	IV
CHD	Pb	2228/91779		1.85 (1.27 to 2.69)	8/0/8/0	65.6	0.460	8	low	IV
Stroke	Pb	NA/94139		1.07 (1.00 to 1.14)	8/0/2/6	74.0	0.279	9	low	IV
Stroke	Cd	9562/52434		1.30 (1.13 to 1.48)	17/0/2/15	53.4	0.051	9	low	III
CVD mortality	Cd	NA/39168		1.45 (1.24 to 1.69)	7/0/7/0	0.0	0.845	9	low	IV
CVD mortality	Pb	NA/47901		1.35 (1.05 to 1.74)	5/0/5/0	43.8	0.593	9	low	IV

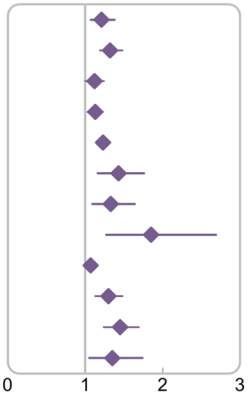


Fig. 4. Associations between EDCs exposure and cardiovascular disease outcomes, EDCs, endocrine-disrupting chemicals; AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; T, total No. of studies; R, randomized controlled trial; C, cohort studies; P, population-based case-control and/or cross-sectional studies; CVD, cardiovascular disease; CHD, Coronary heart disease; PAHs, polycyclic aromatic hydrocarbons; BPA, bisphenol A; Cd, cadmium; Pb, lead; NA, not available.

low-quality evidence (GRADE class IV) (Gui et al., 2023). In addition, Gu et al. found a significant association between Cd exposure and an elevated risk of hyperuricemia (OR 1.20, 95 % CI 1.02–1.41), with low-quality evidence (GRADE class IV) (Gu et al., 2022). Furthermore, a pooled analysis of 10 observational studies that measured urinary BPA revealed a significant association between the highest and lowest urinary BPA levels, with the highest levels linked to a higher risk of obesity (OR 1.53, 95 % CI 1.38–1.70), on the basis of moderate-quality evidence (GRADE class II). Additionally, a dose-response analysis showed that for each 1-ng/mL increase in urinary BPA, the risk of obesity increased by 11 % (Wu et al., 2020) (Fig. 5).

3.4.2. Very low quality evidence

A meta-analysis observed a positive association between Pb exposure (OR 1.21, 95 % CI 1.00–1.48) and Hg exposure (OR 1.26, 95 % CI 1.06–1.48) and an increased risk of MetS (Xu et al., 2021). In another meta-analysis involving 41,320 participants, 16 studies that provided measurements of BPA in blood and urine were included in the analysis. The results demonstrated a positive correlation between BPA concentrations in human biological samples and the risk of T2DM (OR 1.28, 95 % CI 1.14–1.44). Further sensitivity analysis also confirmed a positive relationship between urinary BPA levels and the risk of T2DM (Hwang et al., 2018). Additionally, Khosravipour and colleagues found a significantly higher odds of diabetes in individuals with the highest urinary PAHs levels compared to those with the lowest levels (OR 1.52, 95 % CI 1.40–1.65) (Khosravipour and Khosravipour, 2020). A recent meta-analysis involving adults showed a significant link between the pesticide and an increased risk of hyperuricemia (OR 2.31, 95 % CI 1.27–4.20) (Yu et al., 2023). Furthermore, Pb (OR 1.56, 95 % CI 1.21–2.03) and Cd (OR 1.20, 95 % CI 1.02–1.41) exposure have also been reported to be positively associated with hyperuricemia (Gu et al., 2022). A pooled analysis of 8 cross-sectional studies involving 68,454 participants revealed a significant positive association between PAHs and obesity (OR 1.38, 95 % CI 1.21–1.58). Subgroup analysis indicated that this association was stronger in children, women, smokers, and populations in developing regions (Liu et al., 2023). In a separate meta-analysis, Jalili et al. found that exposure to Cd and Pb may increase the risk of osteoporosis by 35 % (OR 1.35, 95 % CI 1.17–1.56) and 15 % (OR 1.15, 95 % CI 1.00–1.32), respectively. Subgroup analysis showed that the association between Cd and osteoporosis was more prominent in older individuals compared to younger ones, while the link between Pb and osteoporosis was stronger in men than in women (Jalili et al., 2020) (Fig. 5).

We observed no significant associations between Hg exposure and the risk of diabetes (Guo et al., 2023), hyperuricemia (Gu et al., 2022), and osteoporosis (Jalili et al., 2020). In addition, Cd exposure was not associated with the risk of MetS (Xu et al., 2021).

3.5. Neonatal/infant/child related outcomes

3.5.1. Low and moderate quality evidence

A pooled analysis of 43,598 individuals (18,198 cases and 25,400 controls) found that parental pesticide exposure was associated with an increased risk of childhood brain tumors (OR 1.31, 95 % CI 1.17–1.46), with low-quality evidence (GRADE class II). This association remained significant even after considering postnatal and residential pesticide exposure (Feulefack et al., 2021). Additionally, a separate meta-analysis indicated that both prenatal (OR 1.17, 95 % CI 1.01–1.34) and postnatal (OR 1.43, 95 % CI 1.28–1.59) exposure to BPA were linked to a higher risk of childhood asthma, with low-quality evidence (GRADE class IV) (Wu et al., 2021). Furthermore, Zhen et al. reviewed existing epidemiological studies to assess the impact of PAHs on child neurodevelopment. Their findings showed that prenatal exposure to PAHs was associated with an increased risk of adverse neurodevelopmental outcomes in children (OR 2.1, 95 % CI 1.69–2.62), with moderate-quality evidence (GRADE class IV) (Zhen et al., 2023) (Fig. 6). The neurodevelopmental outcomes assessed in this study included adaptation ability, language function, social behavior, attention, and motor skills.

3.5.2. Very low quality evidence

A meta-analysis that included 55 eligible observational studies from over 30 countries/regions assessed more than 200 different pesticide exposures and found that maternal environmental or occupational pesticide exposure increases the risk of acute leukemia (AL) in offspring during childhood (OR 1.94, 95 % CI 1.53–2.47) (Karalexi et al., 2021). A meta-analysis revealed that pesticide exposure during pregnancy significantly increased the risk of birth defects compared with non-exposed pregnant women (OR 4.44, 95 % CI 2.61–7.57) (Demelash Enyew et al., 2023). Similarly, a meta-analysis focused on African children found a significant association between maternal pesticide

Outcome	Category	No of cases /total	Risk estimate (95% CI)	Risk estimate (95% CI)	No of studies (T/R/C/P)	I^2 (%)	Egger test P value	AMSTAR	GRADE	Evidence class
Metabolic syndrome	Pesticides	1981/6789		1.30 (1.22 to 1.37)	12/0/2/10	48.5	NA	8	low	II
Metabolic syndrome	Pb	NA/30570		1.21 (1.00 to 1.48)	12/0/1/11	82.9	0.439	9	very low	IV
Metabolic syndrome	Hg	NA/29344		1.26 (1.06 to 1.48)	11/0/1/10	67.7	0.768	9	very low	IV
T2DM	Pesticides	NA/5364		1.44 (1.00 to 2.07)	7/0/0/7	44.4	0.190	8	moderate	IV
T2DM	BPA	6855/141320		1.28 (1.14 to 1.44)	16/0/0/16	89.2	<0.05	9	very low	III
T2DM	PAHs	NA/24406		1.52 (1.40 to 1.65)	6/0/0/6	35.1	>0.05	6	very low	IV
T2DM	PFAS	NA/68324		1.46 (1.38 to 1.55)	6/0/6/0	0.0	0.133	10	low	IV
Hyperuricemia	Pesticides	270/2368		2.31 (1.27 to 4.20)	3/0/0/3	74.0	NA	5	very low	IV
Hyperuricemia	Pb	NA/26124		1.56 (1.21 to 2.03)	11/0/0/11	72.9	0.048	8	very low	IV
Hyperuricemia	Cd	NA/22139		1.20 (1.02 to 1.41)	11/0/0/11	38.5	0.792	8	low	IV
Obesity	BPA	NA/27993		1.53 (1.38 to 1.70)	10/0/1/9	44.0	0.050	7	moderate	II
Obesity	PAHs	NA/68454		1.38 (1.21 to 1.58)	8/0/0/8	77.0	0.087	7	very low	IV
Osteoporosis	Cd	NA/13833		1.35 (1.17 to 1.56)	12/0/1/11	88.6	0.030	9	very low	IV
Osteoporosis	Pb	NA/3877		1.15 (1.00 to 1.32)	5/0/0/5	75.0	0.041	9	very low	IV

