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Environmental risk factors for endometriosis: A critical evaluation of studies and recommendations from the epidemiologic perspective

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Abstract

Purpose of review: Recent studies of environmental chemicals and endometriosis were critically evaluated from the epidemiologic perspective to identify aspects of study design and analyses that may contribute to discrepant results across studies.

Recent findings: Of the 29 studies reviewed, 12 studies used new approaches to population-based sampling. The remaining studies were conducted primarily among patients undergoing pelvic surgery; controls may not represent the exposure experience of the underlying study base, resulting in biased estimates of associations. Most studies used biologic specimens collected near diagnosis and varied in analytic approaches to minimize bias. Few studies investigated ovarian, deep-infiltrating, and peritoneal endometriosis presentations separately.

Summary: Recommendations to move the field forward include: (1) control selection from a defined study base, (2) exposure characterization during the etiologically-relevant window, (3) employment of best practices to minimize bias in analyses, and (4) separate consideration of endometriosis presentations that may be etiologically-distinct entities.

Keywords

endometriosis; environment; persistent organic pollutants; phthalates; bisphenol A; metals

Introduction

Endometriosis is characterized by the presence of endometrial glands and stroma outside the uterus, usually in the peritoneal cavity. Endometriosis is associated with substantial

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morbidity; women with endometriosis frequently report pain symptoms, including dysmenorrhea, chronic pelvic pain, and dyspareunia [1]. For many women, these symptoms can be chronic and debilitating, substantially interfering with all aspects of life – daily activities, work productivity, school performance, and personal relationships [2–5]. This serious condition is estimated to affect approximately 10% of reproductive-age women globally, although reported prevalence estimates vary widely [6]. This is due to surgical visualization being required to definitively diagnosis the disease.

The etiology of endometriosis is not well understood. Several theories have been hypothesized for disease pathogenesis which fall into two categories – in situ-based and transplantation-based theories (as reviewed by Lagana et al [7]). In situ-based theories hypothesize that endometrial-like stroma and glands originate from local tissues that undergo metaplasia or from cells of primitive endometrial tissue misplaced *in utero*, outside the expected area of Müllerian duct development. On the other hand, transplantation-based theories hypothesize that stroma and glands from the eutopic endometrium are displaced to locations outside the uterus. The most common transplantation-based theory is the retrograde menstruation theory introduced by Sampson in 1927 [8]. In that theory, endometriosis occurs from the reflux of endometrial tissue during menstruation. Although several theories have been proposed, one theory is not able to explain all manifestations of endometriosis.

It is additionally recognized that endometriosis is multifactorial, involving anatomical, hormonal, immunological, estrogenic, genetic, epigenetic, and environmental factors. Central to disease pathogenesis is estrogen. Estrogen regulates the key pathological processes in endometriosis, including immunologic, inflammatory, angiogenic, and antiapoptotic cellular and molecular mechanisms that promote the persistence and progression of endometriotic lesions [1]. Given that estrogen is the driver of disease, it is plausible that endometriosis risk could be affected by exposure to endocrine-disrupting chemicals.

An endocrine-disrupting chemical is defined as “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action” [9]. In the past decade the investigation into the human health effects of endocrine-disrupting chemicals has substantially grown, with a set of prototypical endocrine-disrupting chemicals being well-established (as reviewed by Gore et al [10]). This set includes Bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), the organochlorine pesticide *p,p’*-dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), the perfluoroalkyl substance (PFAS) perfluorooctanoic acid (PFOA), and the dioxin 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

Over the past several decades, these endocrine-disrupting chemicals and others have been investigated in relation to endometriosis risk. Several comprehensive reviews have been conducted of these studies, all reporting a common conclusion: the results across studies are inconsistent [11–17]. The authors of these reviews, and of the individual studies themselves, have offered reasons for the disparate results. The reasons include differences between studies in study population characteristics (geographical, dietary, parity/lactation history),

biologic media used for measurement of environmental chemicals, laboratory method for quantification of analytes, the specific compounds investigated, confounder adjustment, heterogeneity of disease, and undiagnosed disease among controls [11–17].

However, other aspects of study design and analyses may also contribute to the discrepant results. The approach to control selection can have a considerable impact on the validity of a case-control study. If controls are not sampled from the identified study base that gave rise to cases, they may not represent the distribution of exposure of the study base, resulting in biased estimates of associations [18]. Substantial bias can also be introduced from the approaches used in analyses to address samples with non-detectable concentrations of environmental chemicals [19–21] and to adjust for urinary dilution or lipid concentrations for environmental contaminants measured in urine or blood [22, 23].

Hence, the purpose of this review was to critically evaluate studies of environmental chemicals and endometriosis published in the past decade from the epidemiologic perspective, to identify overlooked aspects of study design and approaches to analyses that may contribute to discrepant results. In doing so, this review describes recently published studies not included in prior reviews. This review also highlights the important contributions made by studies in this field over the past decade and provides recommendations to move the field forward.

Article search approach and criteria for inclusion

Although the environment encompasses an array of exposures, including those related to nutrition, pharmaceutics, smoking, alcohol, occupation, zoonotic and vector-borne diseases, radiation, water quality, and food safety, this review focuses on environmental chemicals, including those in air pollution, in relation to endometriosis risk. To identify articles in this area, a search was conducted using PubMed and the search terms environment*, air pollution, dioxin, metal*, cadmium, zinc, manganese, arsenic, mercury, lead, chromium, trace metals, trace elements, polychlorinated, PCB*, organochlorine, pesticide*, perfluoro, phthalate*, benzophenone, and bisphenol. Searches were conducted separately for each environmental search term, with the Boolean operator “AND”, and search term endometrio*. The truncation (“wild card”) option was used to capture endometriosis, endometrioma, and endometriotic disease. All search terms were qualified with the [Title/Abstract] field tag. Articles were also identified from the reference list of reviewed articles.

Studies selected for inclusion in the review were observational human studies written in English and published in the past decade, between January 2010 and December 2019, reflecting the substantial expansion in endocrine disruptive chemical research after the publication of the first Endocrine Society Statement in 2009 [24]. Articles were further restricted to analytic studies in which endometriosis was the outcome of interest, and women with and without endometriosis were compared. Descriptive human studies, *in vitro* studies using endometrial stromal cell samples from women, and studies considering a combined outcome of endometriosis and adenomyosis were not included. Adenomyosis, characterized by the presence of endometrial stoma and glands within the myometrium, is generally considered a separate disease entity from that of endometriosis and the diagnosis of the two conditions substantially differ, with adenomyosis historically being diagnosed after

hysterectomy [25]. Given the movement away from reliance on statistical significance testing and towards interpreting effect size and precision [26, 27], studies not reporting measures of association and precision (e.g., odds ratio and 95% confidence interval) were also excluded. For studies additionally examining gene-environment interactions, only the associations between environmental chemicals and endometriosis were evaluated.

The studies were reviewed with special attention to study design, including study population, outcome definition, and control/non-case selection (Table 1) as well as analyses, including covariate adjustment, modelling of the exposure-disease relationship, approach to handling values below the limit of detection, adjustment for urinary dilution or lipid concentration, and main findings (Table 2). To allow for the comparison of results across studies, the odds ratios (OR) or hazard ratios (HR) and accompanying 95% confidence intervals (CI) are provided for each study in Table 2. For some chemical classes, a substantial number of analytes were investigated. Due to limited space, the ORs and 95% CIs are only provided for the environmental chemicals most frequently reported across studies for the following chemical classes: 1) organochlorine pesticides (OCPs): β-hexachlorocyclohexane (β-HCH), *trans*-nonachlor, hexachlorobenzene (HCB), oxychlordane, *p,p'*-DDE; 2) PCBs: congeners 118, 138, 153, 156; 3) PBDEs: congeners 47, 99, 100, 153, 154; 4) dioxins: 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD; 5) furans: 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,4,7,8,9-HpCDF, OCDF; 6) PFAS: perfluoroalkyls perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorohexane sulfonic acid (PFHxS); 8) metals: lead, cadmium, total mercury; and 9) phthalate metabolites: mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP). The associations for summed chemicals are not provided.

Results

Twenty-four studies were included in the review (Tables 1 and 2) [28–51]. The studies were conducted in ten countries with the corresponding number of studies as follows: United States (n=13), Taiwan (n=2), Korea (n=2), Belgium (n=1), Italy (n=1), Japan (n=1), Spain (n=1), France (n=1), Iran (n=1), and Brazil (n=1) (Table 1). The studies evaluated the following environmental exposures: air pollution (n=1), OCPs/PCBs/dioxins/furans/PBDEs/polybrominated biphenyls (PBB) (n=9), PFAS (n=2), metals (n=2), BPA/phthalate metabolites (n=9), and benzophenone-type ultraviolet (UV) filters (n=1). Five studies used data from the Endometriosis: Natural History, Diagnosis and Outcomes (ENDO) study [35–37, 39, 40] and four studies used data from the Women's Risk of Endometriosis (WREN) study [31, 41, 42, 44]. The remaining 15 studies were conducted among unique study populations. In the ENDO study, results were reported for two cohorts, an operative cohort and population cohort [35–37, 39, 40]. Given the substantial differences in study participant sampling for these two cohorts, going forward, the two cohorts are considered separate studies. A revised total of 29 studies were reviewed.

Hospital or clinic-based studies

Of the 29 studies, 17 studies (59%) were hospital or clinic-based studies conducted among patients. A few of these studies were not defined as case-control studies, but since comparison groups were formed according to endometriosis case status, case-control study terminology is used to describe the studies. One study was conducted among patients of a gynecology and infertility center, with cases being patients referred with ovarian endometrioma and controls being patients who were previously seen at the center for a problem who were returning for routine care [50]. The remaining 16 studies were conducted among women undergoing laparoscopy, laparotomy or other pelvic surgical procedures [28–30, 33–40, 45, 46, 48, 49, 51]. Five of these studies used data from the operative cohort of the ENDO study, which was composed of patients scheduled for laparoscopy or laparotomy at one of five hospital surgical centers in Salt Lake City, Utah and nine clinical centers in San Francisco, CA. Across the 16 studies, the indications for surgery included pelvic pain, pelvic mass, menstrual irregularities, uterine fibroids, tubal ligation, infertility, Fallopian tube abnormalities/disease, ovarian cysts, hydrosalpinx, uterine cervical carcinoma, and genital prolapse.

