Review Article

The association between environmental endocrine-disrupting chemicals and allergic disorders in children: A comprehensive systematic review and meta-analysis

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Background: Endocrine-disrupting chemicals (EDCs), which can interfere with endocrine hormones even before the prenatal period, can disrupt the development and function of the immune system and ultimately increase the susceptibility to allergies later in life. **Materials and Methods:** We performed a meta-analysis of studies examining the impact of environmental EDCs on allergic disorders. We searched PubMed, EMBASE, Medline, Web of Science, and Scopus up to February 2025 for relevant observational human studies. Allergies studied included allergic rhinitis, asthma, wheezing, atopic dermatitis, chicken pox, eczema, food allergy, hay fever, nonatopic asthma, otitis media, rhinoconjunctivitis, and wheeze. **Results:** In the first stage, 2340 studies were included in our review, and finally, we identified 23 studies, including 12736 participants. The pooled results were calculated by the random-effects model. We observed a statistically significant association between EDCs and risk of allergies (pooled RR = 1.07; 95% confidence interval [CI] = 1.04, 1.10; I2 = 42.80%; $P < 0.001$) for overall population. The findings of meta-analysis showed also a positive significant association between exposure to environmental EDCs and risk of allergies in females (pooled RR = 1.12; 95% CI = 1.06, 1.20; I2 = 28.20%; $P = 0.021$) and males (pooled RR = 1.14; 95% CI = 1.09, 1.19; I2 = 20.40%; $P = 0.061$). **Conclusion:** While most allergies showed a clear link with environmental pollution, the limited studies on specific allergies highlight the need for further research to enhance precision. Deeper investigations into underlying mechanisms and clinical implications are crucial for comprehensively understanding this association.

Key words: Allergic disorders, children and adolescents, endocrine disruption, meta-analysis, systematic review

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INTRODUCTION

Allergic diseases in children have increased significantly in recent decades and can affect more than 30% of children.[1] Allergens that cause pathological allergies can be found in the form of food allergy, asthma, or even contact dermatitis.[2-4] Environmental pollutants around us, such as bisphenol A (BPA), phthalates, triclosan–parabens, and so on, can have devastating effects on various body systems, including the endocrine system.[5-7] Concerns over this issue increase when more of the destructive effects of these pollutants on children are seen.[8] Over the past few decades, more than 100,000 new chemicals have been introduced as common consumer products in our environment. Among these chemicals, endocrine-disrupting chemicals (EDCs) are particularly significant due to their toxicity as demonstrated in animal studies and human research. EDCs are found throughout our air, water, and soil.[9] Phthalates are widely used as stabilizers and plasticizers in various products,

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including toys, cosmetics, personal care items, medical equipment, food packaging, and building materials. They are categorized into two groups: high-molecular-weight phthalates, such as di (2-ethylhexyl) phthalate (DEHP) and di-isononyl phthalate, which are commonly found in flooring, roofing, toys, packaging materials, and clothing, and low-molecular-weight phthalates, such as diethyl phthalate and di-n-butyl phthalate, which are typically used in adhesives, detergents, cosmetics, tablet coatings, capsules, and personal care products.[10-12] BPA is an ingredient found in polycarbonate plastics and epoxy resins, which are used in products such as food and beverage containers and thermal paper receipts. Children may be exposed to BPA through oral, dermal, and respiratory pathways.[13,14] Triclosan and various parabens, including methyl, propyl, ethyl, and butyl parabens, are found in a wide range of personal care and other products.[15] Analysis of National Health and Nutrition Examination Survey (NHANES) data shows a positive link between urinary triclosan concentrations and allergic sensitization diagnoses in children aged 6–18 years, as well as an increase in asthma exacerbations among those with asthma aged 6 years and older.[16-19]

So far, the association of EDCs with childhood allergic disease remains to be determined. To our knowledge, this study has yet to evaluate it systematically. Therefore, this systematic review and meta-analysis investigated the association between EDCs and allergic diseases in children. The question addressed in this review is: "What is the association between EDCs and allergic diseases in children?" This question is raised due to the significant rise in allergic diseases among children, potentially linked to various environmental pollutants, including EDCs. The need to address this question arises from the rising concerns over the impact of these pollutants, such as phthalates, BPA, triclosan, and parabens, on children's health, as well as the lack of systematic studies evaluating this association in the past.

METHODS

This systematic review and meta-analysis examines the link between high intake of EDCs during pregnancy or infancy and the development of allergic disorders in children up to 18 years of age. The study follows PRISMA and MOOSE guidelines to ensure methodological rigor and transparency.[20,21]

PECO components of the study

- Population: Children from birth to 18 years of age
- Exposure: High intake of EDCs during pregnancy or infancy
- Comparison: Low EDC intake or no exposure to EDCs
- Outcomes: Allergic disorders, including allergic rhinitis, asthma, wheezing, atopic dermatitis, chicken pox, eczema, food allergy, hay fever, nonatopic asthma, otitis media, rhinoconjunctivitis, and wheeze.

Measurement of outcomes

- Parental reports of symptoms, physician diagnosis, or direct diagnosis by a physician
- Sensitization: Positive skin prick test (SPT) or elevated specific immunoglobulin E (≥0.35 kU/L) to any food or inhalant allergen.

Literature search and selection criteria

PubMed, EMBASE, Medline, Web of Science, and Scopus were searched for records that reported the effects of environmental EDCs on allergic disorders. The search strategy is detailed in Table 1. The most recent search was conducted in February 2025. Two independent reviewers initially examined the records, removed duplicates, and screened the titles and abstracts for relevance, categorizing them as either excluded or needing further assessment. Afterward, we reviewed the full-text articles for inclusion. Additionally, we manually examined the bibliographies of the retrieved articles and previous reviews to identify any additional eligible studies.

Inclusion criteria

- Human studies without geographical restrictions
- Population: Children aged 0–18 years
- Exposure: High intake of EDCs during pregnancy or infancy
- Comparison: Low or no EDC intake
- Outcome: Allergic disorders or sensitization (as defined above)
- Study design: Observational studies (cohort, cross-sectional, and case–control).

Exclusion criteria

- Animal studies
- Non-English language articles
- Studies on specific diseases (e.g., cancer and immunodeficiency).

Quality assessment

The Newcastle–Ottawa Scale for cohort, case–control, and cross-sectional studies[22] was used for quality assessment of the included studies in meta-analysis [Table 2].

Data extraction

The following information was extracted from each study: the name of the first author, the year of publication, the country of origin, the study design, the study population, exposure to EDCs during pregnancy or infancy, and the outcome data (including sensitization, eczema, allergic rhinitis, wheezing, asthma, and food allergies). Additional

details included the type of exposure measurement, the sample type (either urine or dust), the gender distribution (female, male, or both), the mean age of the participants, effect sizes (such as odds ratios [ORs] or relative risks), and statistical methods used to adjust for potential confounding factors. Extracted data were entered into a standardized Excel file. Any disagreements were discussed, verified against the original articles, and resolved.