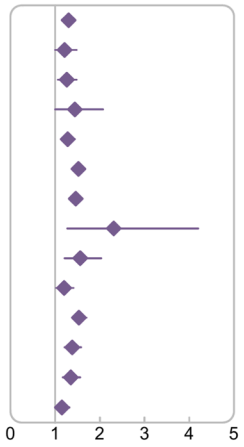


Fig. 5. Associations between EDCs exposure and metabolic disorder outcomes, EDCs, endocrine-disrupting chemicals; AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; T, total No. of studies; R, randomized controlled trial; C, cohort studies; P, population-based case-control and/or cross-sectional studies; T2DM, Type 2 diabetes mellitus; PAHs, polycyclic aromatic hydrocarbons; PFAS, polyfluoroalkyl substance; BPA, bisphenol A; Cd, cadmium; Pb, lead; Hg, mercury; NA, not available.

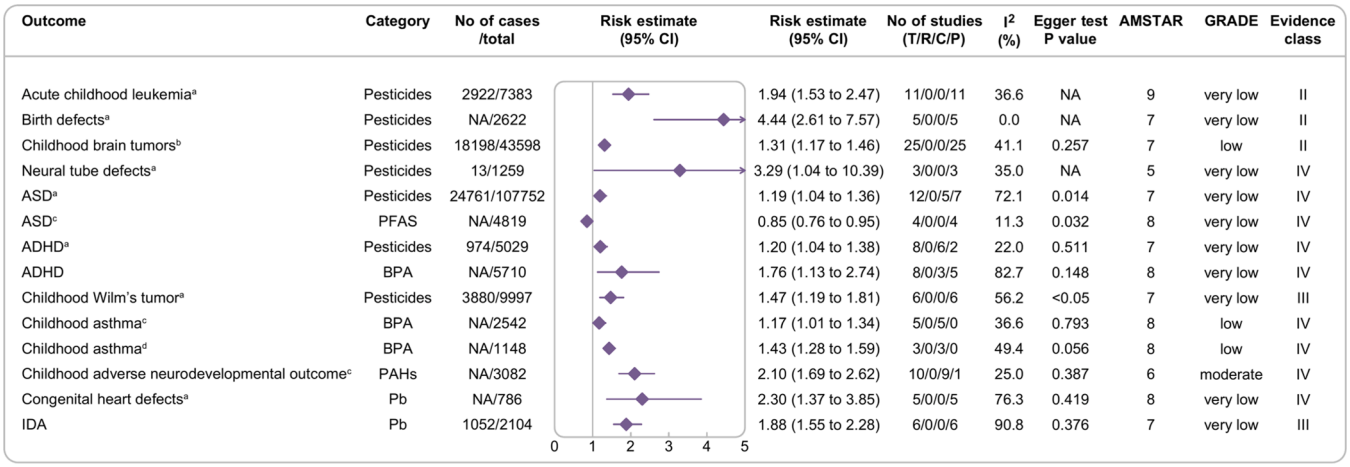


Fig. 6. Associations between EDCs exposure and neonatal/infant/child-related outcomes, EDCs, endocrine-disrupting chemicals; AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; T, total No. of studies; R, randomized controlled trial; C, cohort studies; P, population-based case-control and/or cross-sectional studies; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; IDA, Iron deficiency anemia; PAHs, polycyclic aromatic hydrocarbons; PFAS, polyfluoroalkyl substance; BPA, bisphenol A; Pb, lead; NA, not available. [a] Maternal exposure, [b] Parental exposure, [c] Prenatal exposure, [d] Postnatal exposure.

exposure during pregnancy and neural tube defects (OR 3.29, 95 % CI 1.04–10.39) (Atlaw et al., 2021). In another meta-analysis that included 19 cohort and case-control studies, maternal pesticide exposure was found to increase the risk of autism spectrum disorder (ASD) by 19 % (OR 1.19, 95 % CI 1.04–1.36) and attention-deficit hyperactivity disorder (ADHD) by 20 % (OR 1.20, 95 % CI 1.04–1.38) in offspring (Xu et al., 2023). Yao et al. conducted a meta-analysis, and the pooled results indicated that exposure to PFAS during pregnancy in the highest quartile was negatively associated with ASD compared to the lowest quartile (OR 0.85, 95 % CI 0.76–0.95) (Yao et al., 2023).

A separate meta-analysis involving 5710 children indicated that the highest levels of urinary BPA exposure were associated with an increased risk of ADHD (OR 1.76, 95 % CI 1.13–2.74) compared with the lowest BPA exposure levels (Liu and Wang, 2022). Additionally, Khan et al. reported that parental pesticide exposure before conception or during pregnancy was linked to an increased risk of pediatric Wilms' tumor (OR 1.47, 95 % CI 1.19–1.81) (Khan et al., 2022). Furthermore, a pooled analysis demonstrated that children with maternal Pb exposure had a significantly higher risk of congenital heart defects compared with those without maternal Pb exposure (OR 2.30, 95 % CI 1.37–3.85) (Li et al., 2022). Similarly, children's own exposure to Pb was associated with an increased risk of iron deficiency anemia (IDA) (OR 1.88, 95 % CI 1.55–2.28) (Farkhondeh et al., 2022) (Fig. 6).

No significant associations were found between children's exposure to PAHs (Zhang et al., 2022), prenatal exposure to PFAS (Yao et al., 2023) and the risk of ADHD. Similarly, we did not observe a significant link between children's exposure to Hg or Pb and the risk of asthma (Wang et al., 2022b). Additionally, maternal exposure to Cd and Hg was not associated with an increased risk of congenital heart defects (Li et al., 2022). Furthermore, prenatal exposure to PAHs did not show any significant relationship with the development of depression or anxiety in children (Zhen et al., 2023).

3.6. Pregnancy-related outcomes

A pooled analysis in women revealed a positive association between PFAS exposure and the incidence of preeclampsia (OR 1.17, 95 % CI 1.02–1.34) (low; IV) (Zhen et al., 2023), as well as gestational diabetes (OR 1.09, 95 % CI 1.02–1.16) (low; IV) (Yan et al., 2022). Additionally, a separate meta-analysis in women showed that higher versus lower BPA exposure during pregnancy was linked to a 35 % increased risk of preterm birth (OR 1.35, 95 % CI 1.04–1.67) (very low; IV) (Namat et al., 2021) (Fig. 7).

Current meta-analyses have not revealed a significant association between pesticide exposure and the risk of preterm birth (Lin et al., 2023). Similarly, we found no significant link between PFAS exposure and the risk of preterm birth or miscarriage (Deji et al., 2021). Additionally, BPA exposure was not significantly associated with the risk of preeclampsia (Hirke et al., 2023) or gestational diabetes mellitus (GDM) (Taheri et al., 2021). Furthermore, PFAS exposure showed no association with the risk of gestational hypertension (Zhen et al., 2023) or female infertility (Wang et al., 2023). Lastly, exposure to PAHs did not appear to be linked to term birth weight (Yang et al., 2020).