Eight studies additionally applied exclusion rules to the control group that were not applied to the case group, such as requiring a laparoscopically normal pelvis [30], no complaints of infertility or pelvic pain [38], no history of pelvic surgery [46], no clinical symptoms including chronic pelvic pain, dysmenorrhea, dyspareunia, or history of infertility [49], no abdominal pain, diarrhea, dysmenorrhea, dyspareunia, or serum cancer agent 125 (CA-125) levels greater than 35 U/ml [48], no laparoscopically-confirmed leiomyoma or adenomyosis [29], no adenomyosis, invasive cervix carcinoma or ovarian cancer [34], and no past or present symptoms related to endometrioma [50].

Population-based studies

Twelve of the 29 studies used population-based sampling designs [35, 39, 47, 36, 37, 43, 40, 31, 41, 44, 42, 32]. Four studies used data from the WREN study, a population-based case-control study that was conducted among enrollees of an integrated health care system providing both insurance coverage and health care [31, 41, 44, 42]. Premenopausal female enrollees ages 18–49 years with an intact uterus and at least one ovary enrolled in the health care system for ≥6 months in years 1996–2001 formed the study base; from this study base controls were directly and randomly sampled. Cases diagnosed for the first time with surgically-visualized endometriosis were identified. ICD-9 codes were initially used to identify potential cases whose medical records, including operative notes and pathology reports, were then reviewed to confirm the surgical-visualization of disease.

Five studies were conducted using data from the population cohort of the ENDO study [35, 39, 36, 37, 40]. Study participants in the population cohort were matched to the previously-described operative cohort on age and residence within a 50-mile radius of the clinical centers which was the geographical residential area for ~90% of the operative cohort [52]. Since the operative cohort consisted of patients from one of 14 clinical centers in Utah and California, the population cohort was identified using a population database in Utah and telephone directory in California. Participants in the population cohort were screened by

magnetic resonance imaging (MRI) to detect endometriosis. Using MRI, primarily ovarian endometriomas were visualized [52].

One study was conducted using data from the ongoing U.S.-based prospective cohort study, Nurses' Health Study II (NHSII) [43]. In the NHSII, 116,687 female registered nurses residing in the United States ages 25–43 years enrolled in the study in 1989. Since enrollment, the cohort has been followed every two years by questionnaire. Cases of endometriosis were identified by self-report of laparoscopically-confirmed endometriosis.

Two studies used data from select cycles of the National Health and Nutrition Examination Survey (NHANES), which collects cross-sectional data on a sample representative of the U.S. population [47, 32]. Cases of prevalent endometriosis were ascertained by self-report on whether a doctor or other health professional had ever told the study participant she had endometriosis.

Exposure measurement

Most studies (n=26) used biologic samples collected at or near the time of diagnosis for the measurement of environmental chemicals, although the timing of sample collection was not explicitly stated in eight studies [39, 29, 34, 36, 48, 51]. A single biologic sample was used to characterize past exposure. For two studies using data from cycles of NHANES, exposure measurement transpired a mean of 11.2 years after diagnosis in one study [47] and a median of 9 years in the other study [32].

In the prospective cohort study using NHS II data [43], exposure to air pollution over the years of participant follow-up until diagnosis or censoring was assessed by linking geocoded participant home addresses information to data from the U.S Census Topologically Integrated Geographic Encoding and Referencing System and US Environmental Protection Agency Air Quality System. From this data linkage, distance from roadways and exposure to particulate matter were estimated.

Outcome definition

Many studies used a definition that required surgical visualization of endometriosis (n=20). Four of these studies used data from the operative notes to further restrict cases to those meeting the definition of endometriotic disease [31, 41, 44, 42]; three of these studies also used phenotype information on ovarian and non-ovarian peritoneal endometriosis [31, 41, 44]. Some studies additionally required histopathologic confirmation (n=4) [29, 30, 38, 48], with one of these studies requiring an equal number of cases within each stage of the revised American Fertility Society (rAFS) staging system [30]. Four studies restricted endometriosis to surgical visualization of deep-infiltrating endometriosis (n=1) [46], surgical visualization of deep-infiltrating endometriosis with rAFS staging III or IV (n=1) [49], and surgical and histologic confirmation of ovarian endometriosis restricted to stages III and IV of the American Society of Reproductive Medicine revised (ASRMr) staging (n=2) [34, 45]. For the remaining studies, endometriosis was detected by MRI (primarily ovarian endometriosis) (n=5) [35–37, 39, 40], self-report of ever being told by a health provider they had endometriosis (prevalent disease) (n=2) [32, 47], and sonographic evidence of ovarian endometriosis (n=1) [50]. In one study, cases were those with histologic-confirmation or

MRI-detected endometriosis [51]. Twelve studies reported on the rAFS or ASRMr staging of endometriosis [28, 30, 33–40, 45, 49]. In terms of numbers of cases, ten studies involved <50 endometriosis cases [28, 29, 33, 35–37, 39, 40, 46, 51] and ten studies involved 50–99 cases [30, 32, 34, 38, 42, 45, 47–50]. Nine studies had ≥100 cases [31, 35–37, 39–41, 43, 44].

Covariate adjustment

Of the 29 studies included in this review, three did not adjust for confounding variables in the statistical analyses [33, 38, 51]. A few studies adjusted for parity status at the time of diagnosis or after [34, 45, 50], although infertility may be a consequence of disease. Four studies reported using directed acyclic graphs to select the variables for adjustment [41, 42, 44, 49].

Statistical modeling that allows for a flexible exposure-disease functional form

Two studies did not state how environmental chemicals were modelled in the regression model [34, 50]. Five studies modelled the exposure both continuously and categorically [47, 28, 36, 43, 40]. A nearly equal number of studies modelled exposure continuously (most per 1-standard deviation change) (n=9) [35, 39, 45, 37, 46, 49] and categorically (median, tertiles, or quartiles) (n=11) [33, 29, 48, 51, 30, 31, 41, 44, 42, 38, 32].

Approaches to account for lipids for lipophilic contaminants measured in blood

Of the 9 studies measuring lipophilic chemicals in serum or plasma, four studies lipid-standardized concentrations [30, 33, 38, 49] and five studies included lipids as a covariate in the regression model [28, 31, 35, 41].

Approaches to account for urinary dilution for environmental contaminants measured in urine

Thirteen studies measured environmental chemicals in urine. Two studies (considering the population cohort and operative cohort as separate studies) did not report on the adjustment for urinary dilution for contaminants measured in urine [36] and one study reported that urinary creatinine was not measured [50]. The remaining studies measured urinary creatinine and either standardized concentrations (dividing the contaminant concentration by urinary creatinine concentration) (n=6) [29, 32, 40, 45, 51] or included urinary creatinine as a covariate in the regression model (n=4) [39, 42, 44].

Approaches to handling values below limit of detection

Of the 29 studies reviewed, nearly a quarter of studies (n=7) did not state how samples with concentrations below the limit of detection (LOD) were addressed in the analyses [39, 29, 45, 34, 43, 38]. Of those reporting approaches, the most commonly used were substitution (using 0, LOD, LOD/√2, LOD/2) (n=8) [33, 47, 48, 51, 49, 50, 44, 32] and machine observed values (n=7) [35, 28, 36, 40]. The remaining studies used imputation-based approaches (n=2) [41, 42], recovery-adjusted values (n=2) [37], deletion (n=2) [46, 30], and inclusion of non-detects in lowest category of exposure (n=1)[31]. Several studies did not investigate individual analytes with a substantial percent of non-detectable samples.

Consistencies in results across studies

The results across studies for the same environmental chemical appeared inconsistent. To understand whether studies employing similar approaches yielded similar results, the results for persistent environmental chemicals from studies with similar study population sampling, endometriosis phenotype, exposure measurement, and statistical approaches were compared. Two studies conducted in a similar manner were identified. These two studies were conducted in the United States and used a population-based sampling frame to investigate the OCPs β-HCH, γ-HCH, *trans*-nonachlor, HCB, oxychlordane, *p,p'*-DDE, and *p,p'*-DDT in relation to ovarian endometriosis – the population cohort in the ENDO study and the WREN population case-control study. Both studies measured the OCP analytes in serum, employed covariate adjustment to account for lipid concentrations, and had data on ovarian endometriosis. The directions of associations for ovarian endometriosis were similar for most of the OCP analytes in the two studies (Table 2). The results for PCBs could not be compared between the two studies as the ORs and 95% CIs between PCBs and ovarian endometriosis were not reported in the WREN study.

Comments

The study of environmental chemicals and endometriosis continues to be an active area of research. During the past decade the range of environmental chemicals investigated in relation to endometriosis expanded, and now includes perfluoroalkyl substances, air pollution, and benzophenone-type UV filters. In addition, new population-based study designs were introduced. However, across studies, approaches to control selection and analyses to address issues related to studying environmental chemicals varied substantially. The following discussion describes how some approaches may result in biased estimates of the association and recommendations are provided to move the field forward.

(1) Recommendation: Selection of controls from a defined study base

Over half of the studies in this review were clinic or hospital-based studies in which controls were selected among patients undergoing laparoscopy or other pelvic surgery. The selection of controls in this manner allows for the identification of a disease-free comparison group using the same approach as that used to identify cases. However, this approach does not appear to follow a key principle of valid case-control study design: the identification of a study base from which the cases arose [53]. The selection of controls from a study base allows controls to be selected *independent* of exposure. Violation of this key principle can yield wrong results [54]. Bias can be introduced when controls do not represent the exposure experience of the study base that gave rise to cases. Bias from the selection of surgical controls may be substantial when investigating exposures related to hormonal profiles [55], such as endocrine-disrupting chemicals, as these exposures may be associated with the medical indications warranting surgery. In the studies reviewed, the indications for laparoscopy or other pelvic surgery included menstrual irregularities, uterine fibroids, infertility, and ovarian cysts. Associations between these conditions and exposure to endocrine-disrupting chemicals have been reported [56, 57, 10, 58–60]. Further support that the exposure distribution among surgical controls may differ from the underlying study base was provided in a population-based study of OCPs and endometriosis [41]. Among the

population-based controls, those who had a history of undergoing laparoscopy had greater concentrations of oxychlordane, *trans*-nonachlor, HCB, and mirex compared to those without such a history.