Table 1: Search strategy

Database	Search term
PubMed	((((((((((((((((((“bisphenol A”[Supplementary Concept])) OR (“bisphenol A”[Title/Abstract])) OR (“BPA”[Title/Abstract])) OR (“phthalate”[Title/Abstract])) OR (“diethyl phthalate”[Title/Abstract])) OR (“dimethyl phthalate”[Title/Abstract])) OR (“dibutyl phthalate”[Title/Abstract])) OR (“di (2-ethylhexyl) phthalate”[Title/Abstract])) OR (“diisodecyl phthalate”[Title/Abstract])) OR (“diisononyl phthalate”[Title/Abstract])) OR (“benzyl butylphthalate”[Title/Abstract]))) OR (“parabens”[Title/Abstract])) OR (“parabens”[MeSH Terms])) OR (“4-Hydroxybenzoic Acids”[Title/Abstract])) OR (“para Hydroxybenzoic Acids”[Title/Abstract]) OR (“paraben”[Title/Abstract]))) AND ((((((((“allergic”[Title/Abstract])) OR (“allergy”[Title/Abstract])) OR (“allergies”[Title/Abstract])) OR (“Allergy and Immunology”[MeSH Terms])) OR (“Hypersensitivity”[MeSH Terms])) OR (“Allergy[Title/Abstract] OR Immunology”[Title/Abstract])) OR (“Hypersensitivity”[Title/Abstract])) (child OR adolescent OR school-aged OR youth OR teenager OR boy OR girl OR student OR pediatrics)
SCOPUSE	((TITLE-ABS-KEY (“bisphenol A”) OR TITLE-ABS-KEY (“BPA”) OR TITLE-ABS-KEY (“phthalate”) OR TITLE-ABS-KEY (“diethyl phthalate”) OR TITLE-ABS-KEY (“dimethyl phthalate”) OR TITLEABSKEY (“dibutyl phthalate”) OR TITLE-ABS-KEY (“di (2-ethylhexyl) phthalate”) OR TITLE-ABS-KEY (“diisodecyl phthalate”) OR TITLE-ABS-KEY (“diisononyl phthalate”) OR TITLE-ABS-KEY (“benzyl butylphthalate”) OR TITLE-ABS-KEY (“parabens”) OR TITLE-ABS-KEY (“paraben”) OR TITLEABSKEY (“4-Hydroxybenzoic Acids”) OR TITLE-ABS-KEY (“para Hydroxybenzoic Acids”))) AND ((TITLEABS-KEY (“allergic”) OR TITLE-ABS-KEY (“allergy”) OR TITLE-ABS-KEY (“allergies”) OR TITLEABS-KEY (“Allergy and Immunology”) OR TITLE-ABS-KEY (“Hypersensitivity”) OR TITLE-ABSKEY (“Immunology” [ ))) (child OR adolescent OR school-aged OR youth OR teenager OR boy OR girl OR student OR pediatrics)
Web of Science	(TOPIC: (“bisphenol A”) OR TOPIC: (“BPA”) OR TOPIC: (“phthalate”) OR TOPIC: (“diethyl phthalate”) OR TOPIC: (“dimethyl phthalate”) OR TOPIC: (“dibutyl phthalate”) OR TOPIC: (“di (2ethylhexyl) phthalate”) OR TOPIC: (“diisodecyl phthalate”) OR TOPIC: (“diisononyl phthalate”) OR TOPIC: (“benzyl butylphthalate”) OR TOPIC: (“parabens”) OR TOPIC: (“paraben”) OR TOPIC: (“4-Hydroxybenzoic Acids”) OR TOPIC: (“para Hydroxybenzoic Acids”)) AND (TOPIC: (“allergic”) OR TOPIC: (“allergy”) OR TOPIC: (“allergies”) OR TOPIC: (“Allergy and Immunology”) OR TOPIC: (“Hypersensitivity”) OR TOPIC: (“Immunology”])(child OR adolescent OR school-aged OR youth OR teenager OR boy OR girl OR student OR pediatrics)

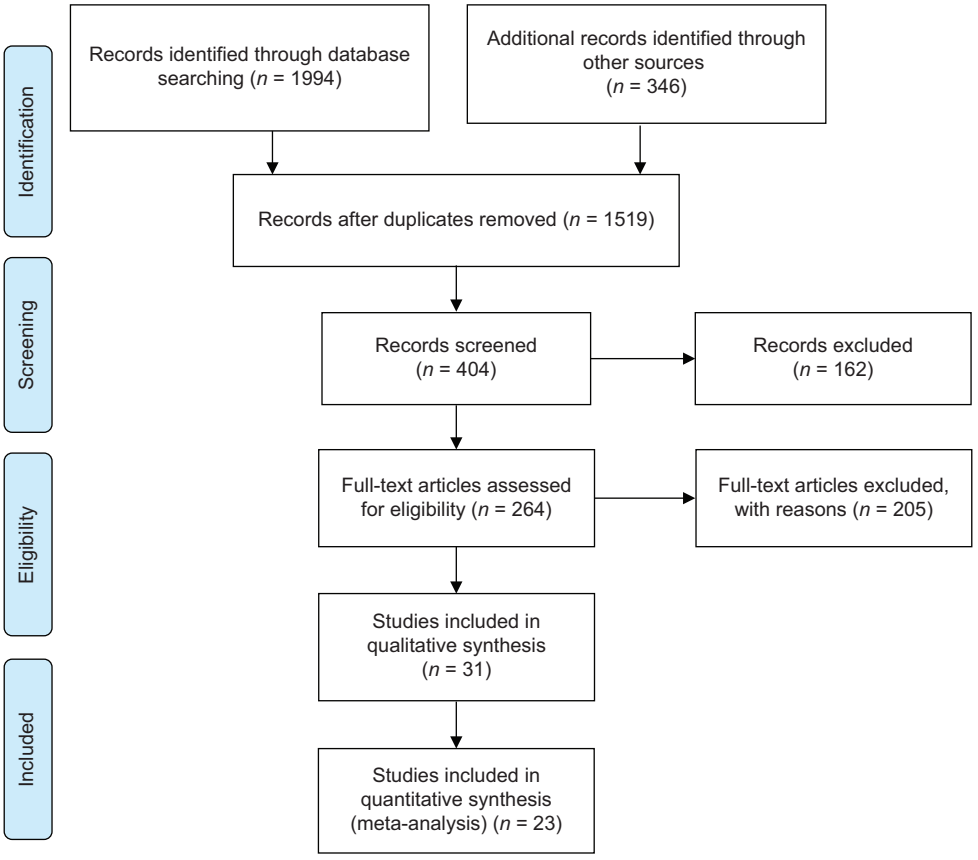

Figure 1: Selection process for the studies included in the meta-analysis

Statistical analysis

The effect sizes of OR (for cross-sectional studies) and relative risk (for cohort studies) were used for meta-analysis. For simplicity, we refer to Risk Ratio (RR) for all two types of measures of association. As the frequency of allergic disorders is relatively low, the OR in cross-sectional studies approximates the risk ratio (RR) from cohort studies, making them comparable for meta-analysis.[23-25] The potential heterogeneity across studies was evaluated using the Cochran's Q-test and expressed using the I^2 index.[26] The pooled results were calculated by the random-effects model.[23,27] Subgroup analyses based on EDC types, allergy types, study type, geographic area, and time of exposure and meta-regression on sample size, year of publication of studies, and mean age were performed to seek the sources of heterogeneity.[28,29] The sensitivity analyses were performed by excluding one study or set of studies at a time to gauge the robustness of our results.[30] Publication bias was evaluated by the funnel plot and Egger's test.[31,32] All statistical analyses were conducted using software STATA 12.0 (STATA Corp, College Station, Texas, USA).