3.7. Other outcomes

A meta-analysis of 28 case-control and cross-sectional studies involving 107,539 participants revealed that Cd exposure was related to an increased risk of proteinuria (OR 1.35, 95 % CI 1.13–1.61) (very low; IV), whereas Pb exposure was associated with a decrease in the estimated glomerular filtration rate (eGFR) (OR 1.12, 95 % CI 1.03–1.22) and an increased risk of proteinuria (OR 1.25, 95 % CI 1.04–1.49) (very low; IV) (Jalili et al., 2021). Another meta-analysis indicated that higher serum BPA concentrations were associated with an increased risk of chronic kidney disease (CKD) (OR 6.94, 95 % CI 3.60–13.36) (very low; IV) (Moreno-Gómez-Toledano et al., 2021). Pesticide exposure was found to be significantly associated with an increased risk of neurological disorders, including Parkinson's disease (RR 1.41, 95 % CI 1.20–1.65) (very low; III) (Chambers-Richards et al., 2023), amyotrophic lateral sclerosis (ALS) (OR 1.57, 95 % CI 1.25–1.98) (very low; III) (Wang et al., 2017), and Alzheimer's disease (OR 1.34, 95 % CI 1.08–1.67) (very low; IV) (Yan et al., 2016). Furthermore, pesticide exposure was also linked to an increased risk of asthma (OR 1.31, 95 % CI 1.17–1.48) (very low; III) (Chittrakul et al., 2021), obstructive pulmonary diseases (OR 1.33, 95 % CI 1.21–1.47) (very low; II) (Pourhassan et al., 2019), myelodysplastic syndrome (MDS) (OR 1.95, 95 % CI 1.23–3.09) (very low; IV) (Jin et al., 2014), and rheumatoid arthritis (OR 1.20, 95 % CI 1.12–1.28) (very low; III) (Chittrakul et al., 2022). In another study, Wang et al. reported that Pb exposure was associated with an increased risk of ALS (OR 1.72, 95 % CI 1.33–2.23) (very low; IV) (Wang et al., 2017). The pooled analysis further indicated that exposure to PAHs was significantly associated with an increased risk of adult depression (OR 1.33, 95 % CI 1.22–1.45) (very low; IV) (Zhen et al., 2023). Finally, a study by Guo et al. performed a pooled

Outcome	Category	No of cases /total	Risk estimate (95% CI)	Risk estimate (95% CI)	No of studies (T/R/C/P)	I^2 (%)	Egger test P value	AMSTAR	GRADE	Evidence class
Preterm birth	BPA	NA/3565		1.35 (1.04 to 1.67)	7/0/3/4	20.5	0.120	9	very low	IV
Preeclampsia	PFAS	NA/31803		1.17 (1.02 to 1.34)	12/0/7/5	0.0	0.562	9	low	IV
Gestational diabetes	PFAS	NA/12823		1.09 (1.02 to 1.16)	11/0/8/3	48.5	0.535	10	low	IV

Fig. 7. Associations between EDCs exposure and pregnancy-related outcomes, EDCs, endocrine-disrupting chemicals; AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; T, total No. of studies; R, randomized controlled trial; C, cohort studies; P, population-based case-control and/or cross-sectional studies; PFAS, polyfluoroalkyl substance; BPA, bisphenol A; NA, not available.

analysis of cohort studies and revealed that both Cd (OR 1.38, 95 % CI 1.25–1.54) (low; IV) and Pb (OR 1.26, 95 % CI 1.06–1.50) (very low; IV) exposure, as measured in urine or blood, was positively correlated with an increased risk of all-cause mortality (Guo et al., 2022) (Fig. 8).

Our study did not find a significant association between pesticide exposure and CKD (González-Quiroz et al., 2018). Similarly, no significant correlation was reported between Cd or Hg exposure and a reduction in eGFR (Jalili et al., 2021). Furthermore, BPA exposure was not associated with an increased risk of early puberty (Bigambo et al., 2020) or the development of endometriosis (Wen et al., 2019).

3.8. Heterogeneity

Among the 109 health outcomes included, 54 demonstrated significant heterogeneity ($I^2 > 50$ %). Additionally, one meta-analysis did not provide results for the heterogeneity assessment. The heterogeneity observed in this review may be attributed to several factors. First, differences in study design may have contributed to inconsistencies in effect estimates. Second, significant variability in study populations, including differences in age distribution, sex ratio, geographic location, and socioeconomic status, could influence the associations between exposures and outcomes. Third, inconsistencies in the assessment methods of EDCs exposure further limit comparability. As this review is based on published systematic reviews and meta-analyses, it was not feasible to conduct new subgroup or sensitivity analyses. Therefore, findings with substantial heterogeneity were interpreted with caution.

3.9. Assessment of risk of bias

Among the 109 health outcomes included, 17 were found to have a risk of bias ($P < 0.05$). Additionally, 22 meta-analyses did not provide information regarding the risk of bias.

3.10. AMSTAR, GRADE, and evidence classification

The median AMSTAR score for all health outcomes was 8, with a range from 5 to 10. The AMSTAR score of 95 (87 %) meta-analyses was greater than or equal to 7, whereas 14 (13 %) of the meta-analyses had an AMSTAR score of less than 7. Most evidence derived from meta-analyses of cohort studies, population-based case-control studies, and cross-sectional studies was classified as “low” or “very low” quality. This classification is attributed to the observational nature of the studies, as well as factors that led to a downgrade in quality, including significant risk of bias, inconsistency, indirectness, imprecision, and potential publication bias. Based on the evidence, outcomes such as lung cancer (PAHs), cardiovascular disease (CVD) (PAHs), metabolic syndrome (pesticides), obesity (BPA), acute childhood leukemia (pesticides), birth defects (pesticides), childhood brain tumors (pesticides), and obstructive pulmonary diseases (pesticides) were assigned to class II. For the other 101 outcomes, 12 (11 %) were classified as class III, 50 (46 %) as class IV, and 39 (36 %) as non-significant (Supplementary Table G).

Outcome	Category	No of cases /total	Risk estimate (95% CI)	Risk estimate (95% CI)	No of studies (T/R/C/P)	I^2 (%)	Egger test P value	AMSTAR	GRADE	Evidence class
CKD	BPA	320/687		6.94 (3.60 to 13.36)	4/0/2/2	0.0	NA	6	very low	IV
Reduced eGFR	Pb	NA/46184		1.12 (1.03 to 1.22)	10/0/0/10	87.8	0.040	9	very low	IV
Proteinuria	Cd	NA/27897		1.35 (1.13 to 1.61)	7/0/0/7	79.7	0.540	9	very low	IV
Proteinuria	Pb	NA/19535		1.25 (1.04 to 1.49)	4/0/0/4	79.6	0.006	9	very low	IV
Parkinson's disease	Pesticides	NA/3016643		1.41 (1.20 to 1.65)	11/0/11/0	26.2	0.003	8	very low	III
ALS	Pesticides	60272/101756		1.57 (1.25 to 1.98)	12/0/0/12	41.8	0.006	6	very low	III
ALS	Pb	310/2540		1.72 (1.33 to 2.23)	7/0/0/7	2.8	NA	6	very low	IV
Alzheimer's disease	Pesticides	1050/6835		1.34 (1.08 to 1.67)	7/0/3/4	0.0	0.660	8	very low	IV
Adult depression	PAHs	NA/26955		1.33 (1.22 to 1.45)	4/0/0/4	69.0	<0.001	6	very low	IV
Asthma	Pesticides	NA/45435		1.31 (1.17 to 1.48)	5/0/2/3	27.0	NA	8	very low	III
Obstructive pulmonary diseases	Pesticides	NA/101353		1.33 (1.21 to 1.47)	9/0/8/1	68.7	>0.05	7	very low	II
MDS	Pesticides	1942/5359		1.95 (1.23 to 3.09)	11/0/0/11	80.8	0.113	7	very low	IV
Rheumatoid arthritis	Pesticides	NA/52896		1.20 (1.12 to 1.28)	5/0/1/4	0.0	NA	8	very low	III
All-cause mortality	Cd	NA/46195		1.38 (1.25 to 1.54)	14/0/14/0	48.0	0.451	9	low	IV
All-cause mortality	Pb	NA/55209		1.26 (1.06 to 1.50)	6/0/6/0	69.1	0.789	9	very low	IV

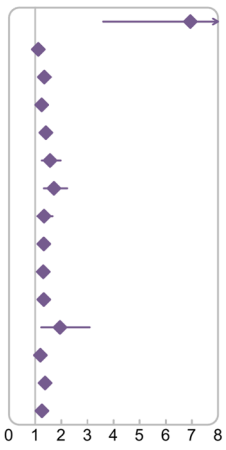


Fig. 8. Associations between EDCs exposure and other outcomes, EDCs, endocrine-disrupting chemicals; AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; T, total No. of studies; R, randomized controlled trial; C, cohort studies; P, population-based case-control and/or cross-sectional studies; ALS, Amyotrophic lateral sclerosis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDS, myelodysplastic syndromes; PAHs, polycyclic aromatic hydrocarbons; BPA, bisphenol A; Cd, cadmium; Pb, lead; NA, not available.

