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Systematic Review

Association Between Endometriosis and Environmental Disruptors: A Literature Review and Meta-Analysis

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Abstract

Endometriosis is a chronic gynecological disease affecting about 10% of reproductive age women, with a significant impact on socio-economic sphere and quality of life. It is a multifactorial phenomenon, in which genetic predisposition, immunologic malfunction, hormone imbalance, and environmental insult play an important role in disease development and progression. The aim of this review is to report the current evidence from the literature related to the association between endometriosis and endocrine disruptors. This study was designed as a systematic review and meta-analysis investigating the association between exposure to endocrine disruptors and the risk of endometriosis. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The systematic search identified 428 records from national and international scientific databases. The included studies were published between 2001 and 2020, with most studies classified as fair-to-good quality. The overall random-effects meta-analysis demonstrated a statistically significant association between exposure to endocrine-disrupting chemicals and endometriosis. This systematic review and meta-analysis provides evidence of a significant association between exposure to endocrine-disrupting chemicals and endometriosis, with the strongest and most consistent association observed for polychlorinated biphenyls.

Keywords: endometriosis; endocrine disruptors; environmental insult

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1. Introduction

Endometriosis is a gynecological chronic disease affecting about 10% of reproductive age women. It still represents a burden for society, as the symptoms associated with it, in particular pain, have a significant socio-economic impact and worsen quality of life [1]. Although endometriosis is a common disease and has a significant impact, still little is known about its etiology and pathophysiology, and the only available treatments are frequently invasive surgery or symptom management [2]. It is a multifactorial phenomenon, in which genetic predisposition, immunologic malfunction, hormone imbalance, and environmental insult [3,4] play an important role in disease development and progression. Several theories have been proposed over the years to explain endometriosis origin and growth, for example, retrograde menstrual flow; however, not all women with retrograde menstrual

flow will develop endometriosis in their lifetime. Thus, a combination of several factors, including environmental ones, is involved in disease progression. Research over the most recent years has focused on this last feature; in particular, endocrine-disrupting chemicals have emerged as a possible contributing cause of endometriosis. Numerous studies have investigated substances such as polychlorinated biphenyls (PCBs), phthalates, dioxins, and bisphenol A (BPA) and their role in contributing to endometriosis development [5–7]. They are external chemicals with the potential to interfere with normal function of the endocrine system through modulation of hormone synthesis, metabolism, and receptor signaling [8]. The proven interference with the endocrine system has led to the term endocrine disruptors (EDCs) being coined for these substances. Among them, dioxins and dioxin-like compounds are extremely resistant to various industrial processes and represent ubiquitous environmental pollutants. Even if daily exposure to these substances is very low, accumulation in the human body causes long-term effects, including endometriosis development [5–7].

Many of these chemicals, which have lipophilic properties, accumulate in fat tissue and peritoneal fluid, causing both estrogenic and immunomodulatory activity. Furthermore, it seems that the higher the concentration of substances with dioxin-like activity, the greater the risk and severity of endometriosis [9]. However, a cut-off in the dose required for disease development has not yet been well established. At a molecular level, in vitro research shows that endocrine disruptors can increase VEGF expression and can also stimulate migration, invasion, and proliferation of endometrial stromal and epithelial cells [10]. Moreover, epigenetic modifications induced by EDCs present another reasonable connection with endometriosis development; these substances cause alterations in the DNA of genes related to immune and hormonal responses, making these changes the cause of progesterone resistance and estrogen dominance in endometriotic lesions [11–13].

Exposure to these substances causes hyperestrogenism, responsible for aberrant endometrial proliferation [14], and, on the other hand, an alteration in the expression of progesterone receptors and downstream signaling mechanisms, which appear to be related to the formation and persistence of endometriotic lesions with resistance to progesterone treatment [15–18]. Based on these data, it is imperative to recognize exposure to chemicals that may predispose to the development of endometriosis to allow for personalized treatment for these patients, first through the elimination of these risk factors and then through the identification of new treatment targets [19]. In a previous review, we reported a plausible link between dioxins and dioxin-like chemicals and endometriosis, due to interference of these substances with the endocrine and immune systems [20], without reaching certain assumptions because of conflicting results due to small sample size, different selection of the controls, different methods of assessment for toxicants, and different statistical tests used in the various studies. Since then, several reports corroborating this association have been published, even if with several disparities among them.

In this scenario, the aim of this review is to report the current evidence from the literature related to the association between endometriosis and endocrine disruptors in order to provide more recent data as well as a starting point for further studies aimed at improving diagnosis and developing personalized treatment for patients affected by endometriosis.

2. Materials and Methods

2.1. Study Design, Protocol, and Reporting Standards

This study was designed as a systematic review and meta-analysis investigating the association between exposure to EDCs and the risk of endometriosis. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21], ensuring methodological trans-

parency, reproducibility, and completeness of reporting (see Supplementary Material for the PRISMA 2020 main checklist).

The methodological approach, including eligibility criteria, search strategy, data extraction, and statistical analysis, was defined a priori to minimize the risk of selective reporting and analytical bias. Given the observational nature of the available evidence and the expected heterogeneity in exposure assessment and study design, particular attention was paid to the evaluation of study quality, confounding factors, and sources of between-study variability.

2.2. Eligibility Criteria

Observational studies assessing the association between exposure to endocrine-disrupting chemicals and the presence or risk of endometriosis were considered eligible. Both retrospective and prospective study designs were included, comprising case–control studies, cross-sectional studies, and cohort studies.

Eligible participants were women of reproductive age (18–49 years) with a diagnosis of endometriosis confirmed by laparoscopy or surgical intervention and histopathological examination. This restriction was applied to reduce outcome misclassification and to ensure diagnostic homogeneity across studies.

The exposure of interest was represented by endocrine-disrupting chemicals measured in blood or serum samples using standardized and validated analytical techniques. Only studies assessing internal exposure through circulating concentrations were included in order to maximize comparability across studies and reduce variability related to short-term exposure biomarkers. The primary outcome was endometriosis in relation to EDC exposure, expressed as effect estimates comparing exposed and non-exposed groups.