The identification of a study base for a disease such as endometriosis which requires surgical visualization for diagnosis can be exceedingly difficult, particularly when the series of cases are identified first. The factors leading to surgical diagnosis can be complex and include the severity of symptoms, referral patterns, health care access, and agreeing to surgical evaluation [61, 62]. When controls cannot be randomly sampled from the study base that gave rise to cases, a non-random subset of hospital or clinic-based controls can be selected if a key assumption can be met: the non-random control subset represents the exposure distribution of the underlying study base [53]. Using hospital controls as the example, Wacholder et al (1992) posited that this assumption is reasonable when two conditions are satisfied: 1) hospital controls would have sought care at the same hospital for the case disease, and cases would have sought care at the same hospital for the control disease, and 2) the reason for hospital admission for the control is unrelated to exposure [53]. Translating these conditions to the clinic-based controls undergoing pelvic surgery, the second condition is difficult to satisfy as the indications for surgery may be associated with exposure, as previously described.

Several studies in this review applied additional exclusion rules to surgical controls, including no complaints of infertility or pelvic pain, no history of pelvic surgery, and no symptoms of chronic pelvic pain, dysmenorrhea, and dyspareunia. Although the rationale for these rules were not provided, it appears that they were employed to minimize undiagnosed endometriosis among the controls, rather than select surgical patients with conditions not associated with exposure. The application of exclusion criteria to only controls violates the study base principle that rules should be applied equally to cases and controls, and could additionally contribute to biased estimates of associations [53].

A common concern mentioned in hospital or clinic-based studies in this review was the presence of undiagnosed endometriosis among controls who have not undergone laparoscopic evaluation – the gold standard in diagnosing endometriosis [62]. Three aspects of sampling from a study base alleviate this concern. First, as discussed previously, the selection of controls from an identified study base allows the controls to represent the exposure experience in the population that gave rise to cases. This provides for valid results. Second, the prevalence of undiagnosed disease among controls is likely to be low, particularly if a disease definition focused on progressive disease with interference of normal physiologic function is employed, such as the endometriotic disease definition proposed by Holt and Weiss [55]. Using this definition, the prevalence of undiagnosed symptomatic disease is estimated to be <2% [55]. Third, the impact of systematic error on the estimate of association from case under-ascertainment and disease misclassification can be evaluated using quantitative bias analyses, considering different levels of case under-ascertainment [63, 64]. In this epidemiologist's opinion, a valid case-control study design with some disease misclassification is preferable to a design that may not yield valid conclusions due to controls not representing the exposure experience of the source population.

Given these challenges, the introduction of new approaches to population-based sampling of study participants in the past decade has been an important advancement in study design for endometriosis research. This is exemplified by the population cohort of the ENDO study, the WREN study, and use of data from NHS II. For the population cohort of the ENDO study, participants were screened by MRI to detect cases of endometriosis. The WREN study employed the optimal approach to case-control study design; controls were directly sampled from a defined integrated health system population that gave rise to cases. By conducting the study among health plan enrollees, the financial barriers to accessing care were minimized and the likelihood that controls would seek care by the same providers as cases if they had symptoms was increased. The use of data from the large, epidemiologic NHS II cohort study shifted the paradigm for epidemiologic endometriosis research from case-control to prospective cohort study design.

(2) Recommendation: Exposure characterization during the etiologically-relevant window for disease onset

In the present review, most studies measured environmental chemical concentrations using a single sample collected at or near the time of endometriosis diagnosis. The measurement of environmental chemicals at diagnosis may not reflect body burden at the time of disease development. Reasons for this include: (1) the documented long diagnostic delay, ranging on average 4 to 10 years between symptom onset and endometriosis diagnosis [5, 65–67]; (2) the measurement of less persistent environmental chemicals for which a single measurement may characterize more recent exposure. At the extreme end, exposure only over the past few hours or day may be characterized by the measurement of non-persistent chemicals such as Bisphenol A and phthalates that are rapidly metabolized by the body after exposure [10]; (3) the use of a biologic matrix (e.g., whole blood, serum, plasma, urine) that captures recent exposure. As one such example, cadmium measured in whole blood is considered a valid marker of recent exposure over the past few months, whereas its measurement in urine captures long-term exposure. The biologic half-life of cadmium in the kidneys is 10–30 years [68]; (4) the underestimation of body burden due to excretion factors. Body burden of persistent organic pollutants may be reduced in women who have given birth or breastfed [69–74]. PFAS body burden could also be underestimated in women with heavier menstrual flow as this has been reported to increase the elimination of PFAS [75]; (5) modifications to lifestyle habits after disease onset to manage symptoms. For example, to manage disease symptoms such as pain, women with endometriosis may change their diet. Since contaminated food and drink are important exposure sources for many environmental chemicals, changes to diet after disease onset could substantially affect environmental chemical concentrations measured at diagnosis; and (6) the potentially broad-range of the etiologically-relevant window for disease susceptibility, which may include periods of development before menarche and symptom onset during the reproductive years. Although the specific windows are not known, several proposed theories for disease pathogenesis postulate aberrations *in utero* may contribute to disease [7]. Exposures *in utero* and during infancy and childhood have also been associated with the increased risk of endometriosis in population-based epidemiologic studies [76–79]. It is also important to note that when the biologic specimen used for environmental chemical measurement is collected at or near the

diagnosis of endometriosis, it is difficult to disentangle the involvement of environmental chemicals on disease progression from disease onset.

One approach to overcome this limitation is to use archived biologic samples collected over the life course. One novel example is the use of teeth lost during childhood. The development of deciduous teeth begins *in utero* and teeth accumulate environmental chemicals during formation. The analysis of childhood teeth allows for the reconstruction of past exposure to an array of environmental chemicals at specific periods of development, including *in utero* [80]. Another example is the use of newborn dried blood spots routinely collected at birth as part of state-based newborn screening programs in the United States. Several states archive the dried blood spots long-term for public health research use [81]. Although only a few drops of blood are collected from the newborn by heel stick, improvements in laboratory analytic methods now allow for the quantification of environmental chemicals in small amounts of biologic sample [82]. Other novel data linkages are possible, such as the geocoding of addresses and linkage to databases on air pollution as was done in the NHS II study [43].

Another approach to characterize exposure over the life course in relation to endometriosis is to build the capacity to collect data on incident endometriosis diagnosis in large, established cohort studies. A model for this approach has been the endometriosis research conducted using data from the NHS II study [83]. The identification of a cohort followed since preconception or *in utero* would be particularly valuable to understand early-life environmental exposures, collected in real-time, that may contribute to endometriosis risk.

(3) Recommendation: Employment of best practices to minimize bias in analyses

In this review, it was observed that studies differed in the sophistication of analyses, with a few studies not adjusting for covariates in statistical analyses, not reporting on the approach to handle environmental chemical concentrations measured below the detection limit, and not accounting for urinary dilution when measuring environmental contaminants in urine. For the remaining studies that considered these issues, the analytic approaches varied.

For environmental contaminants measured in urine, the approach used to correct for urinary dilution may induce bias and affect the estimation of the association. O'Brien et al (2016) suggested that two common approaches using urinary creatinine - standardization (dividing the environmental contaminant by the concentration of urinary creatinine) or covariate adjustment (including urinary creatinine as a covariate in the regression model) - may result in biased results in causal scenarios where disease risk factors (e.g., age) also affect creatinine concentrations [22]. That study proposed another approach to minimize bias in which environmental contaminant concentrations are standardized by the estimated proportion of creatinine solely attributable to hydration. For similar reasons, bias may also be induced from the approach used to adjust for serum lipids for lipophilic environmental contaminants measured in blood. Consideration of the causal scenario using directed acyclic graphs is warranted to inform the selection of the most appropriate approach to adjust for urinary dilution and serum lipids [22, 23].

The method used to handle concentrations quantified below the detection limit can be another source of bias. Two simulation studies have reported that a common method, substitution with a single value (e.g. using values of LOD, LOD/2, LOD/√2), may introduce substantial bias if more than 10% of values are below the limit of detection [20, 21]. In these simulation studies, however, an approach such as multiple imputation that performed well with more than 30% missing began to degrade when >50% of measurements were below the limit of detection [20, 21]. Hence, the approach selected should be appropriate for the percentage of values below the detectable level in the data.

Other aspects of analyses that may affect observed results include the modelling of the functional form of the exposure-disease relationship in the regression analyses. In the field of endocrine-disruption research, it is well-recognized that the exposure-disease relationship may be non-monotonic [10, 84]. Imposing a linear relationship in regression modelling may result in associations being missed. In addition, results may be affected by the inclusion of variables in the regression model that do not operate as confounders. To aid the selection of variables for adjustment, a few studies in this review have used directed acyclic graphs. This allows one to avoid adjusting for variables that may not operate as confounder or whose adjustment may induce bias.

Not considered in this review is the movement in the past decade towards understanding the health effects from exposure to environmental chemical mixtures. This movement reflects the interest in understanding the impact of real-world simultaneous exposure to numerous environmental contaminants. Many approaches to studying chemical mixtures have been proposed, with several more in development. These approaches not only aid in understanding joint effects but may also help to identify “the bad actor” chemicals among highly correlated exposures [85, 86].

(4) Recommendation: Separate consideration of endometriosis presentations that may be etiologically-distinct entities

Most studies in the review considered endometriosis as a single disease entity. This approach may reduce the sensitivity of a study to detect an association with environmental risk factors if endometriosis is comprised of separate etiologically-distinct disease entities [18].