RESULTS

Figure 1 shows the flow diagram for the selection process. A total of 2340 records were initially identified from a

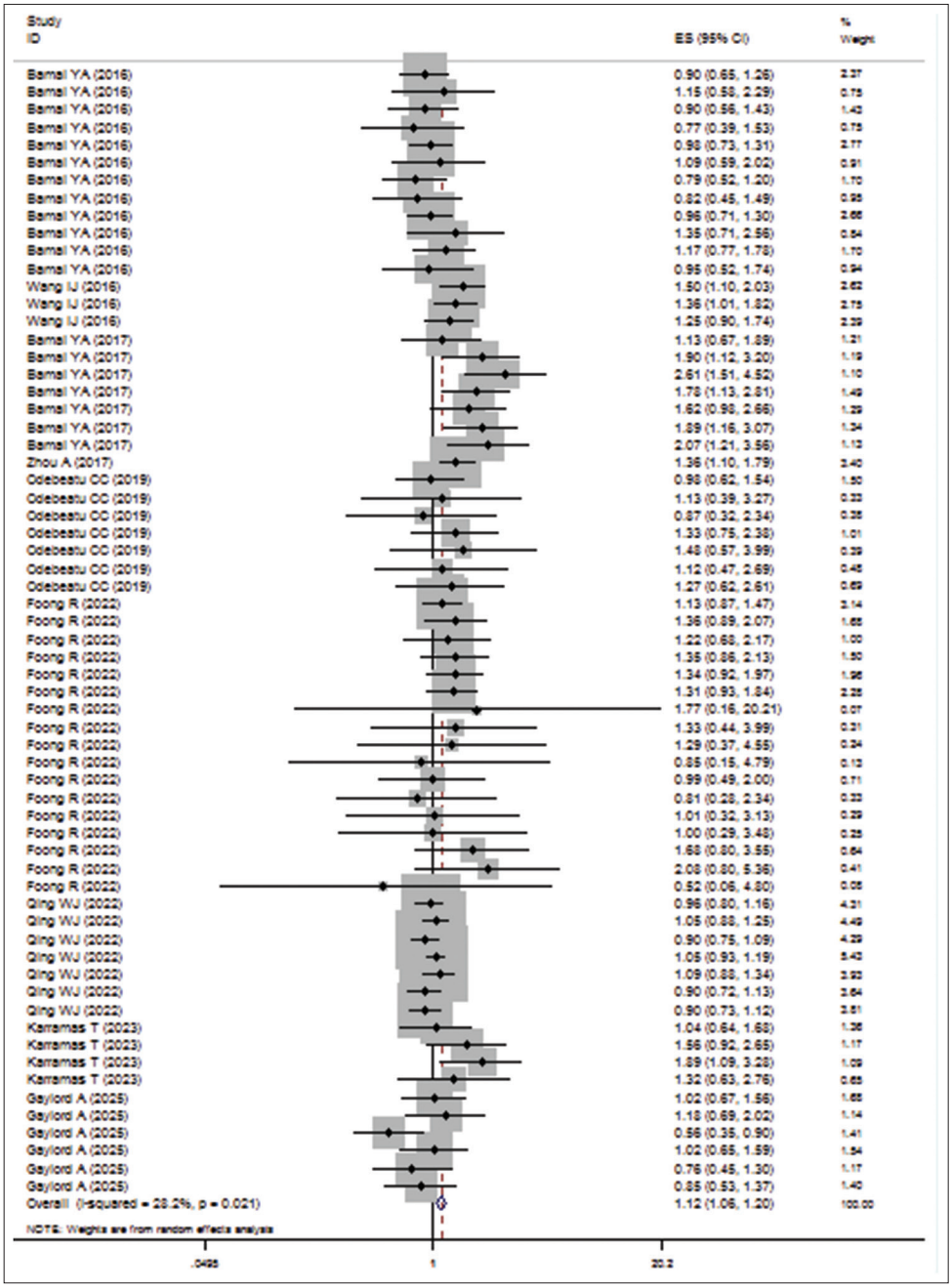

Figure 2: Forest plot for the association between exposure to endocrine-disrupting chemicals and all allergies in females

Table 2: Quality assessment of studies using Newcastle-Ottawa Scale

Cohort Studies	Selection				Comparability	Outcome			
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total score
Hoppin JA (2013)[10]	*	*	*	*	**	*	*	*	8
Podlecka D (2020)[12]	*	*	*	*	*	*	*	*	8
Bamai YA (2016)[43]	*		*	*	**	*	*	*	8
Wang IJ (2016)[44]	*		*	*	**	*	*	*	8
Kim EH[45]	*		*	*	*	*	*	*	7
Bamai YA(2018)[46]	*		*	*	**	*	*	*	8
Zhou A (2017)[47]	*		*	*	**	*	*	*	8
Soomro MH (2018)[48]	*	*	*	*	**	*	*	*	9
Wenming Shi (2018)[49]	*		*	*	**	*	*	*	8
Odebeatu CC (2019)[50]	*	*	*	*	**		*	*	8
Gaylord A (2023)[51]	*		*	*	**	*	*	*	8
Coiffier (2023)[52]	*		*	*	**		*	*	7
Karramass T(2023)[53]	*		*	*	**	*	*	*	8
Miller R(2025)[54]	*		*	*	**	*	*	*	8
Qing WJ(2022)[55]	*		*	*	**	*	*	*	8
Foong RE(2023)[56]	*		*	*	**	*	*	*	8

Case- control Studies	Selection				Comparability	Exposure		
	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of Controls		Ascertainment of Exposure	Non-Response Rate	Total score
Cho WJ(2014)[57]	*	*	*	*	*	*	*	7
Dong Keo (2018)[58]	*	*		*	*	*		5
Hsu NY (2012)[59]	*	*	*	*	*	*	*	7
Zhu C(2022)[60]	*	*		*	*	*	*	6
Whyatt RM (2014)[61]								

Cross-sectionall Studies	Selection				Comparability	Outcome		
	Representativeness of the cases	Sample size	Non-Response rate	Ascertainment of the screening/surveillance tool		Assessment of the outcome	Statistical test	Total score
Mitsui-Iwama M (2018)[62]			*	*	*	*	*	5
Ketema RM(2022)[63]	*		*	**	*	*	*	7