The decision to restrict eligibility to blood/serum measurements merits explicit justification, and its implications differ by chemical class. For PCBs and dioxins—lipophilic, persistent compounds with biological half-lives of years—serum concentrations closely reflect the body burden accumulated in adipose tissue, so blood/serum sampling provides a stable and comparable index of cumulative internal exposure across studies using heterogeneous protocols. For phthalates, however, this restriction is more questionable: phthalates are rapidly metabolized and eliminated (biological half-life of hours), and urinary metabolite concentrations, not serum parent compounds, are the internationally recommended and most widely used biomarker of phthalate exposure. By excluding urine-based studies, we likely excluded a substantial portion of the available phthalate literature and retained only studies measuring parent-compound serum levels, which are more susceptible to background contamination and to reflect a single recent exposure event rather than habitual exposure. This is a plausible explanation for the null pooled association we observed for phthalates, and we now state explicitly, both here and in the Discussion/Limitations, that our phthalate findings should not be interpreted as evidence against a role for phthalates in endometriosis, but rather as a consequence of the matrix restriction adopted for comparability with the PCB/dioxin literature. We also excluded studies using adipose tissue or peritoneal fluid; while these matrices are informative for lipophilic EDCs, they are used far less consistently across the literature and would have introduced an additional axis of methodological heterogeneity (tissue-specific partitioning, invasive sampling only available in surgical patients, and non-standardized reporting units) into an already heterogeneous body of evidence.

Studies were included if they met all of the following criteria: (i) human observational studies; (ii) confirmed histological diagnosis of endometriosis; (iii) assessment of endocrine-disrupting chemicals in blood or serum; (iv) reporting of odds ratios, relative risks, or sufficient data to compute effect estimates; (v) publication in the English language.

Exclusion criteria were as follows: animal studies or in vitro experiments; studies evaluating EDCs in biological matrices other than blood or serum (e.g., urine, adipose tissue, or peritoneal fluid); studies not clearly specifying the endocrine disruptors analyzed; studies focusing exclusively on non-dioxin-like compounds; metabolomics or untargeted exposure studies; narrative reviews, systematic reviews, meta-analyses, editorials, letters, conference abstracts, or case reports; and manuscripts not published in English.

2.3. Search Strategy and Study Selection

A comprehensive literature search was independently performed by two investigators (FF and DC) using the electronic databases PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The search covered the period from January 2000 to August 2025, reflecting the timeframe in which most analytical methods for EDC measurement became standardized and widely available.

Although the electronic search was run through August 2025, no study published after 2020 satisfied the full eligibility criteria; the most recent eligible study dated from 2020. We manually verified this by re-screening titles and abstracts published between January 2021 and August 2025 that matched the search terms: eligible EDC–endometriosis studies published in this window predominantly assessed exposure biomarkers in urine, hair, or adipose tissue rather than blood/serum, or were themselves reviews or meta-analyses, and were therefore excluded under the pre-specified criteria described in Section 2.2. This pattern likely reflects a shift in the exposure-assessment literature toward non-invasive matrices (e.g., urinary phthalate metabolites) over the past decade, which this review's blood/serum restriction (see Section 2.2 for rationale) does not capture. We have retained the full search window in the Methods to accurately reflect what was executed, rather than truncating it to the range of included studies, and we flag this pattern explicitly here rather than leaving it for the reader to infer.

The search strategy combined controlled vocabulary terms and free-text keywords related to endocrine-disrupting chemicals and endometriosis. The following search strings were used:

- "endocrine disrupting chemicals AND endometriosis";
- "polychlorinated biphenyls AND endometriosis";
- "dioxins AND endometriosis";
- "phthalates AND endometriosis".

The complete electronic search strategy for each database is provided in full in Appendix A (Table A1). No additional filters (e.g., study design filters) were applied beyond the language and date restrictions specified above to maximize sensitivity; eligibility was subsequently determined manually during title/abstract and full-text screening according to the criteria in Section 2.2.

The reference lists of all eligible full-text articles were manually screened to identify additional relevant studies not captured by the electronic search.

Study selection was conducted independently by two reviewers (F.F. and D.C.) following a two-step screening process. In the first step, titles and abstracts were screened to exclude clearly irrelevant articles. In the second step, full-text articles were assessed for eligibility according to the predefined inclusion and exclusion criteria. Duplicate records were removed prior to full-text evaluation. Disagreements between reviewers were resolved by discussion and, when consensus could not be reached, by consultation with a third reviewer (A.M.).

2.4. Data Extraction, Synthesis, and Quality Assessment

Data extraction was independently performed by two authors using a standardized and piloted data extraction form. For each eligible study, information on first author, year of publication, country of origin, study design, sample size, number of endometriosis cases and controls, age range and mean age, body mass index (when available), diagnostic method for endometriosis, type of endocrine-disrupting chemicals analyzed, biological matrix used for exposure assessment, analytical methods employed, reported effect estimates (odds ratios [ORs] or relative risks [RRs]) with corresponding 95% confidence intervals (CIs), and variables included in multivariable adjustment was collected. When multiple models were reported, estimates adjusted for the greatest number of relevant confounders were preferentially extracted. Any discrepancies in data extraction were resolved by consensus between reviewers.

Statistical analyses were conducted using R statistical software (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria). The association between exposure to endocrine-disrupting chemicals and endometriosis was quantified using ORs with 95% CIs; reported RRs were converted to ORs using the method of Zhang and Yu [22], $OR = RR/[(1 - P0) + (RR \times P0)]$, where P0 is the baseline (control-group) prevalence of endometriosis reported by the source study; this approximation is appropriate when, as here, the outcome prevalence in the unexposed/control group is not rare, and only two of the twenty-six included studies required this conversion. Adjusted estimates were preferentially used when both crude and adjusted values were available to reduce confounding bias. Due to anticipated clinical and methodological heterogeneity across studies, including differences in study design, populations, exposure assessment methods, and confounder adjustment, a random-effects meta-analysis model (DerSimonian and Laird method) was applied to estimate pooled effect sizes. Between-study heterogeneity was assessed using Cochran's Q test ($p < 0.10$) and quantified with the I^2 statistic, with values of ~25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. Prespecified subgroup analyses were conducted according to the class of endocrine-disrupting chemicals (polychlorinated biphenyls, dioxins, and phthalates), and sensitivity analyses were performed by excluding studies with low methodological quality (Newcastle–Ottawa Scale (NOS) score ≤ 4) or reporting only unadjusted estimates to evaluate the robustness of pooled results. All statistical tests were two-sided, with a significance threshold of $p < 0.05$.