In 1997, it was proposed that three presentations of endometriosis - peritoneal endometriosis, ovarian endometriosis, and deep-infiltrating endometriosis of the rectovaginal septum – may indeed be etiologically-distinct disease entities [87]. Nisolle et al (1997) described the different pathogenic mechanisms for each phenotype as follows: menstrual transplantation into the pelvis for peritoneal endometriosis, metaplasia of coelomic epithelium for ovarian endometriosis, and metaplasia of Müllerian remnants in the rectovaginal septum for deep-infiltrating endometriosis. The possibility exists that environmental exposures may affect each endometriosis phenotype differently.

Hence, the study of the environmental origins of endometriosis may be aided by the investigation of individual endometriosis phenotypes, as was done in some of the studies in this review. Although 41% of studies in the present review collected data on rAFS and ASRMr staging of endometriosis, these staging systems are not correlated with

endometriosis symptom severity and may not fully capture phenotype, since deep lesions are not captured in the staging system [88, 89]. The importance of disaggregating the heterogeneous endometriosis disease entity is recognized by the global effort of the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project to promote the standardized collection of phenotype data, such as lesion location, color, and depth, in endometriosis research [88].

Conclusions

Endometriosis is common and is associated with substantial morbidity. Since endometriosis is an estrogen-driven condition, it is biologically plausible that exposure to endocrine-disrupting chemicals could contribute to the development of this serious condition. However, studies of environmental chemicals and endometriosis risk have yielded inconsistent results. This review, conducted from the epidemiologic perspective, identified several overlooked aspects of study design and analysis that may contribute to the disparate results across studies. Recommendations are provided to move the field of environmental origins of endometriosis research forward. If considered in concert, the recommendations have the potential to allow for the synthesis of findings across studies to further understand disease etiology and inform prevention efforts.

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●● Of major importance

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Table 1.

Study population, study design, outcome definition, and control/non-case selection for investigation of environmental contaminants and endometriosis risk

First author, year (reference)	Location	Years	Study population	Inclusion/Exclusion criteria	Case definition	Control/non-case definition
ENDO Study	***Operative cohort***					
Buck Louis 2012 [35] Kunisue 2012 [36] Louis 2012 [37] Buck Louis 2013 [39] Pollack 2013 [40]	5 hospital surgical centers in Salt Lake City, UT; 9 clinical centers in San Francisco, CA	2007–2009	Operative cohort: Patients scheduled for laparoscopy/ laparotomy (n=473)[a] *Indications:* Pelvic pain (42%), pelvic mass (15%), menstrual irregularities (12%), fibroids (10%), tubal ligation (10%) and infertility (7%) [52]	Inclusion: Currently menstruating, ages 18–44, no breastfeeding for ≥6 months, no injectable hormone treatment within prior 2 years, no cancer history (other than nonmelanoma skin cancer); no history of surgically-confirmed endometriosis, communicate in English or Spanish	Incident, surgically-visualized endometriosis (n=190); rASRM staging conducted	No surgical visualization of endometriosis (n=283)
	Population cohort					
	Geographic catchment areas within 50-mile radius of surgical/ clinical centers in operative cohort	2007–2009	Population cohort: Selected from population registries matched to operative cohort on age and residence within 50-mile radius of clinical center; screened by pelvic MRI (n=127)[a]	Inclusion: Currently menstruating, ages 18–44, communicate in English or Spanish, no history of laparoscopy-confirmed endometriosis, willingness to undergo pelvic MRI	MRI-visualized endometriosis (primarily ovarian endometrioma) (n=14) [52]	No MRI-detected endometriosis (n=113)
WREN Study						
Trabert 2010 [31] Upson 2012 [41] Upson 2013 [42] Upson 2014 [44]	Integrated health care system, western Washington State, USA	1996–2001	Female health plan enrollees	Inclusion: Enrollees ages 18–49, premenopausal, intact uteri, at least one ovary, no prior diagnosis of endometriosis, enrollment in health plan for ≥6 months prior to reference date[b]	Incident, surgically-visualized endometriosis, with definite or possible endometriotic disease (n=310)	Random sample of health plan enrollees without history of endometriosis diagnosis, frequency matched to cases on age (n=747)
Air (1)						
Mahalingaiah 2014 [43]	All 50 United States and District of Columbia	1989–2007	Nurses' Health Study II, female nurses ages 25–43 at enrollment in 1989; followed through May 2007; analyses included 84,060 women and 710,230 person-years of follow-up	Exclusion: Endometriosis diagnosis on or before 1993, no home address that could be geocoded	Self-report of incident physician-diagnosed, laparoscopy-confirmed endometriosis (n=2,486)	No self-report of physician-diagnosed, laparoscopy-confirmed endometriosis (n=81,574)
OCPs, PCBs, Dioxins, Furans, PBDEs, PBB (9)						
Cooney 2010 [28]	Two university hospitals, Location not stated	1999–2000	Women ages 18–40 undergoing incident laparoscopy *Indications:* Not stated	Not stated	Laparoscopy-visualized endometriosis and serum lipid data (n=29); AFSr staging	No endometriosis visualized on laparoscopy, serum lipid data (n=51); Of all controls (n=52), 30 with gynecologic pathology;

First author, year (reference)	Location	Years	Study population	Inclusion/Exclusion criteria	Case definition	Control/non-case definition
						22 without gynecologic pathology (ie. tubal sterilization)
Simsa 2010 [30]	University hospital/ center Leuven, Belgium	2001–2005	Patients undergoing laparoscopy *Indications:* Infertility	Not stated	Laparoscopically and histologically proven endometriosis, with equal numbers for each AFSr stage (n=96)	Patients with laparoscopically "normal pelvis" with no evidence of endometriosis (n=106)
Trabert 2010 [31]	See WREN				Cases, n=251	Controls, n=538
Cai 2011 [33]	University OB/GYN department, Isehara, Kanagawa, Japan	2004–2007	Patients undergoing diagnostic laparoscopy *Indications:* Infertility	Not stated	Surgical visualization of endometriosis during laparoscopy, rASRM staging (n=10)	No surgical visualization of endometriosis during laparoscopy (n=7)
Buck Louis 2012 [35]	See ENDO					
Vichi 2012 [38]	University OB/GYN Department, Rome, Italy	2002–2005	Italian women ages 18–45 undergoing incidental laparoscopy *Indications:* Suspected endometriosis, other benign gynecologic conditions *Additional control selection:* No infertility or pelvic pain complaints, benign gynecologic conditions: 62% benign adnexal masses, 25% fallopian tube abnormalities/diseases, 14% uterine myomas	Inclusion: Age 18–45, residence in Rome past 5 years, nulliparity, no breastfeeding history, absence of immunologic, hormonal disorders, or chronic diseases, and no occupational exposure to PCBs or pesticides	Laparoscopy and histology confirmed endometriosis (n=181), rASRM staged, subset (n=63) with PCB data	No visual evidence of endometriosis with laparoscopy; No complaints of infertility, pelvic pain (n=162), subset (n=63) with PCB data
Upson 2013 [41]	See WREN				Cases, n=248	Controls, n=538
Martinez-Zamora 2015 [46]	University GYN department of tertiary referral hospital, Catalonia, Spain		Referred patients undergoing laparoscopy *Indications: Cases:* Suspected DIE *Controls:* Benign adnexal pathology; 80% ovarian cysts (functional, dermal, cystadenomas); 20% hydrosalpinx	Inclusion: Ages 18–40, BMI 18.5–25.0 kg/m^2 Exclusion: History of cancer, suspected malignancy, previous abdominal surgery, autoimmune diseases, and any other chronic condition, previous pregnancies, previous breastfeeding, change of body weight >5 kg in last 5 years.	Patients underlying laparoscopic surgery due to suspected DIE (n=30)	Next consecutive patient undergoing laparoscopic surgery for benign adnexal gynecological diseases; no history of pelvic surgery; no suspicion of endometriosis during surgery or TVUS (n=30)
Ploteau 2017 [49]	Study site not stated; Region Pays-de-Loire, France	2013–2015	Referred patients	Exclusion: History of cancer, suspected malignancy, autoimmune diseases, and any other chronic condition	Ages 18–45, surgical diagnosis of DIE, 26 with additional ovarian endometrioma, all cases AFSr stages III, IV (n=55)	No endometriosis during surgery for tubal ligation, genital prolapse surgery, ovarian cystectomy, without clinical symptoms, including CPP, dysmenorrhea, dyspareunia, history of infertility; matched to cases on age, race, BMI, breastfeeding history (n=44) [90]

First author, year (reference)	Location	Years	Study population	Inclusion/Exclusion criteria	Case definition	Control/non-case definition
Perfluoroalkyls (2)						
Louis 2012 [37]	See ENDO					
Campbell 2016 [47]	United States	2003–2006	Nationally-representative sample NHANES 2003–2004 and 2005–2006 cycles (n=753, unweighted)	Inclusion: Women ages 20–50, self-report data on doctor-diagnosed endometriosis and serum PFAS measurements	Self-report of doctor-diagnosed endometriosis (n=54, unweighted)	No self-report of doctor-diagnosed endometriosis (n=699, unweighted)
Metals (2)						
Pollack 2013 [40]	See ENDO					
Lai 2017 [48]	University hospital infertility clinic, Taipei, Taiwan	2008–2010	Patients undergoing laparoscopy *Indications:* First visit for infertility	Exclusion: Diagnoses of ovarian cyst, premature ovarian failure, repeated implantation failure or pregnancy; refused to provide blood sample; incomplete questionnaires	Laparoscopy and pathology-confirmed symptomatic endometriosis (chronic abdominal pain, diarrhea, dysmenorrhea, dyspareunia) or serum CA125 >35 U/ml, or ovarian endometrioma on transvaginal ultrasound (n=45)) or recurrent endometriosis and history of endometriomas and surgery (n=23); (n=68 total)	No evidence of endometriosis with laparoscopy or other examination, such as hystero-salpingography, semen analysis, and ultrasonagraphy, for tubal factor infertility, male factor infertility, or uterine myomas; no common symptoms (abdominal pain, diarrhea, dysmenorrhea, dyspareunia), serum CA125 levels >35 U/ml, nor ovarian endometrioma on TVUS) (n=122)
Bisphenol A, phthalate metabolites (9)						
Huang 2010 [29]	OB/GYN diarrhea, dysmenorrhea, dyspareunia), serum CA125 levels >35 U/ml, nor ovarian endometrioma on TVUS) (n=122)	2005–2007	Patients undergoing laparotomy of Chinese descent *Indications:* Not stated	Exclusion: Those with pelvic masses on laparotomy, previous diagnosis of endometriosis, leiomyoma, or adenomyosis	Pathologic-confirmation of endometriosis (n=28)	Laparoscopy-confirmed absence of endometriosis, leiomyoma, and adenomyosis (n=29)
Weuve 2010 [32]	United States	1999–2004	Nationally-representative sample, NHANES 1999–2000, 2001–2002, 2003–2004 cycles	Inclusion: Women ages 20–54 years, urinary phthalate metabolite data, urinary creatinine 30–300 mg/dL, data on key covariates (n=1227); subset with two DEHP metabolite data (years 2001–2004), n=838	Self-report of doctor-diagnosed endometriosis (n=87, unweighted)	No self-report of doctor-diagnosed endometriosis (n=1140, unweighted)
Kim 2011 [34]	Study site not stated; Korea	2009	Patients who underwent pelviscopic surgery, exploratory laparotomy, myomectomy, or transabdominal hysterectomy *Indications:* Provided for controls only	Exclusion: History of occupational exposure to reproductive toxicants, smoking, alcohol, or substance abuse, hormone therapy prior year, endometriosis stages I and II	Surgical and histologic evidence of endometriosis; all had sonographic evidence of ovarian endometrioma; stage III and IV endometriosis (ASRMr) (n=97)	No surgical or histologic evidence of endometriosis; no adenomyosis, invasive carcinoma of uterine cervix or ovarian cancer (n=169); reasons for surgery included ovarian cyst (32%, leiomyoma