(*) function as quality points. (**)stars indicate higher methodological quality

Table 3: Descriptive information of articles

Study name	Author (s) + Ref No.	Study type	Year	EDC/Chemical	Allergy/Outcome	Sample size	Effect size
Phthalate exposure and allergy in the US population (NHANES 2005–2006)	Hoppin JA *et al.*[10]	Cohort	2013	MiBP, MnBP, MEP, MMP, MBzP, MCOP, MCNP, MCPP, ∑DEHP	Wheeze, hay fever, rhinitis, asthma	779	OR
Longitudinal effect of phthalates exposure on allergic diseases in children	Podlecka D *et al.*[12]	Cohort	2020	5oxo-MEHP, MBzP, MnBP, 5OH-MEHP, MEHP, MEP	Food allergy, AR, AD, wheeze	145	OR
Exposure to phthalates in house dust & associated allergies	Ait Bamai Y *et al.*[43]	Cohort	2016	DiBP, DnBP, BBZP, DEHP	Rhinoconjunctivitis, wheeze, AD	184	OR
Bisphenol A exposure & atopic disorders	Wang IJ *et al.*[44]	Cohort	2016	BPA	Asthma, rhinitis, AD	453	OR
Exposure to phthalates & BPA and AD symptoms	Kim EH *et al.*[45]	Cohort	2017	MnBP, BPAG, MEHHP, MEOHP	Atopic dermatitis	460	OR
Prenatal DEHP exposure & allergies (Hokkaido Study)	Ait Bamai Y *et al.*[46]	Cohort	2018	MEHP	Eczema, wheeze, food allergy	654	OR
Prenatal BPA exposure & allergic diseases	Zhou A *et al.*[47]	Cohort	2017	BPA	Any allergies	412	OR
Prenatal phthalates & eczema phenotypes (EDEN Cohort)	Soomro MH *et al.*[48]	Cohort	2018	Multiple phthalates	Eczema	604	OR
Urinary phthalate metabolites & asthma/allergy	Shi W *et al.*[49]	Cross-sectional	2018	Multiple metabolites	Asthma, wheeze, allergies		
Phthalates & asthma in US population (NHANES 2007–2012)	Odebeatu CC *et al.*[50]	Cohort	2019	MEP, MiBP, MnBP, MBzP, MCNP, MCPP, ∑DEHP	Asthma/wheeze	2180	OR
Prenatal BPA/BPS exposure & atopic disease at age 6	Gaylord A *et al.*[51]	Cohort	2023	BPA, BPS	Wheeze, asthma, food allergy	487–501	OR
Prenatal phenols & phthalates exposure & respiratory health	Coiffier O *et al.*[52]	Cohort	2023	DINCH, parabens, BPS	Wheeze, allergies	457	OR
Bisphenol & phthalate exposure and childhood asthma (Generation R)	Karramass T *et al.*[53]	Cohort	2023	BPA, BPF, BPS, DEHP, DNOP	Asthma	907	OR
Bisphenols & asthma/allergies in ECHO Consortium	Miller RL *et al.*[54]	Cohort	2025	BPA, BPF, BPS	Asthma, rhinitis, AD	1305	OR
Maternal phthalates & infant allergic rhinitis	Wang JQ *et al.*[55]	Cohort	2022	MMP, MEP, MBP, MBzP, MEHP, MEOHP, MEHHP	Allergic rhinitis	1149	OR
Prenatal plastic-derived chemical exposure & asthma	Foong RE *et al.*[56]	Cohort	2023	BPA, ΣMBP, MiBP, MnBP, ΣLMWP, ΣHMWP, DEHP, DiNP	Non-atopic asthma	270	RR
DEHP exposure & atopic dermatitis	Choi WJ *et al.*[57]	Case-control	2014	∑DEHP	Atopic dermatitis	448	
Phthalate exposure & acute urticaria	Yon DK *et al.*[58]	Case-control	2018	MiBP, 5OH-MEHP, BPAG	Urticaria	149	OR
Dust/urine phthalate exposure & childhood allergy/asthma	Hsu NY *et al.*[59]	Case-control	2012	MBP, BBzP	Asthma, AR	111	OR
Phthalates in dust & allergies (Tianjin)	Zhu C *et al.*[60]	Case-control	2022	DEP, DiBP, DnBP, BBzP, DEHP, ΣDiNP	Wheeze, rhinitis, eczema	398	OR
Asthma in inner-city children & prenatal phthalates	Whyatt RM *et al.*[61]	Cohort	2014	Phthalates	Asthma	94–419	RR/OR
Daily products containing paraben & triclosan and allergic diseases	Motoko M *et al.*[62]	Cross-sectional	2018	Paraben, Triclosan	AD, rhinitis, wheeze	160	OR
Phthalate mixture & allergies (Hokkaido)	Ketema RM *et al.*[63]	Case-control	2022	MiBP, MnBP, ΣDBP, MBzP, DEHP metabolites	Wheeze, rhinitis, eczema	386	OR
Asthma/wheezing phenotypes in preschool children	Kutzora S *et al.*[64]	Cohort	2018	MnBP	Wheeze, asthma	540	

Table 4: Results of meta-analysis for association between exposure to endocrine-disrupting chemicals and all allergies for overall and by gender

Model type	Number of studies	Pooled effect size				Heterogeneity	
		RR	Lower	Upper	*P*	I^2 (%)	*P*
Overall							
Fixed effect	23	1.05	1.04	1.07	<0.001	42.80	<0.001
Random effect	23	1.07	1.04	1.1	<0.001	42.80	<0.001
Female							
Fixed effect	9	1.09	1.04	1.15	<0.001	28.20	0.021
Random effect	9	1.13	1.06	1.2	<0.001	28.20	0.021
Male							
Fixed effect	11	1.12	1.08	1.16	<0.001	20.40	0.061
Random effect	11	1.14	1.09	1.19	<0.001	20.40	0.061

RR=Risk ratio

database search; 821 of them were excluded after removing duplicates, and 162 records were excluded after screening the titles and abstracts. The remaining 23 full-text articles including 12736 participants were assessed for eligibility [Table 3]. Twenty-three studies, including 17 cohort studies, 4 case–control studies, and 2 cross-sectional studies, were included for EDC exposure; these studies were published between 2011 and 2025.