The methodological quality and risk of bias of included studies were independently assessed by two reviewers using the NOS for observational studies, which evaluates selection of study groups, comparability of cases and controls, and ascertainment of exposure or outcome. Studies were categorized as low quality (0–4 points), moderate quality (5–6 points), or high quality (7–9 points). Disagreements were resolved through discussion and consultation with a third reviewer, and study quality was considered in sensitivity analyses and the interpretation of pooled estimates.

All meta-analytic computations (random-effects pooling, Cochran's Q, I^2, subgroup and sensitivity analyses, forest and funnel plots, and Egger's regression test) were performed in R (version 4.5.1) using the packages meta (version 7.0) and metafor (version 4.6), with the DerSimonian and Laird estimator specified for the between-study variance (τ^2) unless otherwise stated.

Certainty of the body of evidence: We did not perform a formal GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment. GRADE was developed primarily for intervention and prognostic questions, and its direct application to etiological/exposure meta-analyses of observational studies is not standardized; guidance for adapting GRADE to environmental exposure evidence (e.g., OHAT/NTP or GRADE for prognostic factors) exists but was not applied here because it would have required protocol

pre-specification of certainty domains, which was not built into the original review protocol. We consider this a limitation of the present work (see Section 4) and have instead reported NOS-based study quality, heterogeneity, and (newly added) publication-bias assessment as the available markers of the robustness of the evidence base; a formal GRADE or OHAT-style certainty rating is recommended for future updates of this review.

Assessment of potential participant overlap: Because several included studies originated from the same research groups [23–30], we reviewed the original publications for overlapping recruitment periods, centers, and sample sizes to assess the possibility that the same women contributed to more than one included study. The Heilier [23,24] and the Porpora [25,26] reports describe partially overlapping recruitment sites (Belgium and Italy, respectively) but different, non-identical case series (different sample sizes, different inclusion periods, and different comparator groups: adenomyotic nodules vs. peritoneal/deep endometriosis for Heilier; general endometriosis vs. an expanded, later-recruited cohort for Porpora), consistent with sequential, non-duplicated recruitment waves from the same clinical groups rather than re-analysis of an identical dataset. Buck Louis et al. studies (NCC, n = 32/52) [27] and (the ENDO Study, n = 190/283 with a substantially different design, exposure panel, and recruitment strategy) [28] are explicitly reported as distinct studies. The two Reddy et al. reports (BJOG and Fertility & Sterility) [29,30] present different sample sizes (48/59 and 85/135, respectively) and different phthalate/PCB endpoints, consistent with related but non-identical cohorts recruited by the same Indian research group. We cannot fully exclude partial participant overlap using published information alone, as individual patient identifiers are not available; we therefore now list this as an explicit limitation and, as a conservative check, note that the pooled estimate changed minimally when either member of each of these author pairs was excluded in a leave-one-out sensitivity check (results not tabulated; available upon request), suggesting that our conclusions are not driven by a small number of overlapping records.

3. Results

3.1. Study Selection and Characteristics

The systematic search identified 428 records from national and international scientific databases. After exclusion of 61 records flagged as ineligible by automation tools, 367 articles were screened by title and abstract. Among these, 160 studies were excluded because they were reviews or previous meta-analyses. Full-text assessment was performed for 207 articles, of which 181 were excluded due to animal or in vitro design, urinary-only exposure assessment, non-English language, or lack of relevance to the research question. Ultimately, 26 studies fulfilled the inclusion criteria and were included in the qualitative and quantitative synthesis [23–48] (Figure 1).

The included studies were published between 2001 and 2020 and were conducted in Europe, North America, and Asia. Most studies adopted a case–control design, with one non-case-control study and one case series. In total, 1575 women with endometriosis, deep infiltrating endometriosis (DIE), or advanced-stage disease were included, with ages ranging from 20 to 49 years. Endometriosis diagnosis was established by laparoscopy or surgery in all studies except one, in which the diagnostic method was not specified. Body mass index (BMI) was reported in 15 studies. Detailed characteristics of the included studies, including study design, population, diagnostic criteria, endocrine disruptors investigated, confounders, and methodological quality, are summarized in Table 1.