First author, year (reference)	Location	Years	Study population	Inclusion/Exclusion criteria	Case definition	Control/non-case definition
						(59%), and uterine cervix carcinoma (9%)
Buck Louis 2013 [39]	See ENDO					
Upson 2013 [42]	See WREN				Cases, n=92	Controls, n=195
Upson 2014 [44]	See WREN				Cases, n=143	Controls, n=287
Kim 2015 [45]	OB/GYN Department, Seoul, Korea	2012–2013	Patients undergoing pelviscopic surgery, exploratory laparotomy, or transabdominal hysterectomy of Korean origin and from urban areas	Exclusion: History of occupational exposure to reproductive toxicants, smoking, alcohol, substance abuse, malignancy, hormone therapy prior year, minimal or mild-stage endometriosis; sonographic or laparoscopic evidence of leiomyoma or adenomyosis	Surgical and histologic evidence of stage III, IV endometriosis (ASRMr); all had ovarian endometrioma (n=55)	Patients without endometriosis (n=33); indications include ovarian cysts (91%) and carcinoma in situ of cervix (9%)
Rashidi 2017 [50]	Gynecology and infertility center, Tehran, Iran	2013–2014	Center patients *Indications:* *Cases:* Referred with ovarian endometrioma for operative laparoscopy and ovarian cystectomy *Controls:* Those previously seen at center for problem, returning for routine check-up	Exclusion: PCOS, uterine fibroma, diabetes mellitus, metabolic and endocrine disorders, cardiovascular disease history, BP >140/80, renal failure, BMI>30, neoplastic disorders, smoking	Sonographic evidence of endometrioma (n=50)	No sonographic evidence of endometrioma, no past or present symptoms related to endometrioma (n=50)
Moreira Fernandez 2019 [51]	Endometriosis center, university hospital Belo Horizonte, Brazil	Not stated	Brazilian women ages 18–45 undergoing videolaparoscopy surgery with visual inspection of pelvis and biopsy of suspected lesions *Indications:* Not stated	No inclusion or exclusion criteria provided	Cases (n=30): Histologic confirmation of endometriosis (n=27) or MRI (n=3)	No surgical visualization of endometriosis (n=22)
Benzophenone-type UV filters (1)						
Kunisue 2012 [36]	See ENDO					

Abbreviations: AFSr, American Fertility Society revised staging; BMI, body mass index; BP, blood pressure; BPA, Bisphenol A; CA, cancer antigen; CPP, chronic pelvic pain; DEHP, di(2-ethylhexyl) phthalate; DIE, deep infiltrating endometriosis; ENDO Study, Endometriosis: Natural History, Diagnosis and Outcomes Study; GYN, gynecology; MRI, magnetic resonance imaging; NHANES, National Health and Nutrition Examination Survey; OB, obstetrics; OCPs, organochlorine pesticides; PBB, polybrominated biphenyls; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCOS, polycystic ovary syndrome; PFAS, perfluoroalkyl substances; rASRM, revised American Society for Reproductive Medicine classification; TVUS, transvaginal ultrasound; WREN, Women's Risk of Endometriosis Study.

[a] ENDO Study enrolled n=495 for the operative cohort, but 22 cancelled surgeries. ENDO Study also enrolled n=131 for the population cohort, but 4 were insufficient quality for diagnostic purposes [35].

[b] Date of first visit in integrated health care system leading to endometriosis diagnosis in cases.

Table 2.

Exposure measurement, analysis, and main findings of studies investigating environmental contaminants and endometriosis risk

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings
Air pollution (1)					
Mahalingaiah 2014 [43]	Traffic-related exhaust (using distance to largest road types) and PM_{10}, $PM_{2.5}$	Self-reported residential address; geocoded and data linkage	Updated every 2 years by questionnaire	*Adjustment:* Age, calendar time, race, current BMI, smoking status, parity, oral contraceptive use, menarche age, infertility, shift work, region, area-level SES *Exposure units:* Categorized distance to road; 10-μg/m^3 ↑ in PM *Non-Detects:* Not stated for PM	Distance to A1-A3 roads (m)[a], whole country 0–50: HR 1.04, 95% CI: 0.91-1.17 51–199: HR 1.09, 95% CI: 0.99-1.19 ≥200: Reference 2-year exposure averaging time PM_{10}: HR 0.94, 95% CI: 0.87-1.02 $PM_{10–2.5}$: HR 0.91, 95% CI: 0.81-1.02 $PM_{2.5}$: HR 0.95, 95% CI: 0.83-1.10
OCPs, PCBs, Dioxins, Furans, PBDEs, PBB (9)					
Cooney 2010 [28]	OCPs or their metabolites: aldrin, β-BHC, DDE. HCB, mirex, *trans-nonachlor*	Serum	After home interview and before surgery	*Adjustment:* Smoking, other OCPs, serum lipids *Exposure unit:* Tertiles; above/below LOD for aldrin and γ-BHC; continuous log(x+1) transformed, except DDE with Box-Cox transformation *Non-detects:* For analyses using continuous concentrations, used observed values and for aldrin and β-BHC used substitution of expected unobserved values *Lipid adjustment:* Covariate adjustment	*trans*-Nonachlor T_1: Reference T_2: OR 3.0, 95% CI: 0.5-18.3 T_3: OR 4.6, 95% CI: 0.5-41.6 Continuous: OR 5.0, 95% CI: 0.7-35.8 HCB T_1: Reference T_2: OR 2.2, 95% CI: 0.5-10.5 T_3: OR 6.6, 95% CI: 1.0-42.8 Continuous: OR 1.4, 95% CI: 0.5-3.9 DDE T_1: Reference T_2: OR 1.0, 95% CI: 0.2-4.4 T_3: OR 0.1, 95% CI: 0.02-0.8 Continuous: OR 0.5, 95% CI: 0.1-1.7 Null associations with mirex; inconclusive associations with other OCPs due to wide confidence intervals Similar associations when controls restricted to those with no gynecologic pathology noted (n=22)

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings
Simsa 2010 [30]	Dioxin-like compounds (dioxins, furans, and coplanar PCBs)	Plasma	Day of surgery, before surgery	*Adjustment:* Age *Exposure unit:* 75th vs. 25th percentile *Non-Detects:* Excluded one subject with 0 value *Lipid adjustment:* Standardized using plasma lipid content Note: The bioassay screening method identifies presence of compounds that activate the aryl hydrocarbon receptor.	OR 2.44, 95% CI: 1.04-5.70 DIE only: OR 3.55, 95% CI: 0.85-14.84 Peritoneal endometriosis only: 2.93, 95% CI: 0.90-9.57
Trabert 2010 [31]	34 NDL PCB congeners (18, 28, 44, 49, 52, 66, 74, 87, 99, 101, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178 180, 183, 187, 189, 194, 195, 196, 201, 206, 209) 2 weak dioxin-like PCBs 118 and 156[c]	Serum	At interview, after case diagnosis	*Adjustment:* Age, enrollment year, ln-total lipid, alcohol, income, and serum *p,p'*-DDE *Exposure unit:* Quartiles *Non-Detects:* Excluded from analyses congeners detected in <75% of samples PCBs 87, 101, 128, 146, 149, 151, 157, 167, 172, 177, 178, 183, 189, 195; non-detects included in lowest quartile category *Lipid adjustment:* covariate adjustment of ln-transformed total lipids	PCB 118 Q_1: Reference Q_2: OR 1.2, 95% CI: 0.7-1.9 Q_3: OR 1.4, 95% CI: 0.9-2.4 Q_4: OR 1.3, 95% CI: 0.8-2.3 PCB 138 Q_1: Reference Q_2: OR 1.4, 95% CI: 0.8-2.2 Q_3: OR 0.9, 95% CI: 0.5-1.7 Q_4: OR 1.2, 95% CI: 0.7-2.3 PCB 153 Q_1: Reference Q_2: OR 1.1, 95% CI: 0.7-1.8 Q_3: OR 0.8, 95% CI: 0.5-1.5 Q_4: OR 1.2, 95% CI: 0.7-2.2 PCB 156 Q_1: Reference Q_2: OR 0.9, 95% CI: 0.6-1.6 Q_3: OR 0.8, 95% CI: 0.5-1.5 Q_4: OR 1.1, 95% CI: 0.6-2.0 Data suggested OR<1 for PCB 170, 196, 201; OR>1 for PCBs 44, 49 in some quartiles. Results did not differ when cases restricted to those with ovarian endometriosis or non-ovarian pelvic endometriosis
Cai 2011 [33]	29 dioxin and dioxin-like compounds (7 PCDDs, 10 PCDFs, 4 non-ortho PCBs, 8 mono-ortho PCBs)	Serum, peritoneal ascites fluid	Follicular phase; no further information provided	*Adjustment:* No covariate adjustment *Exposure unit:* Used values in ascites; higher level (molar sum PCDDs >0.4pg TEQ/pg lipid with	OR 2.5, 95% CI: 1.17-5.34 Note: odds ratios not provided for molar sum of PCBs, or individual PCDD, PCDF, or PCB analytes.