4. Discussion

4.1. Principal findings and possible explanations

EDCs exposure is harmfully associated with multiple health outcomes across various measurements of exposure, including high vs. low, higher vs. lower, highest vs. lowest, and exposed vs. non-exposed. We included five types of EDCs including pesticides, BPA, PAHs, PFAS, and heavy metals and analyzed the results of 109 meta-analyses, covering the associations with cancer, CVD, metabolic disorders, neonatal/infant/child related outcomes, pregnancy-related outcomes, and other systemic diseases.

Suggestive associations were identified between EDCs exposure and a higher risk of cancer were observed for AML, bladder cancer, thyroid cancer, non-Hodgkin lymphoma, prostate cancer, kidney cancer, lung cancer, larynx cancer, breast cancer, and cancer mortality, especially for pesticides and PAHs exposure. The biological mechanisms underlying this correlation remain incompletely understood. However, several potential mechanisms can be proposed. Exposure to pesticides may lead to an increase in reactive oxygen species (ROS), which results in extensive DNA and protein damage (Alavanja et al., 2013). Furthermore, pesticides can bind to the endogenous ligands of androgen and estrogen receptors, aberrantly activating receptor function and leading to changes in the gene expression network (Schug et al., 2011). PAHs cause cancer by activating the aryl hydrocarbon receptor (AhR) signaling pathway. After PAHs bind to AhR, gene transcription is initiated, and the expression of CYP1 enzymes is induced, generating highly reactive metabolites. These metabolites bind to DNA, causing genetic mutations and promoting cancer development (Holme et al., 2023; Nebert et al., 2013). Additionally, PAHs exacerbate cancer progression through non-genotoxic mechanisms, such as disruption of the cell cycle and cell proliferation (Vondráček and Machala, 2021). In addition, EDCs can influence tumor development and progression through mechanisms such as modulation of the tumor microenvironment and epigenetic modifications (Kim et al., 2021; Buoso et al., 2020).

In addition, suggestive associations were noted between EDCs exposure and cardiovascular disease outcomes, including hypertension, CVD, CHD, stroke, and CVD mortality. Animal studies have shown that pesticides exposure may increase blood pressure by overactivating the renin-angiotensin system (La Merrill et al., 2016), while pesticides contribute to cardiac toxicity through changes in Nrf2 gene transcription and increased calcium influx (Dhivya Vadhana et al., 2013). EDCs also promote cardiovascular disease by reducing PON1 activity, damaging blood vessel walls, and inducing inflammation (Bhattacharyya et al., 2008). Cd causes endothelial dysfunction and atherosclerosis through oxidative stress and DNA damage (Ujueta et al., 2021; Bimonte et al., 2021; Messner et al., 2016; Dong et al., 2014). Cd, as a metal hormone, disrupts the endocrine system, leading to changes in vascular structure and function (Fittipaldi et al., 2019). Mercury exposure increases the risk of atherosclerosis by generating free radicals, disrupting cholesterol metabolism, and promoting inflammation (Zhang et al., 2024).

EDCs exposure showed suggestive associations with various metabolic disorders, including metabolic syndrome, T2DM, hyperuricemia, obesity, and osteoporosis. Notably, the associations between pesticide exposure and T2DM, and between BPA exposure and obesity, were supported by moderate-certainty evidence. EDCs influence metabolic diseases through multiple mechanisms. BPA promotes adipogenesis by activating estrogen receptors, which increases the expression of genes related to fat formation, thereby enhancing adipocyte differentiation and fat accumulation (Wang et al., 2013). DDT fosters adipogenesis by increasing the activity of fatty acid synthase, acetyl-CoA carboxylase, and lipid accumulation (Aaseth et al., 2022; Yang et al., 2017). PFAS affects insulin signaling and glucose metabolism by enhancing the transport of glucose transporter 4 (GLUT4) and insulin receptor substrate 1 (IRS1), which facilitates insulin-stimulated glucose uptake (Aaseth et al., 2022). PAHs have been found to increase the risk of obesity and metabolic diseases by affecting peroxisome proliferator-activated receptor gamma (PPAR-γ) and altering lipid metabolism in adipose tissue (Scinicariello and Buser, 2014). In addition to directly interfering with hormonal signaling pathways, EDCs also alter gene expression through epigenetic modifications, thereby impacting metabolic processes (Legler, 2015).

Furthermore, suggestive associations were observed between EDCs exposure and neonatal/infant/child-related outcomes, including acute childhood leukemia, birth defects, childhood brain tumors, neural tube defects, ASD, ADHD, childhood Wilm's tumor, childhood asthma, congenital heart defects, and IDA. Notably, the association between PAHs exposure and adverse neurodevelopmental outcomes in children was supported by moderate-certainty evidence. Infants and children are more susceptible to the influence of EDCs than adults due to differences in physiology, anatomy, pharmacokinetics, diet, and behavior, resulting in higher exposure and more pronounced negative outcomes (Bujalance-Reyes et al., 2022; Di Pietro et al., 2023). Relative to their body surface area, children consume more water, food, and air than adults. Due to the immaturity of the blood-brain barrier, children are more vulnerable to neurological damage. Additionally, infants' skin is more permeable to water, and children spend more time in environments rich in EDC sources, such as building materials, everyday items, and toys. Infants' tendency to mouth objects increases their exposure to EDCs. During development, the maturity of biological systems and organs varies, making the detoxification system less efficient (Di Pietro et al., 2023).

There were also positive associations between EDCs exposure and pregnancy-related outcomes, including preterm birth, preeclampsia, and gestational diabetes. BPA exposure damages the cell membrane of human placental cells, leading to adverse pregnancy outcomes such as preterm birth, and even miscarriage (Benachour and Aris, 2009). BPA also alters trophoblast development, affecting the secretion of human chorionic gonadotropin (hCG) and increasing apoptosis, which in turn inhibits placental aromatase activity, reducing the synthesis of estradiol and progesterone (Puche-Juarez et al., 2023). This hormone deficiency may result in placental insufficiency, increasing the risk of preterm birth and pregnancy failure (Chu et al., 2018). Several prospective cohort studies have highlighted concerns about the contribution of PFAS exposure to the development of GDM and impaired glucose tolerance (Rahman et al., 2019; Liu et al., 2019). However, the exact biological mechanisms are not fully understood, but they may be similar to the mechanisms mentioned above by which PFAS contribute to metabolic diseases.

In addition to the aforementioned associations, exposure to EDCs has been found to have suggestive associations with a wide range of other outcomes, including CKD, reduced eGFR, proteinuria, Parkinson's disease, ALS, Alzheimer's disease, adult depression, asthma, obstructive pulmonary disease, MDS, rheumatoid arthritis, and all-cause mortality. While the underlying mechanisms for these associations are complex and varied, they highlight the extensive health risks associated with EDCs exposure. Given the wide range of affected outcomes, further research is needed to better understand the specific pathways through which these chemicals influence health.

In general, only one meta-analysis showed beneficial association between parental PFAS exposure and ASD in offspring. This is in contrast to the findings of some animal studies. Several studies have shown that exposure to PFAS during pregnancy leads to hyperactivity in the offspring of rats, and fertilized zebrafish exposed to PFAS exhibit hyperactivity (Reardon et al., 2019; Gaballah et al., 2020). Ghassabian et al. reported a positive correlation between PFAS exposure and behavioral disorders in children (Ghassabian et al., 2018). One possible reason for the discrepancy in results is the difference in exposure doses between animals and humans. The exposure concentrations used in animal experiments are typically higher than the usual exposure levels in humans.