The association between environmental endocrine-disrupting chemicals and allergies

The findings of meta-analysis on 23 studies showed a positive significant association between exposure to environmental EDCs and risk of allergies (pooled RR = 1.07; 95% confidence interval [CI] =1.04, 1.10) using a random-effects model [Table 4]. There was significant heterogeneity (I^2 = 42.8%, P < 0.001). Therefore, the subgroup analysis and meta-regression were used to explore the potential sources of heterogeneity. Results of subgroup analysis and meta-regression were reported in the following. The findings of meta-analysis on 9 studies showed a positive significant association between exposure to environmental EDCs in females and risk of allergies (pooled RR = 1.13; 95% CI = 1.06, 1.20) using a random-effects model [Figure 2]. The findings of meta-analysis on 11 studies showed a positive significant association between exposure to environmental EDCs in males and risk of allergies (pooled RR = 1.14; 95% CI = 1.09, 1.19) using a random-effects model [Table 4 and Figure 3]. The heterogeneity for females and males was I^2 = 28.20%, P = 0.021, and I^2 = 20.40%, P = 0.061, respectively [Figures 2 and 3, Table 4].

Results of subgroup analysis

Association between environmental endocrine-disrupting chemicals and allergies by type of allergy

Table 5 shows the results of subgroup analysis based on type of allergy. The results showed the positive significant effects of environmental EDCs on asthma wheezing (pooled RR = 1.12; 95% CI = 1.05, 1.20; I^2 = 9%), wheeze (pooled RR = 1.10; 95% CI = 1.04, 1.16; I^2 = 22.90%), rhinoconjunctivitis (pooled OR = 1.10; 95% CI = 1.03, 1.18; I^2 = 0%), and nonatopic asthma (pooled RR = 1.13; 95% CI = 1.06, 1.21; I^2 = 22.60%). The heterogeneity was not significant for above allergies. The pooled RR for association between environmental EDCs and atopic dermatitis, eczema, food allergy, and any allergies was not significant (P > 0.05).

Association between environmental endocrine-disrupting chemicals and allergies by the type of chemicals

Table 5 shows the results of subgroup analysis based on the type of pollution. The results showed the positive significant effects of phthalates (all metabolites) (pooled RR = 1.06; 95% CI = 1.03, 1.09; I^2 = 44.20%), bisphenols (pooled RR = 1.12; 95% CI = 1.05, 1.19; I^2 = 13.70%), and paraben (pooled RR = 1.16; 95% CI = 1.03, 1.30; I^2 = 33.40%) on allergies.

There was only a study for the effect of triclosan on allergies. The associations between metabolites of 5oxo MEHP, MBzP, MEHP, MEHHP, MEOHP, MBP, MECPP, MiNP, ΣDINCH, OH_MINP, cx_MINP in the phthalates group, BPAG and BPA in the bisphenols group and parabens, propyl, ethyl, and methyl paraben in the parabens group with all allergies were significant (P < 0.05) [Table 5].

Association between environmental endocrine-disrupting chemicals and allergies by the study type

Table 5 shows the results of subgroup analysis based on study type. The results showed that there was a positive association between the environmental EDC and allergies in cohort studies (pooled RR = 1.07; 95% CI = 1.02, 1.11; I^2 = 42.40%) and cross-sectional studies (pooled RR = 1.18; 95% CI = 1.13, 1.24; I^2 = 0%). The heterogeneity was significant for cohort studies (P = 0.026).

Association between environmental endocrine-disrupting chemicals and allergies by the prenatal and postnatal exposure

Table 5 shows the results of subgroup analysis based on the prenatal and postnatal exposure to EDCs. The results showed

Table 5: Results of subgroup analysis for association between exposure to endocrine-disrupting chemicals and all allergies

Subgroups	Number of studies	Pooled effect size				Heterogeneity	
		RR	Lower	Upper	*P*	I^2 (%)	*P*
Allergy types							
Food allergy	4	1.09	0.90	1.33	0.363	51.80	0.002
Allergic rhinitis	7	1.01	0.97	1.05	0.562	0.00	0.822
Atopic dermatitis	9	1.02	0.91	1.14	0.798	48.80	<0.001
Asthma wheezing	10	1.12	1.05	1.20	<0.001	9.00	0.322
Wheeze	7	1.10	1.04	1.16	0.001	22.90	0.085
Rhinoconjunctivitis	2	1.10	1.03	1.18	0.007	0.00	0.993
Eczema	3	1.03	0.97	1.09	0.415	39.80	0.035
Any allergies	4	1.07	0.99	1.15	0.085	64.30	0.001
Otitis media	1	1.53	1.09	2.15	0.015	-	-
Chicken pox	1	1.52	1.10	2.10	0.011	-	-
Any infectious	1	2.00	1.41	2.83	<0.001	-	-
Nonatopic asthma	3	1.13	1.06	1.21	<0.001	22.60	0.102
Hay fever	1	0.60	0.43	0.85	0.004	73.60	<0.001
Types of EDCs							
5oxo- MEHP	2	1.06	0.70	1.60	0.797	59.70	0.03
MBzP	6	1.18	1.06	1.32	0.003	46.70	0.015
MnBP	7	1.04	0.86	1.26	0.688	67.80	<0.001
5OH-MEHP	3	0.92	0.72	1.18	0.504	36.50	0.15
MEHP	5	1.22	1.04	1.44	0.018	64.10	<0.001
MEP	5	0.95	0.84	1.08	0.47	31.50	0.11
DiBp	2	0.99	0.90	1.08	0.765	56.60	0.024
DnBP	3	0.99	0.95	1.04	0.801	0.00	0.657
BBzP	4	0.95	0.90	1.01	0.134	8.30	0.365
DEHP	4	0.97	0.92	1.03	0.347	0.00	0.745
∑DEHP	5	1.03	0.89	1.19	0.692	53.60	0.005
MiBP	6	1.02	0.88	1.19	0.765	33.90	0.091
MEHHP	1	1.27	1.04	1.55	0.02	0.00	0.931
MEOHP	1	1.28	1.05	1.56	0.017	0.00	0.87
MMP	1	1.04	0.88	1.23	0.656	0.00	0.495
MCOP	1	0.94	0.82	1.08	0.379	0.00	0.533
MCNP	2	0.94	0.79	1.12	0.518	2.70	0.412
MCPP	2	0.99	0.80	1.22	0.886	22.90	0.24
MBP	1	1.16	1.02	1.33	0.03	-	-
MECPP	2	1.29	1.08	1.55	0.005	0.00	0.965
3OH_MnBP	1	1.70	0.59	4.91	0.33	0.00	0.633
MiNP	3	1.18	1.01	1.37	0.033	0.00	0.431
7oh_minp	1	0.44	0.15	1.29	0.133	0.00	0.578
7oxo_minp	1	3.21	0.91	11.28	0.069	0.00	0.561
DOP_MOP	1	1.63	0.64	4.16	0.311	0.00	0.867
LMWP	1	0.83	0.55	1.26	0.378	-	-
HMWP	1	1.07	0.77	1.49	0.688	-	-
DNOP	1	1.14	0.84	1.55	0.407	-	-
PA	1	0.86	0.59	1.25	0.426	-	-
ΣMBP	1	1.30	0.97	1.74	0.078	-	-
ΣLMWP	1	1.20	0.92	1.57	0.186	-	-
MHBP	1	0.76	0.13	4.47	0.761	-	-
ΣHMWP	1	1.51	0.75	3.05	0.25	-	-
MIDP	1	1.04	0.60	1.81	0.89	-	-
ΣDiNP	3	1.05	0.95	1.16	0.318	44.70	0.07
MCiOP	1	0.83	0.26	2.67	0.754	-	-
ΣDINCH	1	1.32	1.01	1.72	0.041	-	-
DEP	1	1.00	0.88	1.12	0.93	37.30	0.172
ΣDBP	1	1.13	0.94	1.35	0.194	0.00	0.731

Contd...