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings		
				detectable PCDFs TEQ levels) vs. lower-level group *Non-Detects:* Used zero as value *Lipid adjustment:* Standardized by lipid content (serum and ascites)			
Buck Louis 2012 [35]	11 OCPs (HCB, β-HCH, γ-HCH, oxychlordane, *cis*- and *trans* nonachlor, *cis*- and *trans*-chlordane, *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, 35 PCB congeners (18, 28, 44, 49, 52, 66, 74, 87, 99, 101, 114, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 201, 206, 209) 6 PBDEs congeners (47, 99, 100, 153, 154, 209)	Omental fat, serum in operative cohort; serum in population cohort	Serum ~2 months before surgery or MRI [37]; Omental fat during surgery (operative cohort only)	*Adjustment:* Age, breastfeeding history, BMI, cotinine, serum lipids *Exposure unit:* Log(x +1) transformed, rescaled by SD *Non-detects:* Used machine-observed concentrations *Lipid adjustment:* Covariate adjustment	*Operative-fat* OR (95% CI) *OCPs* β-HCH: 1.08, 0.86–1.36 *trans*-nonachlor: 0.99, 0.77–1.29 HCB: 1.21, 0.96–1.53 Oxychlordane: 1.13, 0.87–1.48 *p,p'*-DDE: 0.88, 0.69–1.12 *PCBs* PCB-118: 0.94, 0.73–1.20 PCB-138: 1.02, 0.77–1.35 PCB-153: 1.06, 0.80–1.42 PCB-156 0.74, 0.57–0.96 *PBDEs* PBDE-47: 0.70, 0.55, 0.90 PBDE-99: 0.84, 0.66–1.08 PBDE-100: 0.83, 0.66–1.05 PBDE-153: 0.78, 0.62–0.99 PBDE-154: 0.95, 0.74–1.21	*Operative-serum* OR (95% CI) *OCPs* β-HCH: 0.77 0.54, 1.14 *trans*-nonachlor: 1.06, 0.87–1.28 HCB: 0.92, 0.75–1.13 Oxychlordane: 0.99, 0.82–1.19 *p,p'*-DDE: 0.85, 0.67–1.08 *PCBs* PCB-118: 1.01, 0.83–1.24 PCB-138: 0.98, 0.80–1.20 PCB-153: 0.87, 0.71–1.07 PCB-156: 1.16, 0.95–1.41 *PBDEs* PBDE-47: 0.89, 0.70–1.15 PBDE-99: 1.13, 0.92–1.37 PBDE-100: 0.95, 0.75–1.21 PBDE-153: 1.01, 0.82–1.25 PBDE-154: 1.13, 0.92–1.38	*Population-serum* OR (95% CI) *OCPs* β-HCH: 1.72, 1.09–2.72 *trans*-nonachlor: 1.22, 0.74–2.01 HCB: 1.00, 0.56–1.79 Oxychlordane: 1.32, 0.73–2.39 *p,p'*-DDE: 1.32, 0.70–2.47 *PCBs* PCB-118: 1.06, 0.66–1.71 PCB-138: 0.80, 0.40–1.63 PCB-153: 1.13, 0.68–1.89 PCB-156: 0.91, 0.49–1.67 *PBDEs* PBDE-47: 1.03, 0.55–1.92 PBDE-99: 1.02, 0.59–1.77 PBDE-100: 1.09, 0.60–1.98 PBDE-153: 1.14, 0.65–1.97 PBDE-154: 0.86, 0.46–1.60 Data suggested OR>1 for γ-HCH measured in fat in the operative cohort and measured in serum in population cohort; OR<1 for PCB-74 measured in fat in operative cohort. OR>1 for PBDE-209 in population cohort

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings
Vichi 2012 [38]	Non-dioxin-like PCB congeners (28, 52, 101, 138, 153, 180, 170); dioxin-like PCB congeners (105, 118, 156, 167)	Serum	Before laparoscopy, fasting	*Adjustment:* No covariate adjustment *Exposure unit:* Medium/high vs. low, using tertiles *Non-detects:* Not stated *Lipid adjustment:* Lipid-standardization	PCB 118: OR 2.62, 95% CI: 1.18-5.83 PCB 138: OR 2.73, 95% CI: 1.24-6.00 PCB 153: OR 3.72. 95% CI: 1.63-8.51 Note: Data suggested OR>1 for PCBs 170, 180; data not reported for remaining individual analytes
Upson 2013 [41]	OCPs or metabolites: β-HCH, γ-HCH, heptachlor epoxide, oxychlordane, trans-nonachlor, *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, dieldin, HCB, mirex	Serum	At interview, after case diagnosis (median 1.2 years, range 6 months to 5.8 years)	*Adjustment:* ln-total lipids, education, race/ethnicity, smoking, alcohol, age, reference year; selected using DAG *Exposure unit:* Quartiles; categories ≤LOD, ≤median, >median for mirex and γ-HCH *Non-detects:* Distribution-based multiple imputation for continuous concentrations *Lipid adjustment:* Covariate adjustment with total lipids	*Endometriosis* OR, 95% CI β-HCH Q_1: Reference Q_2: 0.8, 0.5–1.4 Q_3: 1.7, 1.0–2.8 Q_4: 1.3, 0.8–2.4 Trans-nonachlor Q_1: Reference Q_2: 1.0, 0.6–1.6 Q_3: 1.0, 0.6–1.6 Q_4: 1.4, 0.8–2.4 Hexachlorobenzene Q_1: Reference Q_2: 1.4, 0.9–2.1 Q_3: 1.4, 0.9–2.1 Q_4: 0.9, 0.6–1.5 Oxychlordane Q_1: Reference Q_2: 0.8, 0.5–1.3 Q_3: 1.0, 0.6–1.6 Q_4: 1.2, 0.7–2.1 *p,p'*-DDE Q_1: Reference Q_2: 1.2, 0.8–2.0 Q_3: 1.1, 0.7–1.7 Q_4: 1.0, 0.6–1.7 *Ovarian endometriosis* OR, 95% CI β-HCH Q_1: Reference Q_2: 1.2, 0.5–2.4 Q_3: 2.5, 1.2–5.2 Q_4: 2.5, 1.1–5.3 Trans-nonachlor Q_1: Reference Q_2: 1.4, 0.7–2.7 Q_3: 1.3, 0.7–2.6 Q_4: 1.8, 0.9–3.7 Hexachlorobenzene Q_1: Reference Q_2: 1.6, 0.9–3.0 Q_3: 1.4, 0.7–2.6 Q_4: 1.1, 0.6–2.1 Oxychlordane Q_1: Reference Q_2: 0.8, 0.4–1.6 Q_3: 1.2, 0.6–2.4 Q_4: 1.5, 0.8–3.0 *p,p'*-DDE Q_1: Reference Q_2: 1.4, 0.8–2.6 Q_3: 1.1, 0.6–2.1 Q_4: 1.2, 0.6–2.4 Note: Data suggested OR>1 for endometriosis with mirex, heptachlor epoxide and γ-HCH.
Martinez-Zamora 2015 [46][b]	7 PCDDs (2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-	Adipose tissue	Fasting, sampled day of surgery	*Adjustment:* Age, smoking, BMI *Exposure unit:* Toxic equivalence (TEQ), continuous, units not stated *Non-detects:* Excluded	*Deep infiltrating endometriosis* OR (95% CI) *PCBs* PCB-118: 1.97, 0.84–3.15 PCB-156: 3.26, 1.98–6.15 *Dioxins* 2,3,7,8-TCDD: 1.41, 1.12–2.10 1,2,3,7,8-PeCDD: 1.82, 1.36–7.14