4.2. Strengths and weaknesses of the study

This study incorporated three widely recognized evaluation tools including AMSTAR, GRADE, and evidence classification criteria to systematically assess the included studies from three key dimensions: methodological quality, certainty of evidence, and robustness of findings. However, several limitations should be noted. First, there is substantial heterogeneity among the included meta-analyses, which may stem from differences in study design, population characteristics, and exposure assessment methods. Most primary studies relied on indirect exposure indicators such as questionnaires, self-reports, or occupational classifications which are prone to exposure misclassification and may compromise the comparability of results across studies. Second, the current body of evidence is still primarily based on observational studies, limiting the ability to infer causality. Third, most original studies did not adequately account for the combined or synergistic effects of multiple EDCs, even though real-world exposures typically involve complex mixtures. This may have led to underestimation or overestimation of certain associations. The observed inconsistencies between GRADE ratings and evidence classification levels also highlight the limitations of subjective appraisal tools compared to algorithm-based classification, underscoring the need for cautious interpretation of the findings.

5. Conclusions

This umbrella review suggests that exposure to EDCs is associated with a wide range of adverse health outcomes. However, as the included evidence is primarily derived from observational studies, causality cannot be inferred. Existing research also faces methodological limitations, including heterogeneity in exposure assessment and population characteristics. Given the consistent associations observed across various health outcomes, it is recommended that public health authorities and policymakers, while fully acknowledging the limitations of the current evidence, adopt precautionary measures. These may include refining regulatory standards, promoting the development of safer alternatives, enhancing public health education, and supporting high-quality prospective research to further strengthen the evidence base. In light of the widespread, persistent, and often involuntary exposure to EDCs, early intervention based on potentially associated evidence represents a feasible and meaningful public health strategy.

CRediT authorship contribution statement

Chao Li: Investigation, Data curation. **Pan Song:** Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Junhao Chen:** Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Weigang Yan:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Zhien Zhou:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Yi Zhou:** Investigation, Data curation. **Lei Zhang:** Investigation, Data curation. **Hengjia Liu:** Investigation, Data curation.

Funding

This study is supported by National Key R&D Program of China (Grant number: 2023YFC3605703) and the National High Level Hospital Clinical Research Funding (Grant number: 2022-PUMCH-A-063 and 2022-PUMCH-B-009).

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.

Acknowledgements

Thanks to all authors of original studies that were included in this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118574.

Data availability

Data will be made available on request.

References

Aaseth, J., Javorac, D., Djordjevic, A.B., Bulat, Z., Skalny, A.V., Zaitseva, I.P., et al., 2022. The role of persistent organic pollutants in obesity: a review of laboratory and epidemiological studies. Toxics 10 (2).
Alavanja, M.C., Ross, M.K., Bonner, M.R., 2013. Increased cancer burden among pesticide applicators and others due to pesticide exposure. CA a cancer journal clinicians 63 (2), 120–142.
Alicandro, G., Rota, M., Boffetta, P., La Vecchia, C., 2016. Occupational exposure to polycyclic aromatic hydrocarbons and lymphatic and hematopoietic neoplasms: a systematic review and meta-analysis of cohort studies. Arch. Toxicol. 90 (11), 2643–2656.
Atlaw, D., Tekalegn, Y., Sahiledengle, B., Seyoum, K., Solomon, D., Gezahegn, H., et al., 2021. Magnitude and determinants of neural tube defect in Africa: a systematic review and meta-analysis. BMC Pregnancy Childbirth 21 (1), 426.
Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M.R., Sadeghi, M., 2021. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Front. Pharmacol. 12, 643972.
Bao, Q.J., Zhao, K., Guo, Y., Wu, X.T., Yang, J.C., Yang, M.F., 2022. Environmental toxic metal contaminants and risk of stroke: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 29 (22), 32545–32565.
Barbosa Jr., F., Rocha, B.A., Souza, M.C.O., Bocato, M.Z., Azevedo, L.F., Adeyemi, J.A., et al., 2023. Polycyclic aromatic hydrocarbons (PAHs): updated aspects of their determination, kinetics in the human body, and toxicity. J. Toxicol. Environ. Health Part B Crit. Rev. 26 (1), 28–65.
Benachour, N., Aris, A., 2009. Toxic effects of low doses of Bisphenol-A on human placental cells. Toxicol. Appl. Pharmacol. 241 (3), 322–328.
Bhattacharyya, T., Nicholls, S.J., Topol, E.J., Zhang, R., Yang, X., Schmitt, D., et al., 2008. Relationship of paraoxonase 1 (PON1) gene polymorphisms and functional activity with systemic oxidative stress and cardiovascular risk. Jama 299 (11), 1265–1276.
Bigambo, F.M., Sun, H., Yan, W., Wu, D., Xia, Y., Wang, X., et al., 2020. Association between phenols exposure and earlier puberty in children: a systematic review and meta-analysis. Environ. Res. 190, 110056.
Bimonte, V.M., Besharat, Z.M., Antonioni, A., Cella, V., Lenzi, A., Ferretti, E., et al., 2021. The endocrine disruptor cadmium: a new player in the pathophysiology of metabolic diseases. J. Endocrinol. Investig. 44 (7), 1363–1377.
Bujalance-Reyes, F., Molina-López, A.M., Ayala-Soldado, N., Lora-Benitez, A., Mora-Medina, R., Moyano-Salvago, R., 2022. Analysis of indirect biomarkers of effect after exposure to low doses of bisphenol A in a study of successive generations of mice. Anim. Open Access J. MDPI 12 (3).
Buoso, E., Masi, M., Racchi, M., Corsini, E., 2020. Endocrine-disrupting chemicals' (EDCs) effects on tumour microenvironment and cancer progression: emerging contribution of RACK1. Int. J. Mol. Sci. 21 (23).
Chambers-Richards, T., Su, Y., Chireh, B., D'Arcy, C., 2023. Exposure to toxic occupations and their association with Parkinson's disease: a systematic review with meta-analysis. Rev. Environ. Health 38 (1), 65–83.
Chittrakul, J., Sapbamrer, R., Sirikul, W., 2021. Insecticide exposure and risk of asthmatic symptoms: a systematic review and meta-analysis. Toxics 9 (9).
Chittrakul, J., Sapbamrer, R., Sirikul, W., 2022. Pesticide exposure and risk of rheumatoid arthritis: a systematic review and meta-analysis. Toxics 10 (5).
Chowdhury, R., Ramond, A., O'Keeffe, L.M., Shahzad, S., Kunutsor, S.K., Muka, T., et al., 2018. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. BMJ (Clin. Res. Ed.) 362, k3310.
Chu, P.W., Yang, Z.J., Huang, H.H., Chang, A.A., Cheng, Y.C., Wu, G.J., et al., 2018. Low-dose bisphenol A activates the ERK signaling pathway and attenuates steroidogenic gene expression in human placental cells. Biol. Reprod. 98 (2), 250–258.
Costa, H.E., Cairrao, E., 2024. Effect of bisphenol A on the neurological system: a review update. Arch. Toxicol. 98 (1), 1–73.
Deji, Z., Liu, P., Wang, X., Zhang, X., Luo, Y., Huang, Z., 2021. Association between maternal exposure to perfluoroalkyl and polyfluoroalkyl substances and risks of adverse pregnancy outcomes: A systematic review and meta-analysis. Sci. Total Environ. 783, 146984.
Demelash Enyew, H., Bogale, B.G., Hailu, A.B., Mereta, S.T., 2023. Environmental exposures and adverse pregnancy outcomes in Ethiopia: a systematic review and meta-analysis. PloS One 18 (7), e0288240.