Table 5: Contd...

Subgroups	Number of studies	Pooled effect size				Heterogeneity	
		RR	Lower	Upper	*P*	I^2 (%)	*P*
OH_MINP	1	1.24	1.05	1.46	0.012	0.00	0.638
cx_MINP	1	1.22	1.03	1.45	0.023	14.70	0.31
Phthalates	14	1.06	1.03	1.09	<0.001	44.20	<0.001
BPAG	2	1.21	1.02	1.43	0.026	39.90	0.172
Bisphenol A	5	1.13	1.05	1.22	0.001	0	0.635
BPS	4	1.07	0.89	1.29	0.454	43.10	0.08
BPF	2	1.13	0.94	1.35	0.191	0.00	0.999
BP	1	1.24	0.75	2.05	0.402	-	-
Bisphenol	8	1.12	1.05	1.19	<0.001	13.70	0.262
Paraben	1	2.18	0.78	6.11	0.14	49.90	0.136
Propyl paraben	1	1.09	1.00	1.18	0.041	-	-
Ethyl paraben	1	1.18	0.98	1.42	0.075	-	-
Methyl paraben	1	1.19	1.01	1.40	0.037	-	-
Parabens	2	1.16	1.03	1.30	0.015	33.40	0.186
Triclosan	1	0.60	0.26	1.39	0.229	8.80	0.349
Triclosan	1	0.60	0.26	1.39	0.229	8.80	0.349
Time of exposure							
Prenatal	9	1.15	1.10	1.21	<0.001	17.10	0.097
Postnatal	11	1.05	1.02	1.08	0.001	44.40	<0.001
Both	1	1.00	0.87	1.15	0.991	59.30	<0.001
Type of studies							
Cohort	13	1.07	1.02	1.11	0.002	42.40	0.0262
Case-control	4	1.00	0.96	1.03	0.804	45.20	0.0051
Cross-sectional	2	1.18	1.13	1.24	<0.001	0.00	<0.001
Geographical area							
Europe	4	1.06	0.99	1.15	0.106	34.80	0.003
Asia	11	1.08	1.05	1.11	<0.001	45.90	<0.001
Americas	4	1.00	0.94	1.07	0.983	48.80	<0.001
Oceania	1	1.07	1.04	1.10	<0.001	0.00	0.997

RR=Risk ratio; EDCs=Endocrine-disrupting chemicals

that there was a positive association between the prenatal (pooled RR = 1.15; 95% CI = 1.10, 1.21; I^2 = 17.10%) and postnatal (pooled RR = 1.05; 95% CI = 1.02, 1.08; I^2 = 44.40%) exposure to EDCs with allergies. The heterogeneity was significant for postnatal exposure ($P < 0.001$).

Association between environmental endocrine-disrupting chemicals and allergies by geographical area

Table 5 shows the results of subgroup analysis based on the geographical area to the association between environmental pollution and allergies. The Americas, Asia, Europe, and Oceania were included in this study. The results showed that the association between environmental pollution and allergies was significant in Asia (pooled RR = 1.08; 95% CI = 1.05, 1.11; I^2 = 45.90%). The heterogeneity was significant for Asia ($P < 0.001$). The associations for other areas were not significant.

Association between environmental endocrine-disrupting chemicals and allergies in studies with similar types of allergy and environmental endocrine-disrupting chemicals

Table 6 shows the results of the association between phthalates, bisfenols, and parabens (all metabolites) with allergies that a number of studies were 2 or more than 2. Results showed that the association between bisphenols and asthma wheezing was significant (pooled RR = 1.16; 95% CI = 1.05, 1.28; I^2 = 0%). As well, there were a positive association between phthalates and allergies of nonatopic asthma (pooled RR = 1.12; 95% CI = 1.05, 1.21; I^2 = 24%), rhinoconjunctivitis (pooled RR = 1.10; 95% CI = 1.03, 1.18; I^2 = 0%), and wheeze (pooled RR = 1.10; 95% CI = 1.04, 1.16; I^2 = 23.50%).

Meta-regression

The findings indicate that prenatal and postnatal exposure to EDCs are both significantly associated with the risk of allergic disorders in children. Results of meta-regression showed the effect of sample size (β [standard error]: 0.0002 [0.00005]; $P < 0.001$), year of publication of studies (β [standard error]: 0.017 [0.004]; $P < 0.001$), and mean age (β [standard error]: −0.001 [0.001]; $P = 0.457$) on effect sizes (RRs). The results of the meta-regression analysis revealed that both sample size (β = 0.0002, SE = 0.00005, $P < 0.001$) and year of publication (β = 0.017, SE = 0.004, $P < 0.001$) were statistically significant predictors of effect sizes. Furthermore, these variables were identified as the main

sources of heterogeneity, with sample size explaining 14.61% of the variance (accounting for 70.34% of the explained heterogeneity) and publication year explaining 11.18% of the variance (accounting for 72.13% of the explained heterogeneity).

Sensitivity analysis

Sensitivity analyses were performed by removing a particular study or set of studies at a time which had the highest impact on the pooled effect size and the heterogeneity tests.