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings	
	HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD); 10 PCDFs (2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, OCDF); and 12 PCBs (105, 114, 118, 123, 156, 157, 167, 189, 77, 81, 126, 169)			*Lipid adjustment:* Lipid standardization	1,2,3,4,7,8-HxCDD: 1.16, 0.72–2.08 1,2,3,6,7,8-HxCDD: 1.03, 0.86–1.77 *Furans* 2,3,4,7,8-PeCDF: 1.94, 1.27–5.16 1,2,3,4,7,8-HxCDF: 1.09, 0.91–1.49 1,2,3,4,7,8,9-HpCDF: 0.59, 0.23–1.11 OCDF: 1.19, 0.72–1.47 Note: Associations provided for measured concentrations, not toxic equivalence values for comparison purposes. Similar associations observed using toxic equivalence values. Data suggested OR>1 for PCBs 114, 126, 157, 169, 189	
Ploteau 2017 [49][b]	17 dioxins (PCDD/F) 2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,6,7,8-HpCDD OCDD, 2,3,7,8-TCDF 1,2,3,7,8-PeCDF 2,3,4,7,8-PeCDF 1,2,3,4,7,8-HxCDF 1,2,3,6,7,8-HxCDF 1,2,3,7,8,9-HxCDF 2,3,4,6,7,8-HxCDF 1,2,3,4,6,7,8-HpCDF 1,2,3,4,7,8,9-HpCDF OCDF 12 dioxin-like PCBs (77, 81, 126, 169, 105, 114, 118, 123,156, 157, 167, 189), 6 NDL PCBs (28, 52, 101, 138, 153, 180); 8 PBDEs (28, 47, 99, 100, 153, 154, 183, 209); 3 PBBs (153), α-HBCD; 30 OCPs	Serum, Parietal fat, omental fat	Serum day before surgery; adipose tissue collected during surgery	*Adjustment:* Adjusted for age and BMI; selected using DAGs *Exposure unit:* Used parietal fat data; log-transformed, rescaled by SD *Non-detects:* Used LOD value; excluded analytes detected <50% of samples *Lipid adjustment:* Lipid-standardization (serum)	*DIE* OR 95% CI *OCPs* β-HCH 1.58, 0.94–2.80 *trans*-nonachlor 2.21, 1.24–4.28 HCB 2.06, 1.20–3.91 oxychlordane 3.22, 1.60–7.70 *PCBs* PCB-118: 2.30, 1.31–4.36 PCB-138: 1.65, 0.93–3.09 PCB-153: 1.66, 0.88–3.29 PCB-156: 1.10, 0.55–2.22 *Dioxins* 2,3,7,8-TCDD: 1.65, 0.95–3.02 1,2,3,7,8-PeCDD: 2.20, 1.23–4.25 1,2,3,4,7,8-HxCDD: 1.60, 0.92–2.90 1,2,3,6,7,8-HxCDD: 1.55, 0.91–2.74 *Furans* 2,3,4,7,8-PeCDF: 1.41, 0.82–2.51 1,2,3,4,7,8-HxCDF: 1.25, 0.79–2.04 1,2,3,4,7,8,9-HpCDF: 1.33, 0.87–2.11 OCDF 5.42, 2.73–12.85 *PBB* PBB-153 3.91, 1.60–11.60	*DIE and OvE* OR 95% CI *OCPs* β-HCH 3.64, 1.52–11.15 *trans*-nonachlor 3.66, 1.40–12.71 HCB 2.09, 0.93–5.38 oxychlordane 5.82, 1.84–27.69 *PCBs* PCB-118: 2.93, 1.38–7.07 PCB-138: 2.35, 1.06–5.97 PCB-153: 2.94, 1.17–8.67 PCB-156: 1.93, 0.74–5.55 *Dioxins* 2,3,7,8-TCDD: 2.31, 1.12–5.22 1,2,3,7,8-PeCDD: 3.56, 1.60–9.51 1,2,3,4,7,8-HxCDD: 2.22, 1.06–5.26 1,2,3,6,7,8-HxCDD: 2.35, 1.16–5.25 *Furans* 2,3,4,7,8-PeCDF: 2.21, 1.06–5.16 1,2,3,4,7,8-HxCDF: 1.92, 1.03–3.79 1,2,3,4,7,8,9-HpCDF: 2.09, 1.15–4.18 OCDF 6.98, 2.94–22.27 *PBB* PBB-153 8.26, 2.27–44.41

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings	
	(HCB, β-HCH, trans-nonachlor, oxychlordane, cis-heptachlor epoxide, dieldrin, *p,p'*-DDT, *p,p'*-DDE); Not all individual analytes listed in manuscript				Data suggested OR>1 for 1,2,3,7,8-PeCDD, PCBs 105, 114, 123, 167, cis-heptachlor epoxide, dieldrin. Note: Data only presented for analytes with statistically significant associations.	
Perfluoroalkyls (2)						
Louis 2012 [37]	PFDA, PFHxS, PFNA, PFOA, PFOS, PFDoDA, PFHpA, PFOSA, PFUnDA	Serum	~2 months before surgery or MRI	*Adjustment:* Age, BMI *Exposure unit:* log(x +1) transformed and presented per logarithm unit change *Non-Detects:* Concentrations "recovery adjusted" (0–15% ND); 4 not included in analyses due to 63–98% of samples <LOQ (PFDoDA, PFHpA, PFOSA, PFUnDA)	*Operative cohort* *OR, 95% CI* PFOS: 1.39, 0.98–1.98 PFOA: 1.89, 1.17–3.06 PFNA: 2.20, 1.02–4.75 PFDA: 2.95, 0.72–12.1 PFHxS: 1.14, 0.58–2.24	*Population cohort* *OR, 95% CI* PFOS: 1.29, 0.48–3.45 PFOA: 1.28, 0.35–4.62 PFNA: 1.52 0.15–15.1 PFDA: 0.06, 0.00–12.3 PFHxS: 1.52, 0.40–5.80
Campbell 2016 [47][c]	PFOA, PFOS, PFHxS, EPAH, MPAH, PFDA, PFBS, PFHpA, PFNA, PFOSA, PFUA, PFDoDA	Serum	Time of NHANES interview, a mean 11.2 years after diagnosis	*Adjustment:* Age, race, BMI, poverty income ratio, serum cotinine. *Exposure unit:* Per unit ln-transformed and quartiles *Non-detects:* Used LOD/√2 (0.2–5.8% ND); 8 not included due to 47–99% samples <LOD (EPAH, MPAH, PFDA, PFBS, PFHpA, PFOSA, PFUnDA, PFDoDA)	PFOS: Q_1: (Reference) Q_2: OR 1.89, 95% CI: 0.35-10.17 Q_3: OR 3.56, 95% CI: 0.86-14.74 Q_4: OR 3.48, 95% CI: 1.00-12.00 Continuous: OR 1.43, 95% CI: 0.88-2.30 PFOA: Q_1: (Reference) Q_2: OR 1.07, 95% CI: 0.20-5.78 Q_3: OR 5.45, 95% CI: 1.19-25.04 Q_4: OR 2.86, 95% CI: 0.63-12.91 Continuous: OR 1.33, 95% CI: 0.82-2.17 PFNA: Q_1: (Reference) Q_2: OR 3.76, 95% CI: 0.69-20.66 Q_3: OR 5.27, 95% CI: 1.20-23.06 Q_4: OR 3.24, 95% CI: 0.81-12.91 Continuous: OR 1.22, 95% CI: 0.84-1.78	

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings
					PFHxS Q_1: (Reference) Q_2: OR 1.74, 95% CI: 0.41-7.35 Q_3: OR 1.70, 95% CI: 0.57-5.07 Q_4: OR 1.47, 95% CI: 0.40-5.41 Continuous: OR 1.05, 95% CI: 0.79-1.41
Metals (2)					
Pollack 2013 [40]	Cd, Pb, total Hg, Sb, As, Ba, Be, Cd, Cs, Cr, Co, Cu, Pb, Mn, Hg, Mo, Ni, Te, Tl, Sn, W, U, Zn	Whole blood: Cd, Pb, total Hg Urine: Sb, As, Ba, Be, Cd, Cs, Cr, Co, Cu, Pb, Mn, Hg, Mo, Ni, Te, Tl, Sn, W, U, Zn	~2 months before surgery or MRI [37]	*Adjustment:* Age, BMI, current smoking, site, race, vitamin use; *Exposure unit:* log(x +1) transformed continuous and tertiles *Non-detects:* Machine-observed concentrations *Urinary dilution:* Creatinine-standardized concentrations	*Operative cohort* *OR, 95% CI* Blood Pb T_1: Reference T_2: 0.73, 0.45–1.17 T_3: 0.84, 0.50–1.41 Blood Cd T_1: Reference T_2: 0.74, 0.46–1.21 T_3: 0.55, 0.31–0.98 Blood Hg T_1: Reference T_2: 1.08, 0.67–1.74 T_3: 1.00, 0.60–1.67 *Population cohort* *OR, 95% CI* Blood Pb T_1: Reference T_2: 0.92, 0.20–4.16 T_3: 1.70, 0.39–7.38 Blood Cd T_1: Reference T_2: 1.73, 0.45–6.67 T_3: 0.14, 0.01–1.58 Blood Hg T_1: Reference T_2: 0.69, 0.16–2.90 T_3: 0.81, 0.19–3.39 For metals measured in urine, data from the operative cohort suggested OR<1 for Sb, OR>1 for Cr, Cu, Pb, Sn. Associations for remaining urinary metals in the operative and population cohorts were null or inconclusive due to wide CIs. Authors report no associations when exposure modelled continuously (data not reported).
Lai 2017 [48]	Zn, Cu Mn, Fe, Hg, Pb, Cd, Cr	Whole blood	Not stated	*Adjustment:* Age, body fat proportion, education, menarche age, menstrual cycle regularity Exposure unit: Tertiles based on control distribution Non-detects: Used LOD/√2	Blood Pb T1: Reference T2: 1.73, 95% CI: 0.77-3.88 T3: 2.59, 95% CI: 1.11-6.06 Blood Cd T1: Reference T2: 1.03, 95% CI: 0.45-2.37 T3: 1.73, 95% CI: 0.78-3.92 Blood Hg T1: Reference T2: 0.66, 95% CI: 0.29-1.54 T3: 1.54, 95% CI: 0.72-3.29 OR<1 with Zn, Cu; Associations unclear for Mn, Fe, and Cr
Bisphenol A, phthalate metabolites (9)					