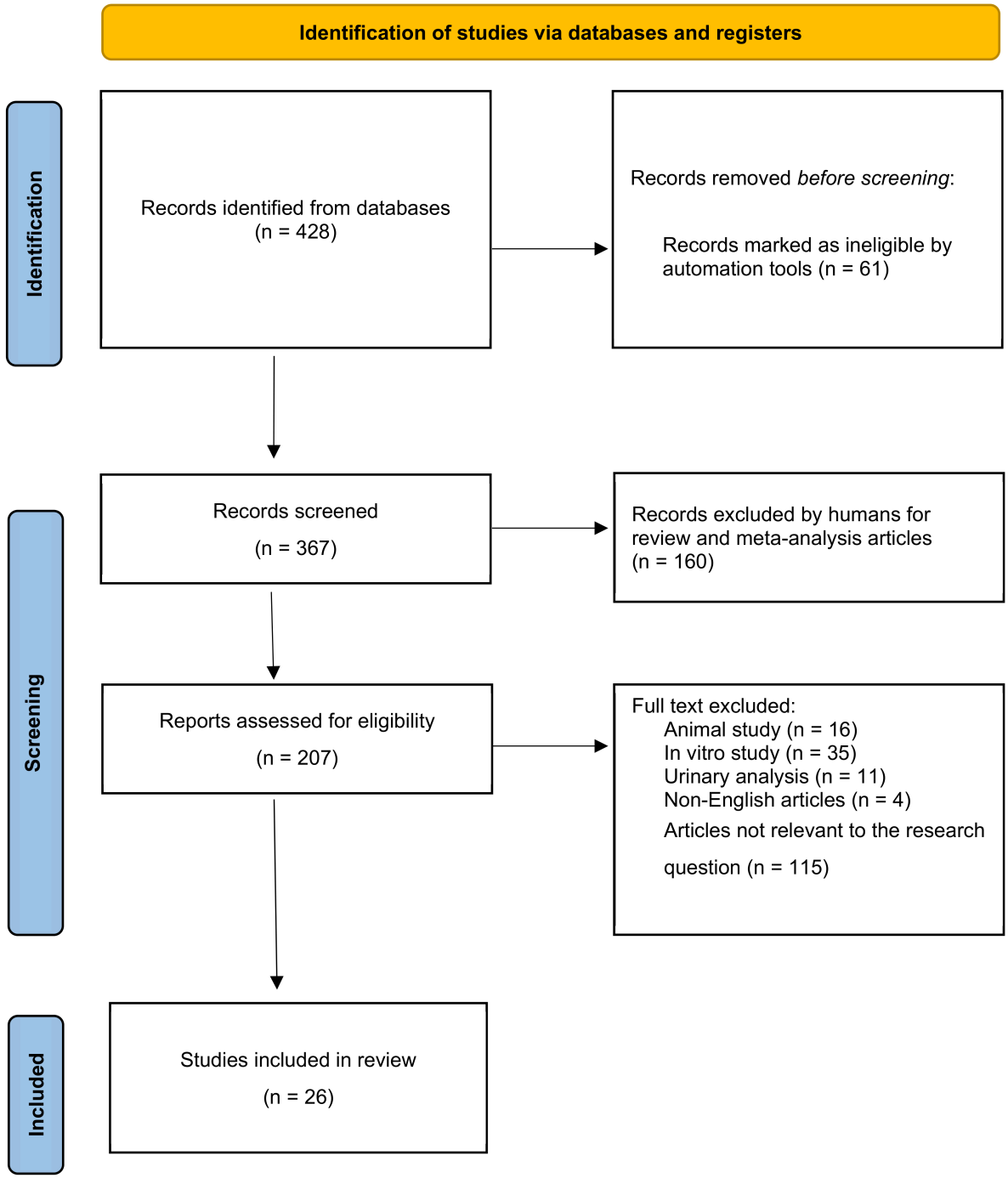


Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only.

Table 1. Study characteristics of studies included in the meta-analysis.

Study	Year	Study Location	Study Design	Study Population Case/Control	Age Range Case/Control (Mean ± SD)	BMI Case/Control (Mean ± SD)	Diagnose	Outcome	Confounders	Endocrine Disrupting Chemicals	Quality
Pauwels et al. [31]	2001	Belgium	CC	34/27	31 (25–42)/32 (24–41)	21.2 (17.2–30.7)/22.9 (18.4–36.4)	LAP	ENDO	BMI	PCB	6
Eskenazi et al. [32]	2002	USA	CC	19/277	20–≥ 40	≤20–≥25	Surgery	ENDO	Age, BMI, age at menarche, alcohol consumption, cumulative duration of oral contraceptive use, and pregnancies	Dioxin	6
Cobellis et al. [33]	2003	Italy	CC	35/24	(36.8 ± 6.7)/ (37.8 ± 5.1)	------	LAP	ENDO	------	Phthalate	5
De Felip et al. [34]	2004	Italy and Belgium	CC	23/17	18–40	------	LAP	ENDO	------	Dioxin, PCB	5
Buck Louis et al. [27]	2005	USA	NCC	32/52	(32.7 ±4.4/ (31.6 ± 4.9)	------	LAP	ENDO	Pregnancies, cigarette smoking, and serum lipids	PCB	6
Heilier et al. [23]	2004	Belgium	CC	7/10	22–45	------	Surgery	ENDO	------	PCB	5
Tsukino et al. [35]	2005	Japan	CC	58/81	(32.4 ± 3.4)/ (32.9 ± 3.9)	------	LAP	ENDO Stage >/= II	Menstrual regularity (regular or irregular) and average cycle length (days)	Dioxin, PCB	4
Heilier et al. [24]	2005	Belgium	CC	50/21	(31.3 ± 6.8)/ (31.1 ± 6)	(22.8 ± 3.5) /(24 ± 5.5)	Surgery	DIE	Age, BMI, age at menarche, cumulative duration of oral contraceptive use, familial history, and menstrual cycle	Dioxin, PCB	6
Porpora et al. [25]	2006	Italy	CC	40/40	(31.6 ± 6)/ (29.5 ± 6.1)	(21.1 ± 2.8)/(22.4 ± 4.6)	LAP	ENDO	Age and smoking habits	PCB	6

Table 1. *Cont.*

Study	Year	Study Location	Study Design	Study Population Case/Control	Age Range Case/Control (Mean ± SD)	BMI Case/Control (Mean ± SD)	Diagnose	Outcome	Confounders	Endocrine Disrupting Chemicals	Quality
Reddy et al. [29]	2006	India	CC	48/38 + 21	(26.2 ± 4.2)/ (27.4 ± 4.7) (27.1± 3.4)	(24.1 ± 2.2)/ (23.5 ±1.2) (23.9 ± 2.2)	LAP	ENDO	------	Phthalate	8
Quaranta et al. [36]	2006	Italy	CC	10/8	18–45	------	LAP	ENDO	------	PCB	4
Reddy et al. [30]	2006	India	CC	85/135	(30.6 ± 5.4)/ (30.9 ± 6.1)	(23.7 ± 4.7)/ (24.0 ± 4.5)	LAP	ENDO	------	PCB Phthalate	8
Tsuchiya et al. [37]	2007	Japan	CC	48/59	(32.6 ± 3.7) /(33.1 ± 4.1	(20.2 ± 2.1) /(21 ± 3.4)	LAP	Advanced ENDO	Age	Dioxin, PCB	7
Niskar et al. [38]	2008	USA	CC	60/64	20–45	------	LAP	ENDO	Age, pregnancies, and lipids	PCB	5
Porpora et al. [26]	2009	Italy	CC	80/78	(31.6 ± 6)/ (29.5 ± 6.1)	(21.1± 2.8)/ (22.4 ± 4.6)	LAP	ENDO	Age, smoking habits, BMI, and evidence of weight modification	Dioxin, PCB	6
Trabert et al. [39]	2010	USA	CC	251/538	18–49	------	Surgery	ENDO	Age, serum lipids, income, alcohol consumption, and DDE exposure	PCB	6
Simsa et al. [40]	2010	Belgium	CC	96/105	20–46	------	LAP	ENDO	Age	Dioxin	5
Cai et al. [41]	2010	Japan	CC	10/7	(33.5 ± 3.6)/ (36.4 ± 5.9)	(20.9 ± 2.3)/ (22.8 ± 4.6)	LAP	ENDO	------	Dioxin, PCB	5
Kim et al. [42]	2011	Korea	CC	97/169	(34.8 ± 0.7)/ (34.9 ± 0.5)	(22.7 ± 0.3)/ (21.4 ± 0.3)	Surgery	ENDO Stage III-IV	BMI, pregnancies	Phthalate	7
Buck Louis et al. [28]	2012	USA	C	190/283	(32 ± 6.8)/ (33.6 ± 7.1)	(26.3 ± 7.2)/ (29.2 ± 8.4)	LAP	ENDO	Age, BMI, breastfeeding, serum cotinine, and serum lipids	PCB	7
Vichi et al. [43]	2012	Italy	CC	63/63	(32.1 ± 6.3)/ (29.3 ± 6.5)	(21.1 ± 3)/ (22.6 ± 4.9)	LAP	ENDO	Age	PCB	7