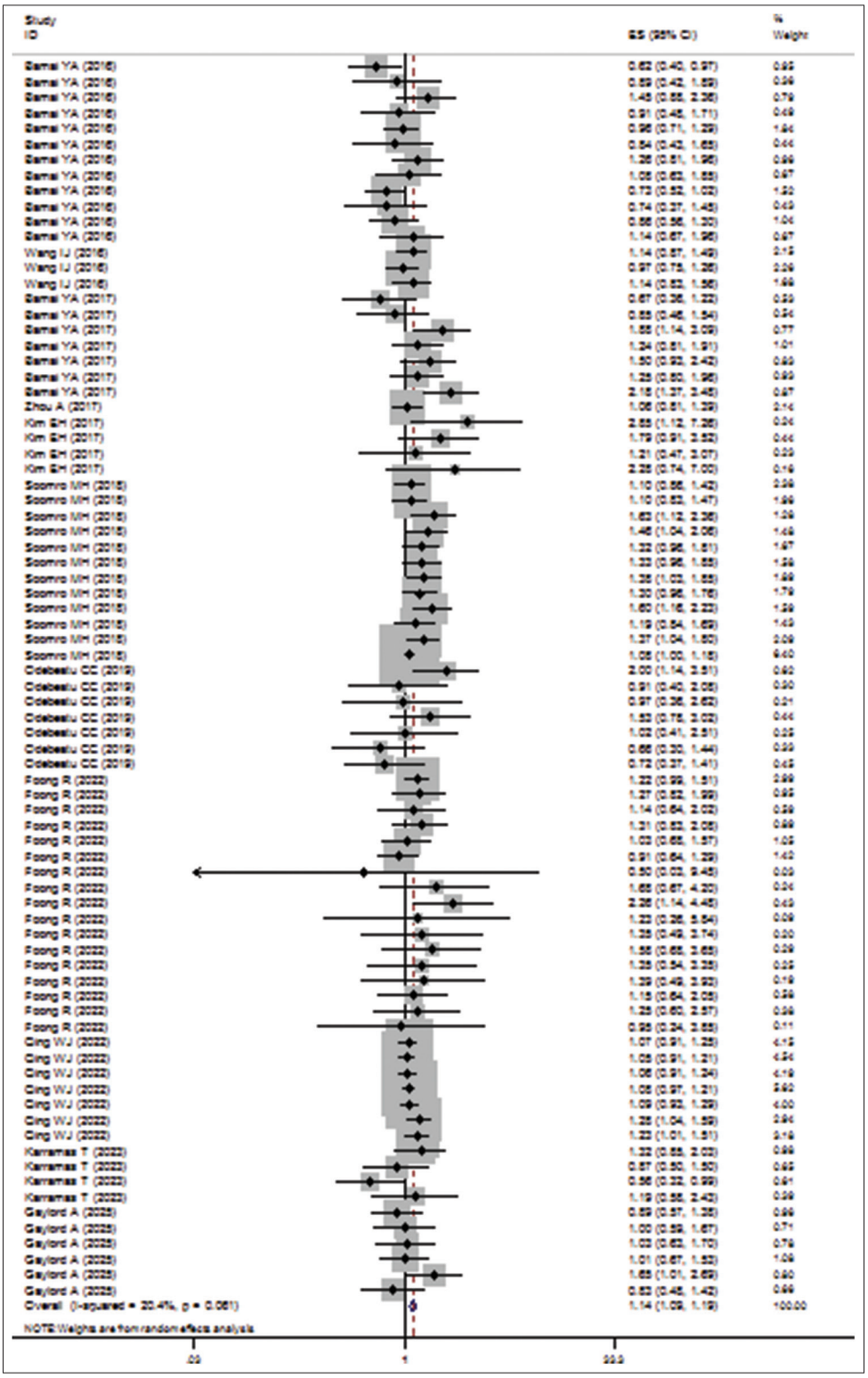

Figure 3: Forest plot for the association between exposure to endocrine-disrupting chemicals and all allergies in males

Table 6: Results of meta-analysis for association between phthalates and bisphenols with types of allergies

Subgroups	Number of studies	Pooled effect size				Heterogeneity	
		RR	Lower	Upper	*P*	I^2 (%)	*P*
Atopic dermatitis							
Phthalates	6	0.99	0.87	1.13	0.91	45.30	0.004
Bisphenols	3	1.07	0.85	1.35	0.552	59.10	0.044
Allergic rhinitis							
Phthalates	4	1.01	0.96	1.05	0.808	0.00	0
Bisphenols	2	1.05	0.94	1.18	0.409	13.30	0.0018
Asthma wheezing							
Phthalates	4	1.09	0.99	1.20	0.073	27.50	0.125
Bisphenols	5	1.16	1.05	1.28	0.005	0.00	0.714
Eczema							
Phthalates	3	1.03	0.97	1.09	0.415	39.80	0.035
Nonatopic asthma							
Phthalates	3	1.12	1.05	1.21	0.001	24.00	0.089
Rhinoconjunctivitis							
Phthalates	2	1.10	1.03	1.18	0.007	0.00	0.993
Wheeze							
Phthalates	5	1.10	1.04	1.16	0.001	23.50	0.088
Food allergy							
Phthalates	3	1.09	0.86	1.36	0.482	54.50	0.002
Atopic dermatitis							
Phthalates	6	0.99	0.87	1.13	0.91	45.30	0.004

RR=Risk ratio

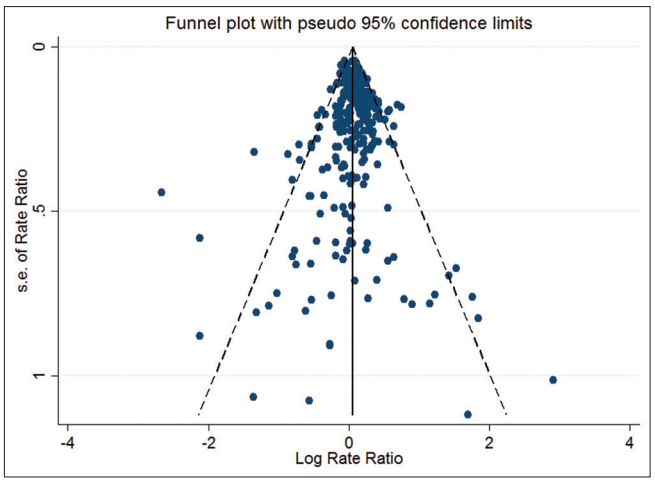

Figure 4: Funnel plot of included studies in meta-analysis in overall

Results of sensitivity analysis showed that the pooled effect size (RR) was not influenced after excluding studies one by one. In addition, with excluding a set of studies with effect sizes of relative risk (M. Whyatt R [2014] and Foong R [2022]), the pooled OR was 1.06 (95% CI = 1.03, 1.09; $I^2 = 44.3\%$; $P < 0.001$). As well, with excluding a set of studies with EDCs in samples of house dust (HSu NY [2011] and Zhu C [2023]), the pooled RR for urine samples was 1.10 (95% CI = 1.06, 1.13; $I^2 = 38.2\%$; $P < 0.001$). The changes in effect sizes and heterogeneities were not noticeable. We applied both fixed-effects and random-effects models to assess the robustness of our findings. The fixed-effects model yielded slightly more conservative estimates (pooled RR = 1.05; 95% CI = 1.04, 1.07) compared to the random-effects model (RR = 1.07; 95% CI: 1.04, 1.10), though both reached statistical significance ($P < 0.001$) [Tables 2 and 3].

Publication bias

Publication bias was assessed by visual inspection of funnel plots and formal statistical assessment using Egger's regression asymmetry test. In the funnel plots, the RRs were displayed against the standard error of RR. Funnel plot for overall data showed symmetry [Figure 4]. The *P* value for Egger's test was 0.354 that revealed no obvious publication bias among these studies. As well, Funnel plots for females and males showed symmetry [Figure 5]. The *P* values for Egger's tests for females and males were 0.165 and 0.203, respectively, that revealed no obvious publication bias among these studies in females and males.