Dhivya Vadhana, M.S., Siva Arumugam, S., Carloni, M., Nasuti, C., Gabbianelli, R., 2013. Early life permethrin treatment leads to long-term cardiotoxicity. Chemosphere 93 (6), 1029–1034.
Di Pietro, G., Forcucci, F., Chiarelli, F., 2023. Endocrine disruptor chemicals and children's health. Int. J. Mol. Sci. 24 (3).
Dong, F., Guo, F., Li, L., Guo, L., Hou, Y., Hao, E., et al., 2014. Cadmium induces vascular permeability via activation of the p38 MAPK pathway. Biochem. Biophys. Res. Commun. 450 (1), 447–452.
Evich, M.G., Davis, M.J.B., McCord, J.P., Acrey, B., Awkerman, J.A., Knappe, D.R.U., et al., 2022. Per- and polyfluoroalkyl substances in the environment. Science (New York NY) 375 (6580), eabg9065.
Farkhondeh, T., Mansouri, B., Binkowski, L.J., Błaszczyk, M., Pirsaheb, M., Azadi, N.A., et al., 2022. Blood lead concentrations in children with iron deficiency anemia: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 29 (3), 3199–3212.
Feulefack, J., Khan, A., Forastiere, F., Sergi, C.M., 2021. Parental pesticide exposure and childhood brain cancer: a systematic review and meta-analysis confirming the IARC/WHO monographs on some organophosphate insecticides and herbicides. Children 8 (12).
Fittipaldi, S., Bimonte, V.M., Soricelli, A., Aversa, A., Lenzi, A., Greco, E.A., et al., 2019. Cadmium exposure alters steroid receptors and proinflammatory cytokine levels in endothelial cells in vitro: a potential mechanism of endocrine disruptor atherogenic effect. J. Endocrinol. Investig. 42 (6), 727–739.
Foucault, A., Vallet, N., Ravalet, N., Picou, F., Bene, M.C., Gyan, E., et al., 2021. Occupational pesticide exposure increases risk of acute myeloid leukemia: a meta-analysis of case-control studies including 3,955 cases and 9,948 controls. Sci. Rep. 11 (1), 2007.
Fu, X., Xu, J., Zhang, R., Yu, J., 2020. The association between environmental endocrine disruptors and cardiovascular diseases: a systematic review and meta-analysis. Environ. Res. 187, 109464.
Gaballah, S., Swank, A., Sobus, J.R., Howey, X.M., Schmid, J., Catron, T., et al., 2020. Evaluation of developmental toxicity, developmental neurotoxicity, and tissue dose in zebrafish exposed to GenX and other PFAS. Environ. Health Perspect. 128 (4), 47005.
Gamboa-Loira, B., López-Carrillo, L., Mar-Sánchez, Y., Stern, D., Cebrián, M.E., 2022. Epidemiologic evidence of exposure to polycyclic aromatic hydrocarbons and breast cancer: a systematic review and meta-analysis. Chemosphere 290, 133237.
Ghassabian, A., Bell, E.M., Ma, W.L., Sundaram, R., Kannan, K., Buck Louis, G.M., et al., 2018. Concentrations of perfluoroalkyl substances and bisphenol A in newborn dried blood spots and the association with child behavior. Environ. Pollut. (Barking Essex 1987) 243 (Pt B), 1629–1636.
González-Quiroz, M., Pearce, N., Caplin, B., Nitsch, D., 2018. What do epidemiological studies tell us about chronic kidney disease of undetermined cause in Meso-America? A systematic review and meta-analysis. Clin. Kidney J. 11 (4), 496–506.
Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., et al., 2015. EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 36 (6), E1–e150.
Gu, T., Cao, G., Luo, M., Zhang, N., Xue, T., Hou, R., et al., 2022. A systematic review and meta-analysis of the hyperuricemia risk from certain metals. Clin. Rheumatol. 41 (12), 3641–3660.
Gui, S.Y., Qiao, J.C., Xu, K.X., Li, Z.L., Chen, Y.N., Wu, K.J., et al., 2023. Association between per- and polyfluoroalkyl substances exposure and risk of diabetes: a systematic review and meta-analysis. J. Expo. Sci. Environ. Epidemiol. 33 (1), 40–55.
Guo, Y., Lv, Y., Liu, X., Wang, G., 2023. Association between heavy metal mercury in body fluids and tissues and diabetes mellitus: a systematic review and meta-analysis. Ann. Transl. Med. 11 (2), 114.
Guo, X., Su, W., Li, N., Song, Q., Wang, H., Liang, Q., et al., 2022. Association of urinary or blood heavy metals and mortality from all causes, cardiovascular disease, and cancer in the general population: a systematic review and meta-analysis of cohort studies. Environ. Sci. Pollut. Res. Int. 29 (45), 67483–67503.
Guyatt, G., Oxman, A.D., Akl, E.A., Kunz, R., Vist, G., Brozek, J., et al., 2011. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J. Clin. Epidemiol. 64 (4), 383–394.
Han, M.A., Kim, J.H., Song, H.S., 2019. Persistent organic pollutants, pesticides, and the risk of thyroid cancer: systematic review and meta-analysis. Eur. J. Cancer Prevention Off. J. Eur. Cancer Prevention Organisation (ECP) 28 (4), 344–349.
Hernández-Mariano, J., Baltazar-Reyes, M.C., Salazar-Martínez, E., Cupul-Uicab, L.A., 2022. Exposure to the pesticide DDT and risk of diabetes and hypertension: systematic review and meta-analysis of prospective studies. Int. J. Hyg. Environ. Health 239, 113865.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Hirke, A., Varghese, B., Varade, S., Adela, R., 2023. Exposure to endocrine-disrupting chemicals and risk of gestational hypertension and preeclampsia: s systematic review and meta-analysis. Environ. Pollut. 317, 120828.
Holme, J.A., Vondráček, J., Machala, M., Lagadic-Gossmann, D., Vogel, C.F.A., Le Ferrec, E., et al., 2023. Lung cancer associated with combustion particles and fine particulate matter (PM(2.5)) - The roles of polycyclic aromatic hydrocarbons (PAHs) and the aryl hydrocarbon receptor (AhR). Biochem. Pharmacol. 216, 115801.
Huang, Y., Chen, Z., Chen, B., Li, J., Yuan, X., Li, J., et al., 2023. Dietary sugar consumption and health: umbrella review. BMJ 381, e071609.
Hwang, S., Lim, J.E., Choi, Y., Jee, S.H., 2018. Bisphenol A exposure and type 2 diabetes mellitus risk: a meta-analysis. BMC Endocr. Disord. 18 (1), 81.
Jalili, C., Kazemi, M., Cheng, H., Mohammadi, H., Babaei, A., Taheri, E., et al., 2021. Associations between exposure to heavy metals and the risk of chronic kidney disease: a systematic review and meta-analysis. Crit. Rev. Toxicol. 51 (2), 165–182.