Table 1. *Cont.*

Study	Year	Study Location	Study Design	Study Population Case/Control	Age Range Case/Control (Mean ± SD)	BMI Case/Control (Mean ± SD)	Diagnose	Outcome	Confounders	Endocrine Disrupting Chemicals	Quality
Ploteau et al. [44]	2016	France	CC	68/45	(34.4 ± 6.4)/ (32.8 ± 6.4)	(23.2 ± 4.4) /(24.3 ±4.6)	Surgery	DIE	------	Dioxin, PCB	7
Ploteau et al. [45]	2017	France	CC	24 + 25/44	(32.8 ± 6.5) (36.0 ± 5.4)/ (33.9 ± 5.9)	(23.2 ± 3.9 (23.5 ± 5.1)/ (24.7 ± 5.2)	Surgery	DIE + OvE	Serum lipids	Dioxin, PCB	7
Nazir et al. [46]	2018	Pakistan	CC	50/50	20–40	------	LAP	ENDO	Age	Phthalate	4
Pednekar et al. [47]	2018	India	CC	11/34	20–40	------	Not Definied	ENDO	Age	Phthalate	5
Kim et al. [48]	2020	Korea	CC	61/99	(29.8 ± 4.7)/ (35.6 ± 7.0)	(21.1 ± 2.7)/ (22.4 ± 3.6)	Surgery	Advanced ENDO	Age, BMI	PCB	7

Abbreviations: CC, case–control study; C, cohort study; NCC, nested case–control study; LAP, laparoscopy; ENDO, endometriosis (any stage); DIE, deep infiltrating endometriosis; OvE, ovarian endometrioma; BMI, body mass index; SD, standard deviation; PCB, polychlorinated biphenyls. Quality score refers to the NOS total score (range 0–9), detailed in Table 2. "------" indicates data not reported by the original study; "" indicates data not retrievable at the time of extraction.*

Table 2. Appraisal of methodological quality NOS assessment of the included studies in this meta-analysis. Within the table, each '*' denotes one star awarded for that specific criterion, and '**' denotes two stars awarded in the comparability domain (where applicable), consistent with the standard NOS scoring system; blank cells indicate that no star was awarded for that criterion. Thresholds for converting the NOS to AHRQ standards (good, fair, and poor): Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Study	Selection				Comparability	Exposure			Score
	Case Definition	Representativeness of Cases	Selection of Controls	Definition of Controls	Comparability by Design and Analysis	Ascertainment of Exposure	Same Method for Case & Control	Non-Response Rate	
Pauwels et al. (2001) [31]	*			*	*	*	*	*	6
Eskenazi et al. (2002) [32]	*	*				**	*	*	6
Cobellis et al. (2003) [33]	*			*	*	*	*		5

Table 2. *Cont.*

Study	Selection			Comparability		Exposure			Score
	Case Definition	Representativeness of Cases	Selection of Controls	Definition of Controls	Comparability by Design and Analysis	Ascertainment of Exposure	Same Method for Case & Control	Non-Response Rate	
De Felip et al. (2004) [34]	*			*	*	*	*		5
Buck Louis et al. (2005) [27]		*	*		**	*	*		6
Heilier et al. (2004) [23]	*			*	*	*	*		5
Tsukino et al. (2005) [35]	*				*	*	*		4
Heilier et al. (2005) [24]	*			*	*	*	*	*	6
Porpora et al. (2006) [25]	*			*	*	*	*	*	6
Quaranta et al. (2006) [36]	*			*		*	*		4
Reddy et al. (2006) [29]	*	*	*	*	**	*	*		8
Reddy et al. (2006) [30]	*	*	*	*	**	*	*		8
Tsuchiya et al. (2007) [37]	*			*	**	*	*	*	7
Niskar et al. (2008) [38]	*			*	*	*	*		5
Porpora et al. (2009) [26]	*			*	**	*	*		6
Trabert et al. (2010) [39]	*		*	*	*	*		*	6
Simsa et al. (2010) [40]	*			*	*	*	*		5
Cai et al. (2010) [41]	*			*	*	*	*		5
Kim et al. (2011) [42]	*	*	*	*	*	*	*		7
Buck Louis et al. (2012) [28]	*	*	*	*	*	*	*		7
Vichi et al. (2012) [43]	*			*	**	*	*	*	7
Ploteau et al. (2016) [44]	*	*	*	*	*	*	*		7
Ploteau et al. (2017) [45]	*	*	*	*	*	*	*		7
Nazir et al. (2018) [46]	*			*	*		*		4
Pednekar et al. (2018) [47]	*			*	*	*	*		5
Kim et al. (2020) [48]	*	*	*	*	*	*	*		7

3.2. Study Quality, Exposure Assessment, and Confounders

Methodological quality assessment using the NOS yielded scores ranging from 4 to 8 points. According to AHRQ thresholds, most studies were classified as fair-to-good quality. The selection and exposure domains were generally well addressed, whereas greater variability was observed in the comparability domain, reflecting heterogeneity in confounder adjustment strategies. A detailed appraisal of methodological quality is reported in Table 2.

Across the included studies, exposure to three main classes of EDCs was evaluated: PCBs, dioxins, and phthalates. Several studies assessed more than one class of EDCs. The most frequently considered confounding variables were age and BMI, followed by age at menarche, parity, cumulative duration of oral contraceptive use, smoking status, alcohol consumption, serum lipid levels, breastfeeding history, menstrual characteristics, evidence of weight modification, serum cotinine, and family history of endometriosis. When multiple effect estimates were available, the most fully adjusted estimates were preferentially included in the meta-analysis.