DISCUSSION

Our systematic review and meta-analysis included 23 studies that investigated the intake of EDCs. Our findings indicated that EDC intake was associated with an increased risk of asthma, wheezing, nonatopic asthma, and rhinoconjunctivitis. However, EDC intake did not appear to affect hay fever, eczema, food allergies, atopic dermatitis, or allergic rhinitis. Specifically, chemicals such as BPA, BPAG, MBzP, MEHP, and MiNP were linked to an increased risk of various allergies. Overall, groups of phthalates, bisphenols,

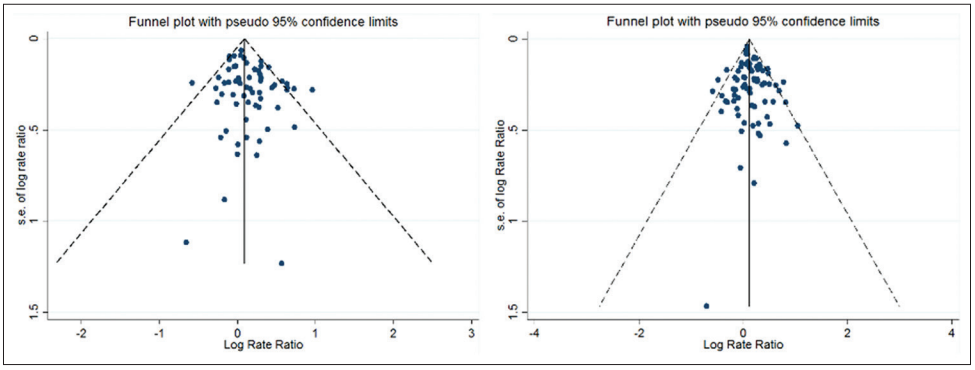

Figure 5: Funnel plot of included studies in meta-analysis for females (left) and males (right)

and parabens for all metabolites were associated with a heightened risk of allergic reactions.

Allergies, also referred to as allergic diseases, are conditions that arise from the immune system's hypersensitivity to certain substances. These diseases include asthma, wheezing, atopic dermatitis, eczema, food allergies, rhinoconjunctivitis, chickenpox, nonatopic asthma, otitis media, and wheezing. Symptoms may include red eyes, itchy rashes, sneezing, a runny nose, shortness of breath, and swelling.[33]

Recently, evidence has appeared to advocate that there is an association between prenatal exposure to EDCs and asthma and allergic diseases.[34] The literature on EDC exposures and their link to allergic disorders needs to be synthesized more effectively. The evidence regarding these associations should be strengthened due to factors such as differences in chemical usage between countries, variations in the sociodemographic characteristics of study populations, misclassification of exposure resulting from significant variability within subjects, and inconsistencies in defining health outcomes. A recent systematic review indicates that there is consistent evidence supporting associations between exposure to secondhand smoke, inhaled chemicals, mold, respiratory viruses, and ambient air pollutants, all of which are linked to an increased risk of asthma.[35] Epidemiological data indicate that exposure to mold can worsen asthma severity in infants. Specifically, wheezing has been independently linked to several factors: male gender, eczema, having siblings with asthma, a family history of allergic diseases, attending daycare, living in damp housing, and experiencing asphyxia. Additionally, recurrent wheezing is independently associated with eczema, having siblings with asthma, and attending daycare. Among these, the most significant modifiable risk factor for wheezing in the 1st year of life is dampness in the home.[36]

EDCs can alter airway cell differentiation and gut microbiota, shift the immune response toward TH2, alter the expression of T regulatory cells and TH17, and weaken innate immunity. In addition, the unfolding data also advocate that EDCs are correlated with the perturbation of DNA methylation patterns. Potential mechanisms could function through epigenetic modulation of the glucocorticoid receptor gene or changes in the neuroendocrine system or cytokine responses.[34,37,38]

Propylparaben is the benzoate ester that is the propyl ester of 4-hydroxybenzoic acid. Preservatives are typically found in many water-based cosmetics, such as creams, lotions, shampoos, and bath products, and are also used as a food additive. It has a role as an antifungal agent and an antimicrobial agent. It is a benzoate ester, a member of phenols, and a paraben. It is derived from a propane-1-ol and a 4-hydroxybenzoic acid.[39] Studies by Savage *et al.* and Lee-Sarwar *et al*.[17,40] showed that propyl paraben plays an essential role in food allergies.

Phthalates are reported to have estrogenic, antiestrogenic, and antiandrogenic effects, depending on the specific congener and metabolite analyzed. For instance, DEHP exhibits estrogenic activity, while MBzP, a metabolite of BBzP, appears to have antiestrogenic activity.[34] In 2017, Li *et al*.[41] performed a meta-analysis including 5 out of 13 studies and observed that prenatal exposure to MBzP was associated with an increased risk of asthma. Our study highlighted the role of MBzP in the development of atopic dermatitis.

Zhang *et al*., in a 2016 meta-analysis study examining the association between fish intake during infancy and fish intake by the mother during pregnancy, showed that fish intake during infancy is associated with a reduced risk of allergies in children. However, it does not affect it during pregnancy.[42]

The number of studies examining the association between EDCs and hay fever, chicken pox, nonatopic asthma, otitis media, and wheezing was lower than other allergies. It could be a reason why their effects were not significant.

Study limitations and strengths

As only some included studies were longitudinal, and others were cross-sectional or case–control designs, we could examine the associations and not the causal effects. The other limitation was the variety of definitions used in different studies to assess allergic disorders.

The main strength of our study was its novelty in the pediatric age group and its application of advanced methods for analyses.

Suggestions for future studies

For future studies, it is crucial to conduct in-depth, longitudinal research on the specific interactions between EDCs and various allergic conditions, especially in pediatric populations. Standardized methodologies for defining and assessing allergic disorders are necessary for accurate comparisons between studies. Exploring genetic factors' influence on EDC susceptibility can offer personalized insights into allergic responses. Long-term studies extending into adolescence and adulthood are essential to understand the lasting impacts of EDC exposure. Interdisciplinary collaboration among researchers, clinicians, and environmental scientists is vital for a comprehensive understanding of EDC-induced allergies, leading to targeted interventions and policy recommendations.

CONCLUSIONS

In the present work, we systematically appraised and synthesized the available evidence on the association between environmental EDCs and allergic disorders in children by evaluating 23 studies and 9970 participants. We observed a statistically significant association between most types of allergies and environmental pollution. Several types of allergies were studied in a small number of studies, and the study of the association between these allergies and environmental pollution will provide more accurate results. Further studies are necessary to assess the underlying mechanisms and the clinical impact of the current findings. Some allergies were examined in limited studies, indicating the need for further research to enhance result accuracy. Moving forward, it is crucial to delve into the underlying mechanisms and clinical implications of these findings. In conclusion, we should discuss the practical implications of policy recommendations and outline directions for future research rather than merely repeating the study results.

Data reproducibility

The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

Authors' contribution

Study concept and design: N.A, R.K, N.T; search and review of articles: N.T,R.K and N.A.; argumentation and analysis: All of authors; drafting of the manuscript: N.A, R.K, N.T, M.M, A.Y; critical revision of the manuscript for important intellectual content: N.T,R.K,N.A,M.M, A.Y; All the authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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