Jalili, C., Kazemi, M., Taheri, E., Mohammadi, H., Boozari, B., Hadi, A., et al., 2020. Exposure to heavy metals and the risk of osteopenia or osteoporosis: a systematic review and meta-analysis. Osteoporos. Int. a J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 31 (9), 1671–1682.
Jin, J., Yu, M., Hu, C., Ye, L., Xie, L., Jin, J., et al., 2014. Pesticide exposure as a risk factor for myelodysplastic syndromes: a meta-analysis based on 1,942 cases and 5,359 controls. PloS One 9 (10), e110850.
Kahn, L.G., Philippat, C., Nakayama, S.F., Slama, R., Trasande, L., 2020. Endocrine-disrupting chemicals: implications for human health. Lancet Diabetes Endocrinol. 8 (8), 703–718.
Karalexi, M.A., Tagkas, C.F., Markozannes, G., Tseretopoulou, X., Hernández, A.F., Schüz, J., et al., 2021. Exposure to pesticides and childhood leukemia risk: a systematic review and meta-analysis. Environ. Pollut. 285, 117376.
Kaur, R., Choudhary, D., Bali, S., Bandral, S.S., Singh, V., Ahmad, M.A., et al., 2024. Pesticides: an alarming detrimental to health and environment. Sci. Total Environ. 915, 170113.
Khan, A., Feulefack, J., Sergi, C.M., 2022. Exposure to pesticides and pediatric Wilms' tumor. A meta-analysis on pre-conception and pregnancy parental exposure with an IARC/WHO commentary. Hum. Exp. Toxicol. 41, 9603271221136211.
Khosravipour, M., Khosravipour, H., 2020. The association between urinary metabolites of polycyclic aromatic hydrocarbons and diabetes: a systematic review and meta-analysis study. Chemosphere 247, 125680.
Kim, S., Thapar, I., Brooks, B.W., 2021. Epigenetic changes by per- and polyfluoroalkyl substances (PFAS). Environ. Pollut. 279, 116929.
La Merrill, M.A., Sethi, S., Benard, L., Moshier, E., Haraldsson, B., Buettner, C., 2016. Perinatal DDT exposure induces hypertension and cardiac hypertrophy in adult mice. Environ. Health Perspect. 124 (11), 1722–1727.
Lamat, H., Sauvant-Rochat, M.P., Tauveron, I., Bagheri, R., Ugbolue, U.C., Maqdasi, S., et al., 2022. Metabolic syndrome and pesticides: a systematic review and meta-analysis. Environ. Pollut. 305, 119288.
Lauretta, R., Sansone, A., Sansone, M., Romanelli, F., Appetecchia, M., 2019. Endocrine disrupting chemicals: effects on endocrine glands. Front. Endocrinol. 10, 178.
Legler, J., 2015. J. The role of epigenetics in the latent effects of early life exposure to obesogenic endocrine disrupting chemicals. Endocrinology 156 (10), 3466–3472.
Lewis-Mikhael, A.M., Bueno-Cavanillas, A., Ofir, Giron T., Olmedo-Requena, R., Delgado-Rodríguez, M., Jiménez-Moleón, J.J., 2016. Occupational exposure to pesticides and prostate cancer: a systematic review and meta-analysis. Occup. Environ. Med. 73 (2), 134–144.
Li, S., Wang, Q., Luo, W., Jia, S., Liu, D., Ma, W., et al., 2022. Relationship between maternal heavy metal exposure and congenital heart defects: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 29 (37), 55348–55366.
Liang, Z., Wang, X., Xie, B., Zhu, Y., Wu, J., Li, S., et al., 2016. Pesticide exposure and risk of bladder cancer: a meta-analysis. Oncotarget 7 (41), 66959–66969.
Lin, S., Li, J., Yan, X., Pei, L., Shang, X., 2023. Maternal pesticide exposure and risk of preterm birth: a systematic review and meta-analysis. Environ. Int. 178, 108043.
Liu, G., Cai, W., Liu, H., Jiang, H., Bi, Y., Wang, H., 2021. The association of bisphenol A and phthalates with risk of breast cancer: a meta-analysis. Int. J. Environ. Res. Public Health 18 (5).
Liu, C., Liu, Q., Song, S., Li, W., Feng, Y., Cong, X., et al., 2023. The association between internal polycyclic aromatic hydrocarbons exposure and risk of Obesity-a systematic review with meta-analysis. Chemosphere 329, 138669.
Liu, H., Wang, J., 2022. The association between bisphenol a exposure and attention deficit hyperactivity disorder in children: a meta-analysis of observational studies. Rev. Environ. Health.
Liu, X., Zhang, L., Chen, L., Li, J., Wang, Y., Wang, J., et al., 2019. Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women. Environ. Int. 127, 85–93.
Lu, W., Zheng, F., Li, Z., Zhou, R., Deng, L., Xiao, W., et al., 2022. Association between environmental and socioeconomic risk factors and hepatocellular carcinoma: a meta-analysis. Front. Public Health 10, 741490.
Messner, B., Türkcan, A., Ploner, C., Laufer, G., Bernhard, D., 2016. Cadmium overkill: autophagy, apoptosis and necrosis signalling in endothelial cells exposed to cadmium. Cell. Mol. life Sci. CMLS 73 (8), 1699–1713.
Metcalfe, C.D., Bayen, S., Desrosiers, M., Muñoz, G., Sauvé, S., Yargeau, V., 2022. An introduction to the sources, fate, occurrence and effects of endocrine disrupting chemicals released into the environment. Environ. Res. 207, 112658.
Mirzababaei, A., Daneshzad, E., Moradi, S., Abaj, F., Mehranfar, S., Asbaghi, O., et al., 2022. The association between urinary metabolites of polycyclic aromatic hydrocarbons (PAHs) and cardiovascular diseases and blood pressure: a systematic review and meta-analysis of observational studies. Environ. Sci. Pollut. Res. Int. 29 (2), 1712–1728.
Moon, S., Yu, S.H., Lee, C.B., Park, Y.J., Yoo, H.J., Kim, D.S., 2021. Effects of bisphenol A on cardiovascular disease: An epidemiological study using National Health and Nutrition Examination Survey 2003-2016 and meta-analysis. Sci. Total Environ. 763, 142941.
Moreno-Gómez-Toledano, R., Arenas, M.I., Vélez-Vélez, E., Coll, E., Quiroga, B., Bover, J., et al., 2021. Bisphenol a exposure and kidney diseases: systematic review, meta-analysis, and NHANES 03-16 study. Biomolecules 11 (7).
Namat, A., Xia, W., Xiong, C., Xu, S., Wu, C., Wang, A., et al., 2021. Association of BPA exposure during pregnancy with risk of preterm birth and changes in gestational age: a meta-analysis and systematic review. Ecotoxicol. Environ. Saf. 220, 112400.