3.3. Quantitative Synthesis

The overall random-effects meta-analysis demonstrated a statistically significant association between exposure to endocrine-disrupting chemicals and endometriosis. The pooled log odds ratio (log OR) was 0.43 (standard error [SE] = 0.12), with a z-value of 3.45 and a *p*-value of 0.0006. The corresponding 95% confidence interval (0.18–0.67) did not include the null value, indicating a positive association between EDC exposure and endometriosis. Substantial between-study heterogeneity was observed ($\tau^2 = 0.19$; $I^2 = 74.45\%$), and Cochran's Q-test confirmed significant heterogeneity (Q = 69.93, df = 27; $p < 0.0001$). Individual and pooled effect estimates are illustrated in the forest plot (Figure 2).

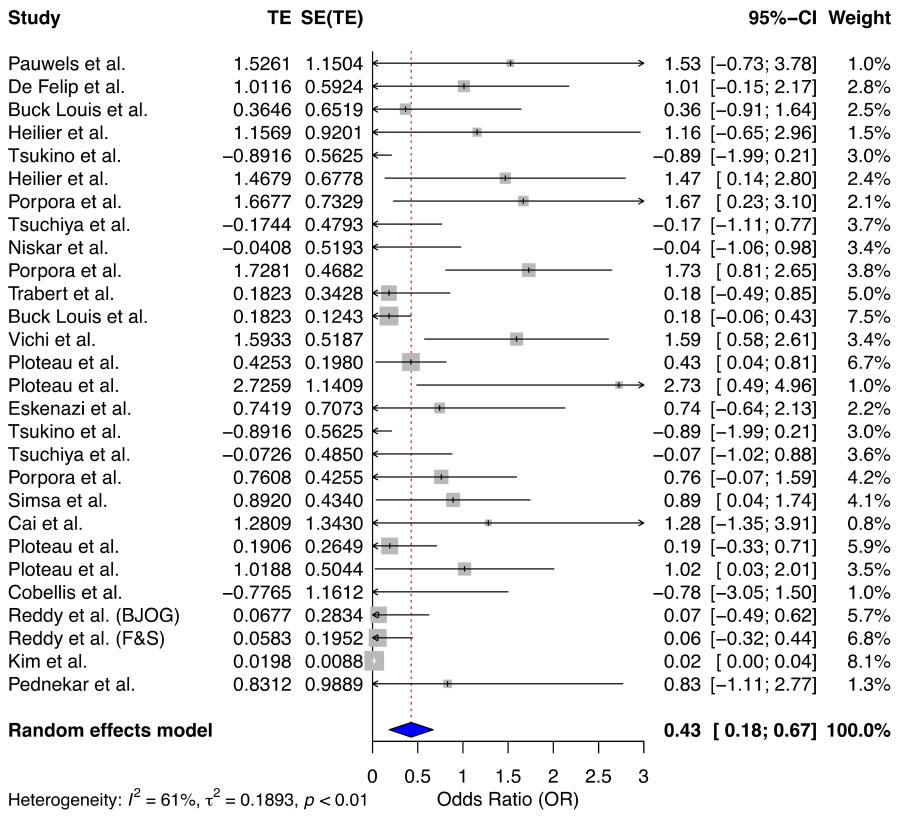


Figure 2. Forest plot of the association between EDC exposure and endometriosis, displayed on the log odds ratio (log OR) scale [23–35,37–45,47]. Blue rectangles (squares) represent the study-specific

effect estimates (log ORs), with the area of each rectangle proportional to the inverse-variance weight assigned to that study in the random-effects meta-analysis. Dashed horizontal lines extending from each rectangle denote the corresponding 95% CI. The central vertical dashed line at log OR = 0 (equivalent to OR = 1) marks the line of no effect; estimates to the right indicate a positive association, while those to the left indicate an inverse association. The grey shaded vertical band highlights the null-effect region (or the reference area around the line of no effect). Arrows at the ends of some horizontal lines indicate that the 95% CI extends beyond the plotted x-axis limits. The blue diamond at the bottom of the forest plot summarises the overall pooled estimate: its centre indicates the pooled log OR, and its lateral tips mark the 95% CI for the summary effect.

A higher-resolution, vector-based version of the forest plot (Figure 2) with enlarged confidence-interval markers and study labels has been generated and will be supplied as the production-quality figure file upon acceptance, per the Editor's formatting requirements.

Subgroup analyses by class of endocrine disruptors showed a significant association between PCB exposure and endometriosis (log OR = 0.67; 95% CI: 0.24–1.10; $p = 0.0021$), with high heterogeneity across studies ($\tau^2 = 0.40$; $I^2 = 72.21\%$; Q = 36.51; $p = 0.0009$). For dioxins, the pooled analysis did not reach statistical significance (log OR = 0.40; 95% CI: −0.03–0.83; $p = 0.0653$), although moderate heterogeneity was observed ($\tau^2 = 0.13$; $I^2 = 37.17\%$). No significant association was observed between phthalate exposure and endometriosis (log OR = 0.01; 95% CI: −0.01–0.03; $p = 0.33$), with low-to-moderate heterogeneity ($\tau^2 \approx 0$; $I^2 = 31.84\%$).

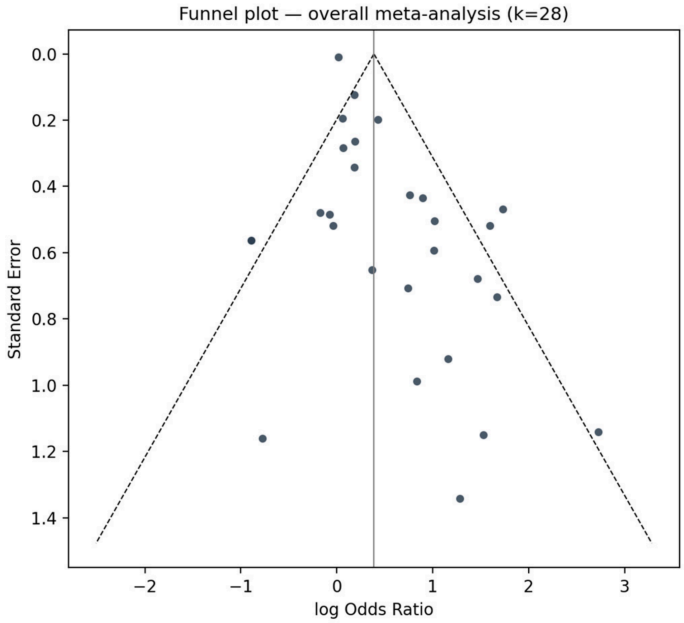
For the purpose of forest plot construction, a limited number of studies lacking effect estimates or complete authorship information were excluded. This exclusion involved three studies and did not materially affect the pooled results or heterogeneity estimates.

3.4. Sensitivity Analysis

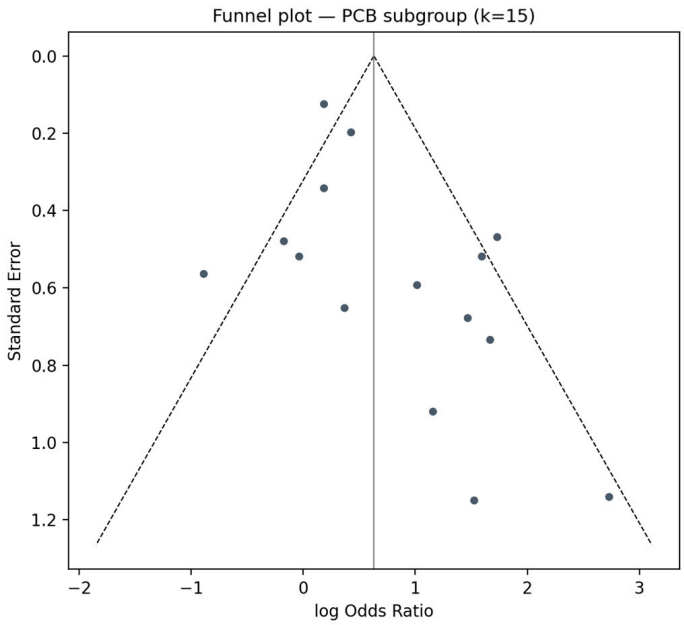
The prespecified sensitivity analysis excluding studies of low methodological quality (NOS score ≤ 4; Tsukino et al. [35]) yielded a pooled OR of 1.57 (95% CI: 1.28–1.94; k = 26) versus 1.47 (95% CI: 1.20–1.81; k = 28) in the primary analysis, with comparable heterogeneity ($I^2 = 61.3\%$ vs. 61.4%). Restricting the analysis to studies reporting adjusted, rather than unadjusted, estimates did not materially change the direction, magnitude, or precision of the pooled estimate. These sensitivity analyses indicate that the overall association between EDC exposure and endometriosis is not driven by lower-quality or unadjusted studies.

3.5. Publication Bias

Publication bias was assessed visually using funnel plots (Figure 3) and formally using Egger's regression test for funnel plot asymmetry. For the overall pooled analysis (k = 28), the funnel plot showed some asymmetry, and Egger's test was statistically significant (intercept = 1.02, 95% CI: 0.49–1.54; t = 3.98, df = 26, $p = 0.0005$), indicating evidence of small-study effects, publication bias, or both. For the PCB subgroup (k = 15), Egger's test was also significant (intercept = 1.31; t = 2.19, df = 13, $p = 0.047$). For dioxins (k = 8) and phthalates (k = 5), Egger's test was not statistically significant ($p = 0.66$ and $p = 0.72$, respectively), but the number of studies in these subgroups is below the threshold ($k \geq 10$) generally recommended for reliable interpretation of this test, so these subgroup results should be regarded as exploratory. Taken together, these findings suggest that the overall and PCB-specific pooled estimates may be inflated by publication or small-study effects, and we now state this explicitly as a limitation of the quantitative synthesis (see Discussion).



(**a**)



(**b**)

Figure 3. Funnel plots for the assessment of publication bias and small-study effects. (**a**) Funnel plot of the overall meta-analysis (log odds ratio vs. standard error [SE]). Each circle (dot) represents an individual study included in the meta-analysis, plotted on the x-axis by its log odds ratio (log OR) and on the y-axis by its standard error (SE, displayed on an inverted scale, with smaller SEs for larger studies at the top and larger SEs for smaller studies at the bottom). The central vertical dashed line corresponds to the pooled summary log OR from the random-effects model. The outer diagonal dashed lines represent the pseudo 95% confidence limits around the pooled estimate, forming the expected funnel-shaped region within which 95% of studies would be expected to fall in the absence of heterogeneity and publication bias. Asymmetry in the distribution of dots (e.g., missing studies in the lower left or lower right corners) suggests the presence of small-study effects, publication bias, or both. (**b**) Funnel plot restricted to the polychlorinated biphenyls (PCB) subgroup analysis, following the same plotting conventions as panel (**a**).

4. Discussion

In this systematic review and meta-analysis, we evaluated the association between exposure to selected EDCs and the risk of endometriosis by synthesizing evidence from observational studies with surgically confirmed diagnoses. The pooled analysis indicates a statistically significant association between overall exposure to EDCs and endometriosis, with a particularly robust signal emerging for PCBs. In contrast, the evidence for dioxins suggests a trend toward increased risk that does not reach statistical significance, while no association was observed for phthalates.

The most consistent finding of this meta-analysis is the significant association between PCB exposure and endometriosis. PCBs are persistent organic pollutants characterized by long biological half-lives and strong lipophilicity, leading to accumulation in adipose tissue and prolonged internal exposure. These properties may partly explain the stronger and more consistent association observed for PCBs compared with other classes of EDCs. Experimental and mechanistic studies have shown that PCBs can interfere with estrogen signaling, immune modulation, and inflammatory pathways, all of which are central to the pathophysiology of endometriosis. The present quantitative synthesis supports these biological hypotheses by demonstrating increased odds of endometriosis among women exposed to PCBs, albeit with substantial heterogeneity across studies.

The high heterogeneity observed in the PCB subgroup likely reflects differences in study populations, exposure assessment methods, congener profiles, timing of exposure, and confounder adjustment. PCBs comprise a heterogeneous group of compounds with varying degrees of estrogenic or anti-estrogenic activity, and most epidemiological studies assess aggregated PCB measures rather than individual congeners. Moreover, exposure is typically measured at a single time point, which may not accurately reflect cumulative or early-life exposure relevant to disease initiation. These factors may contribute to between-study variability and should be considered when interpreting the pooled estimates.

For dioxins, the pooled analysis showed a non-significant association with endometriosis, accompanied by moderate heterogeneity. Although experimental and animal studies have consistently suggested a role for dioxins in the development of endometriosis-like lesions, epidemiological evidence remains less conclusive. The lack of statistical significance observed in this meta-analysis may be attributable to limited sample sizes, reduced statistical power, and variability in exposure levels across populations. Additionally, background exposure to dioxins in the general population has decreased over time in many countries, potentially attenuating detectable associations in more recent studies.