Nebert, D.W., Shi, Z., Gálvez-Peralta, M., Uno, S., Dragin, N., 2013. Oral benzo[a]pyrene: understanding pharmacokinetics, detoxication, and consequences–Cyp1 knockout mouse lines as a paradigm. Mol. Pharmacol. 84 (3), 304–313.
Paget-Bailly, S., Cyr, D., Luce, D., 2012. Occupational exposures and cancer of the larynx-systematic review and meta-analysis. J. Occup. Environ. Med. 54 (1), 71–84.
Papatheodorou, S., 2019. Umbrella reviews: what they are and why we need them. Eur. J. Epidemiol. 34 (6), 543–546.
Park, J.H., Cha, E.S., Ko, Y., Hwang, M.S., Hong, J.H., Lee, W.J., 2014. Exposure to dichlorodiphenyltrichloroethane and the risk of breast cancer: a systematic review and meta-analysis. Osong Public Health Res. Perspect. 5 (2), 77–84.
Pourhassan, B., Meysamie, A., Alizadeh, S., Habibian, A., Beigzadeh, Z., 2019. Risk of obstructive pulmonary diseases and occupational exposure to pesticides: a systematic review and meta-analysis. Public Health 174, 31–41.
Puche-Juarez, M., Toledano, J.M., Moreno-Fernandez, J., Gálvez-Ontiveros, Y., Rivas, A., Diaz-Castro, J., et al., 2023. The role of endocrine disrupting chemicals in gestation and pregnancy outcomes. Nutrients 15 (21).
Rahman, M.L., Zhang, C., Smarr, M.M., Lee, S., Honda, M., Kannan, K., et al., 2019. Persistent organic pollutants and gestational diabetes: a multi-center prospective cohort study of healthy US women. Environ. Int. 124, 249–258.
Reardon, A.J.F., Karathra, J., Ribbenstedt, A., Benskin, J.P., MacDonald, A.M., Kinniburgh, D.W., et al., 2019. Neurodevelopmental and metabolomic responses from prenatal coexposure to perfluorooctanesulfonate (PFOS) and methylmercury (MeHg) in sprague-dawley rats. Chem. Res. Toxicol. 32 (8), 1656–1669.
Rehman, K., Fatima, F., Waheed, I., Akash, M.S.H., 2018. Prevalence of exposure of heavy metals and their impact on health consequences. J. Cell. Biochem. 119 (1), 157–184.
Rota, M., Bosetti, C., Boccia, S., Boffetta, P., La Vecchia, C., 2014. Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. Arch. Toxicol. 88 (8), 1479–1490.
Schug, T.T., Janesick, A., Blumberg, B., Heindel, J.J., 2011. Endocrine disrupting chemicals and disease susceptibility. J. Steroid Biochem. Mol. Biol. 127 (3-5), 204–215.
Scinicariello, F., Buser, M.C., 2014. Urinary polycyclic aromatic hydrocarbons and childhood obesity: NHANES (2001-2006). Environ. Health Perspect. 122 (3), 299–303.
Shea, B.J., Grimshaw, J.M., Wells, G.A., Boers, M., Andersson, N., Hamel, C., et al., 2007. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med. Res. Methodol. 7, 10.
Singh, A., Kamal, R., Ahamed, I., Wagh, M., Bihari, V., Sathian, B., et al., 2018. PAH exposure-associated lung cancer: an updated meta-analysis. Occup. Med. 68 (4), 255–261.
Stanganelli, I., De Felici, M.B., Mandel, V.D., Caini, S., Raimondi, S., Corso, F., et al., 2020. The association between pesticide use and cutaneous melanoma: a systematic review and meta-analysis. J. Eur. Acad. Dermatol. Venereol. JEADV 34 (4), 691–708.
Taheri, E., Riahi, R., Rafiei, N., Fatehizadeh, A., Iqbal, H.M.N., Hosseini, S.M., 2021. Bisphenol A exposure and abnormal glucose tolerance during pregnancy: systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 28 (44), 62105–62115.
Theodoratou, E., Tzoulaki, I., Zgaga, L., Ioannidis, J.P., 2014. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ (Clin. Res. Ed.) 348, g2035.
Thompson, L.A., Darwish, W.S., 2019. Environmental chemical contaminants in food: review of a global problem. J. Toxicol. 2019, 2345283.
Ujueta, F., Navas-Acien, A., Mann, K.K., Prashad, R., Lamas, G.A., 2021. Low-level metal contamination and chelation in cardiovascular disease-a ripe area for toxicology research. Toxicol. Sci. Off. J. Soc. Toxicol. 181 (2), 135–147.
Vondráček, J., Machala, M., 2021. The role of metabolism in toxicity of polycyclic aromatic hydrocarbons and their non-genotoxic modes of action. Curr. Drug Metab. 22 (8), 584–595.
Wallace, T.C., Bailey, R.L., Blumberg, J.B., Burton-Freeman, B., Chen, C.O., Crowe-White, K.M., et al., 2020. Fruits, vegetables, and health: a comprehensive narrative, umbrella review of the science and recommendations for enhanced public policy to improve intake. Crit. Rev. Food Sci. Nutr. 60 (13), 2174–2211.
Wang, W., Hong, X., Zhao, F., Wu, J., Wang, B., 2023. The effects of perfluoroalkyl and polyfluoroalkyl substances on female fertility: a systematic review and meta-analysis. Environ. Res. 216 (Pt 3), 114718.
Wang, M.D., Little, J., Gomes, J., Cashman, N.R., Krewski, D., 2017. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology 61, 101–130.
Wang, Z., Ng, K., Warner, R.D., Stockmann, R., Fang, Z., 2022a. Reduction strategies for polycyclic aromatic hydrocarbons in processed foods. Compr. Rev. Food Sci. Food Saf. 21 (2), 1598–1626.
Wang, J., Sun, B., Hou, M., Pan, X., Li, X., 2013. The environmental obesogen bisphenol A promotes adipogenesis by increasing the amount of 11β-hydroxysteroid dehydrogenase type 1 in the adipose tissue of children. Int. J. Obes. (2005) 37 (7), 999–1005.
Wang, J., Yin, J., Hong, X., Liu, R., 2022b. Exposure to heavy metals and allergic outcomes in children: a systematic review and meta-analysis. Biol. Trace Elem. Res. 200 (11), 4615–4631.
Wen, X., Xiong, Y., Qu, X., Jin, L., Zhou, C., Zhang, M., et al., 2019. The risk of endometriosis after exposure to endocrine-disrupting chemicals: a meta-analysis of 30 epidemiology studies. Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol. 35 (8), 645–650.
Wu, W., Li, M., Liu, A., Wu, C., Li, D., Deng, Q., et al., 2020. Bisphenol A and the risk of obesity a systematic review with meta-analysis of the epidemiological evidence. DoseResponse. a Publ. Int. Hormesis Soc. 18 (2), 1559325820916949.
Wu, M., Wang, S., Weng, Q., Chen, H., Shen, J., Li, Z., et al., 2021. Prenatal and postnatal exposure to Bisphenol A and Asthma: a systemic review and meta-analysis. J. Thorac. Dis. 13 (3), 1684–1696.
Xie, B., Hu, Y., Liang, Z., Liu, B., Zheng, X., Xie, L., 2016. Association between pesticide exposure and risk of kidney cancer: a meta-analysis. OncoTargets Ther. 9, 3893–3900.
Xu, P., Liu, A., Li, F., Tinkov, A.A., Liu, L., Zhou, J.C., 2021. Associations between metabolic syndrome and four heavy metals: a systematic review and meta-analysis. Environ. Pollut. (Barking Essex 1987) 273, 116480.
Xu, Y., Yang, X., Chen, D., Xu, Y., Lan, L., Zhao, S., et al., 2023. Maternal exposure to pesticides and autism or attention-deficit/hyperactivity disorders in offspring: a meta-analysis. Chemosphere 313, 137459.
Yan, D., Jiao, Y., Yan, H., Liu, T., Yan, H., Yuan, J., 2022. Endocrine-disrupting chemicals and the risk of gestational diabetes mellitus: a systematic review and meta-analysis. Environmental health a global access science source 21 (1), 53.
Yan, D., Zhang, Y., Liu, L., Yan, H., 2016. Pesticide exposure and risk of Alzheimer's disease: a systematic review and meta-analysis. Sci. Rep. 6, 32222.
Yang, C., Kong, A.P.S., Cai, Z., Chung, A.C.K., 2017. Persistent organic pollutants as risk factors for obesity and diabetes. Curr. Diabetes Rep. 17 (12), 132.
Yang, L., Shang, L., Wang, S., Yang, W., Huang, L., Qi, C., et al., 2020. The association between prenatal exposure to polycyclic aromatic hydrocarbons and birth weight: a meta-analysis. PloS One 15 (8), e0236708.
Yao, H., Fu, Y., Weng, X., Zeng, Z., Tan, Y., Wu, X., et al., 2023. The association between prenatal per- and polyfluoroalkyl substances exposure and neurobehavioral problems in offspring: a meta-analysis. Int. J. Environ. Res. Public Health 20 (3).
Yilmaz, B., Terekeci, H., Sandal, S., Kelestimur, F., 2020. Endocrine disrupting chemicals: exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. Rev. Endocr. Metab. Disord. 21 (1), 127–147.
Yu, Y., Quan, X., Wang, H., Zhang, B., Hou, Y., Su, C., 2023. Assessing the health risk of hyperuricemia in participants with persistent organic pollutants exposure - a systematic review and meta-analysis. Ecotoxicol. Environ. Saf. 251, 114525.
Zhang, L., Rana, I., Shaffer, R.M., Taioli, E., Sheppard, L., 2019. Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: a meta-analysis and supporting evidence. Mutat. Res. Rev. Mutat. Res. 781, 186–206.
Zhang, M., Wang, C., Zhang, X., Song, H., Li, Y., 2022. Association between exposure to air pollutants and attention-deficit hyperactivity disorder (ADHD) in children: a systematic review and meta-analysis. Int. J. Environ. Health Res. 32 (1), 207–219.
Zhang, A., Wei, P., Ding, L., Zhang, H., Jiang, Z., Mi, L., et al., 2024. Associations of serum lead, cadmium, and mercury concentrations with all-cause and cause-specific mortality among individuals with cardiometabolic multimorbidity. Ecotoxicol. Environ. Saf. 280, 116556.
Zhen, H., Zhang, F., Cheng, H., Hu, F., Jia, Y., Hou, Y., et al., 2023. Association of polycyclic aromatic hydrocarbons exposure with child neurodevelopment and adult emotional disorders: a meta-analysis study. Ecotoxicol. Environ. Saf. 255, 114770.
Zoeller, R.T., Brown, T.R., Doan, L.L., Gore, A.C., Skakkebaek, N.E., Soto, A.M., et al., 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology 153 (9), 4097–4110.