Phthalates did not show any significant association with endometriosis in the present analysis, and heterogeneity was relatively low. Unlike PCBs and dioxins, phthalates are non-persistent chemicals with short biological half-lives, and their exposure is highly variable over time. Most studies included in this meta-analysis relied on single measurements, which may inadequately capture long-term exposure patterns relevant to chronic disease development. Furthermore, differences in the specific phthalate metabolites assessed and in analytical methods may further limit comparability across studies. Therefore, the absence of an observed association should be interpreted cautiously and does not necessarily exclude a potential role of phthalates in specific subgroups or exposure windows.

An important strength of this meta-analysis is the restriction to studies with surgically confirmed endometriosis, which minimizes outcome misclassification and enhances diagnostic specificity. In addition, we preferentially included adjusted effect estimates to reduce confounding bias, and methodological quality was systematically assessed using the NOS. Nevertheless, several limitations must be acknowledged. First, all included studies were observational in nature, precluding causal inference. Second, residual confounding cannot be excluded, as adjustment strategies varied and not all relevant factors, such as dietary

habits, occupational exposure, or early-life environmental exposures, were consistently accounted for. Third, reverse causality remains a concern, as endometriosis itself may influence body composition or lipid metabolism, potentially affecting circulating levels of lipophilic pollutants.

Additional limitations should be acknowledged. First, the pooled effect estimates should be interpreted alongside the publication-bias analysis presented in Section 3.5: Egger's test indicated significant funnel-plot asymmetry for the overall and PCB-specific analyses, raising the possibility that small studies with null or negative findings were less likely to be published or identified, which could inflate the apparent strength of association; the true effect size for PCBs and for EDCs overall may therefore be smaller than reported herein. Second, this review was registered in PROSPERO only in 2026 (CRD420261373282), after data extraction and analysis had already begun; because the included evidence itself spans 2001–2020, this registration was necessarily retrospective and cannot be considered to provide the same protection against selective outcome reporting or post hoc modification of the review protocol that prospective registration affords. We report this transparently as a limitation, rather than presenting registration as evidence of a priori methodological rigor. Third, a small number of included studies shared research groups and, in some cases, overlapping recruitment sites (see Section 2.4); although available information suggested non-identical case series, participant-level overlap could not be definitively excluded using published data alone. Fourth, we did not perform a formal GRADE (or equivalent) certainty-of-evidence assessment (see Section 2.4), so our conclusions rely on NOS-based study quality and standard heterogeneity statistics rather than a structured certainty rating; this should be incorporated in future updates of this review.

The substantial heterogeneity observed in the overall analysis underscores the complexity of studying environmental exposures in relation to endometriosis. Differences in study design, population characteristics, exposure assessment, and statistical modeling likely contribute to variability in effect estimates. In particular, laboratory quantification of PCBs and dioxins varied across studies (gas chromatography–mass spectrometry with differing congener panels, lipid-adjustment procedures, and limits of detection), which is a plausible additional source of the observed I^2 beyond the population- and design-related factors discussed above and is not fully separable from them using study-level (rather than individual-participant) data. Future research should prioritize harmonized exposure assessment protocols, longitudinal study designs, and the evaluation of critical windows of susceptibility, including prenatal and early-life exposure. Moreover, disentangling the effects of individual compounds and their mixtures represents a crucial challenge for advancing the field.

5. Conclusions

This systematic review and meta-analysis provides evidence of a significant association between exposure to endocrine-disrupting chemicals and endometriosis, with the strongest and most consistent association observed for polychlorinated biphenyls. In contrast, the evidence for dioxins remains inconclusive, and no significant association was identified for phthalates. The heterogeneity observed between studies highlights the influence of methodological differences, variability in exposure assessment, and potential residual confounders.

Although these findings do not establish causality, they support the hypothesis that persistent endocrine-disrupting chemicals, particularly PCBs, may contribute to the development or progression of endometriosis. Further high-quality longitudinal studies with standardized exposure assessment and comprehensive adjustment for confounding factors are needed to clarify the role of specific compounds, timing of exposure, and biological

mechanisms. A better understanding of environmental risk factors could ultimately contribute to more effective prevention strategies and personalized management approaches for women with endometriosis.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/women6030049/s1. The PRISMA 2020 Main Checklist.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Search strategies used for the systematic review, executed for the period January 2000–August 2025, restricted to English-language records. Searches combined controlled vocabulary (MeSH/Emtree) with free-text keywords using Boolean operators, as detailed below.

Table A1. Full electronic search strategies.

Database (Interface)	Full Search String
PubMed (pubmed.ncbi.nlm.nih.gov)	((“Endometriosis”[MeSH Terms] OR “endometriosis”[Title/Abstract]) AND (“Endocrine Disruptors”[MeSH Terms] OR “endocrine disrupt*”[Title/Abstract] OR “polychlorinated biphenyls”[MeSH Terms] OR “PCB*”[Title/Abstract] OR “dioxins”[MeSH Terms] OR “dioxin*”[Title/Abstract] OR “phthalates”[MeSH Terms] OR “phthalate*”[Title/Abstract] OR “bisphenol A”[MeSH Terms] OR “BPA”[Title/Abstract])) AND (“2000/01/01”[Date-Publication]: “2025/08/31”[Date-Publication]) AND English[Language]
EMBASE (Ovid interface)	1. exp endometriosis/ 2. endometrio*.ti,ab. 3. 1 OR 2. 4. exp endocrine disruptor/ 5. exp polychlorinated biphenyl/ 6. exp dioxin/ 7. exp phthalate/ 8. exp bisphenol A/ 9. (endocrine disrupt* OR PCB* OR dioxin* OR phthalate* OR bisphenol*).ti,ab. 10. 4 OR 5 OR 6 OR 7 OR 8 OR 9. 11. 3 AND 10. 12. limit 11 to (english language and yr = “2000–2025”)
Cochrane CENTRAL (Cochrane Library)	#1 MeSH descriptor: [Endometriosis] explode all trees; #2 endometrio*:ti,ab,kw; #3 #1 OR #2; #4 MeSH descriptor: [Endocrine Disruptors] explode all trees; #5 (endocrine disrupt* OR PCB* OR polychlorinated biphenyl* OR dioxin* OR phthalate* OR bisphenol*):ti,ab,kw; #6 #4 OR #5; #7 #3 AND #6, limited to records published 2000–2025

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