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings	
Huang 2010 [29]	MMP, MEP, MnBP, MBzP, MEHP, MEOHP, MEHHP	Spot urine, single sample	Not stated	*Adjustment:* GSTM1 polymorphism, BMI *Exposure unit:* Median cutpoint *Non-detects:* Not stated *Urinary dilution:* Urinary creatinine standardization	MnBP: OR 2.93, 95% CI: 0.92-9.31 MBzP: OR 1.07, 95% CI: 0.35-3.28 MEHP: OR 1.42, 95% CI: 0.45-4.50 MEOHP: OR 2.03, 95% CI: 0.64-6.37 MEHHP: OR 1.55, 95% CI: 0.51-4.77 Data suggested OR>1 with MMP; association unclear with MEP.	
Weuve 2010 [32]	MEHP, MBP[d], MEP, MBzP, MEHHP, MEOHP MECPP	Urine	Time of NHANES interview, <1 to 34 years after diagnosis in cases (median, 9 years)	*Adjustment:* Age, race/ethnicity, menarche age, current pregnancy status and current breastfeeding status *Exposure unit:* Quartiles *Non-detects:* Used LOD/√2 (0.2% to 20.5% ND) *Urinary dilution:* Creatinine standardization	*NHANES cycles 1999–2004* MBzP: Q_4 vs $Q_{1–3}$: OR 1.16, 0.58, 2.33 MEHP: Q_4 vs $Q_{1–3}$: OR 0.44, 95% CI: 0.19-1.02 *NHANES cycles 2001–2004* MEOHP: Q_4 vs $Q_{1–3}$: OR 0.62, 95% CI: 0.27-1.44 MEHHP: Q_4 vs $Q_{1–3}$: OR 0.46, 95% CI: 0.18-1.21 Data suggested OR>1 with MBP, null association with MEP.	
Kim 2011 [34]	DEHP, MEHP	Plasma	Not stated	*Adjustment*: Number of deliveries, BMI, DEHP (or MEHP) *Exposure unit:* Not stated *Non-detects:* Not stated	MEHP: OR 1.020, 95% CI: 1.003-1.038	
Buck Louis 2013 [39]	Total BPA, MMP, MEP, MCPP, MPB, MiBP, MECPP, MCMHP, MEHHP, MEOHP, MCHP, MBzP, MEHP, MOP, MiNP	Spot urine, single sample	Not stated	*Adjustment:* Age, BMI, urinary creatinine *Exposure unit:* log(x +1) transformed, standardized by SD (continuous) *Non-detects:* Not stated *Urinary dilution:* Covariate adjustment for creatinine	*Operative cohort OR, 95% CI* BPA 0.96, 0.79–1.19 MnBP: 1.11, 0.86–1.43 MBzP: 0.84, 0.65–1.07 MEHP: 1.20, 0.97–1.49 MEOHP: 1.06, 0.85–1.32 MEHHP: 1.10, 0.89–1.36 Data suggested null association with MMP, MCPP, MiBP, MEP, MECPP, MiBP, MCMHP, MCHP, MOP; suggestion of OR<1 with MCPP, MiNP	*Population cohort OR, 95% CI* BPA 1.68, 0.96–2.92 MnBP: 2.62, 1.14–6.05 MBzP: 1.47, 0.76–2.85 MEHP: 2.59, 1.17–5.75 MEOHP: 2.33, 1.26–4.29 MEHHP: 2.20, 1.23–3.94 Data suggested OR>1 with MMP, MCPP, MiBP, MECPP, MCMHP; null association with MEP, MiNP; association unclear with MCHP, MOP
Upson 2013 [42]	MEHP, MEHHP, MEOHP, MECPP, MBzP, MiBP, MnBP MEP	Spot urine, single sample	At interview, after case diagnosis	*Adjustment:* ln-transformed urinary creatinine, age, and reference year, informed using DAG *Exposure unit:*	OR, 95% CI MnBP Q_1: Reference Q_2: 1.2, 0.5–2.8 Q_3: 1.5, 0.6–3.9	OR 95% CI MEHP Q_1: Reference Q_2: 0.6, 0.3–1.3 Q_3: 0.7, 0.3–1.5

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings	
				Quartiles *Non-detects:* Single imputation (0–16% ND) *Urinary dilution:* Covariate adjustment for creatinine	Q_4: 1.3, 0.4–3.9 MBzP Q_1: Reference Q_2: 1.7, 0.8–3.8 Q_3: 1.5, 0.6–4.0 Q_4: 1.3, 0.4–4.0	Q_4: 0.3, 0.1–0.7 MEOHP Q_1: Reference Q_2: 1.4, 0.6–2.9 Q_3: 0.8, 0.3–2.1 Q_4: 0.6, 0.2–1.7 MEHHP Q_1: Reference Q_2: 1.1, 0.5–2.4 Q_3: 0.8, 0.3–2.0 Q_4: 0.5, 0.2–1.5
					Data suggested OR>1 for MEP; null association with MiBP; association unclear for MECPP	
Upson 2014 [44]	Total BPA	Spot urine, single sample	At interview; median 3.4 years (range 6 months to 5.8 years) after endometriosis diagnosis date	*Adjustment:* ln-transformed urinary creatinine, age, reference year using DAG *Exposure unit:* Quartiles *Non-detects:* LOQ/√2 (<8% ND) *Urinary dilution:* Covariate adjustment for creatinine	*OR, 95% CI* *All cases* Q_1: Reference Q_2: 1.2, 0.6–2.2 Q_3: 1.5, 0.8–3.0 Q_4: 1.5, 0.7–3.1	
					Non-ovarian pelvic endometriosis cases (n=68) Q_1: Reference Q_2: 3.0, 1.2–7.3 Q_3: 3.0, 1.1–7.6 Q_4: 1.7, 0.6–5.0	*Ovarian endometriosis cases (n=75)* Q_1: Reference Q_2: 0.5, 0.2–1.2 Q_3: 1.0, 0.4–2.2 Q_4: 1.5, 0.6–3.4
Kim 2015 [45]	MEHHP, MEOHP, MnBP, MBzP, MECPP	Spot urine, single sample	Obtained preoperatively	*Adjustment:* Age and number of deliveries *Exposure unit:* log-transformed (continuous) *Non-detects:* Not stated *Urinary dilution:* Creatinine-standardization	MnBP: OR 1.41, 95% CI: 0.66-3.03 MBzP: 0.92, 95% CI: 0.57-1.48 MEOHP: OR 2.89, 95% CI: 1.04-8.04 MEHHP: OR 2.52, 95% CI: 1.03-6.14 Data suggested OR>1 for MECPP	
Rashidi 2017 [50]	Total BPA	First morning urine, single sample	Before surgery or medical visit	*Adjustment:* Age, BMI, parity, education *Exposure unit:* Not stated	*Ovarian endometriosis* BPA OR 1.74. 95% CI: 1.40-2.16 Note: Unit change in BPA not stated	

First author, year (reference)	Exposure	Matrix	Timing of collection	Covariate adjustment/exposure units/Handling values <DL	Main findings
				Non-detects: LOD/2 (14–18% NDs) *Urinary dilution:* Urinary creatinine not measured	
Moreira Fernandez 2019 [51]	MMP, MiBP, MBP[e], MCHP, MiNP, MOP, MBzP, MEHP, BPA	Urine, no further information provided	Not stated	*Adjustment:* No covariate adjustment *Exposure unit:* Dichotomized using median *Non-detects:* Used 0 value (40–100% ND) *Urinary dilution:* Creatinine standardization	MBzP: OR 0.569, 95% CI: 0.448-0.7222[f] MEHP: OR 1.267, 95% CI: 0.269-5.972 BPA: OR 0.560, 95% CI: 0.438-0.716 Note: Quantification issue; phthalate metabolites not detectable in 40–97% of cases and 68-100% of controls; BPA not detected in 90% cases and 95% controls; MOP and MBzP not quantified in controls; associations unclear for MMP,MBP, MiBP, MCHP, MiNP
Benzophenone-type UV filters (1)					
Kunisue 2012 [36]	Benzophenone derivatives: 2OH-4MeO-BP; 2,4OH-BP; 2,2'OH-4MeO-BP; 2,2', 4,4'OH-BP, 4OH-BP	Urine	Not stated	*Adjustment:* Study site and hair color *Exposure unit:* log(x +1) transformed (continuous) (results not reported), quartiles using non-case distribution *Non-detects:* Used machine observed concentrations <LOD (1–14% ND); did not evaluate 2,2',4,4'OH-BP and 2,2'OH-4MeO-BP due to low detection *Urinary dilution:* Not stated	*Operative cohort* OR, 95% CI 2OH-4MeO-BP Q1: Reference Q_2: 0.82, 0.48–1.38 Q_3: 0.99, 0.59–1.67 Q_4: 1.24, 0.73–2.10 2,4OH-BP Q_1: Reference Q_2: 0.76, 0.44–1.31 Q_3: 1.16, 0.68–1.97 Q_4: 1.59, 0.94–2.66 4OH-BP Q_1: Reference Q_2: 0.92, 0.55–1.54 Q_3: 1.03, 0.62–1.73 Q_4: 0.87, 0.51–1.48 *Population cohort* OR, 95% CI 2OH-4MeO-BP Q_1: Reference Q_2: 0.89, 0.11–7.25 Q_3: 2.36, 0.39–14.2 Q_4: 1.67, 0.28–10.1 2,4OH-BP Q_1: Reference Q_2: 0.48, 0.07–3.40 Q_3: 0.73, 0.14–3.97 Q_4: 0.89, 0.17–4.61 4OH-BP Q_1: Reference Q_2: 1.51, 0.25–9.20 Q_3: 2.20, 0.38–12.7 Q_4: 1.69, 0.31–9.21

Abbreviations: 2OH-4MeO-BP, 2-hydroxy-4-methoxybenzophenone; 2,4OH-BP; 2,4-dihydroxybenzophenone; 2,2'OH-4MeO-BP; 2,2'-dihydroxy-4-methoxybenzophenone; 2,2'4,4'OH-BP, 2,2'4,4'-tetrahydroxybenzophenone; 4OH-BP, 4-hydroxybenzophenone; As, arsenic; β-BHC, beta-benzene hexachloride; Ba, barium; Be, beryllium; beta-benzene hexachloride; BMI, body mass index; BPA, Bisphenol A; Cd, cadmium; CI, confidence interval; Co, cobalt; Cs, cesium; Cr, chromium; Cu, copper; DAG, directed acyclic graph; DDE, dichloro-2,2-bis(p-chlorophenyl)ethylene; p,p'-DDE, *p,p'*-dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEHP, di-(2-ethylhexyl) phthalate; DIE, deep-infiltrating endometriosis; DL, detection limit; EPA, Environmental Protection Agency; EPAH, 2-(N-ethyl-PFOSA) acetate; Fe, iron; GSTM1, glutathione S-transferase M1, HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; Hg, mercury; HR, hazard ratio; LOD, limit of detection; LOQ, limit of quantification; MBzP, mono-benzyl phthalate; MCHP, monocyclohexyl phthalate; MCMHP, mono-[(2-carboxymethyl)hexyl] phthalate; MCPP, mono(3-caroboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MEP, mono-ethyl phthalate; MiBP, mono-iso-butyl phthalate; MMP, mono-methyl phthalate; Mn, manganese; MnBP, mono-n-butyl phthalate; MNP, monoisonoyl phthalate; Mo, molybdenum; MOP, monooctyl phthalate; MPAH, 2-(N-methyl-PFOSA) acetate; MRI, magnetic resonance imaging; NHANES, National Health and Nutrition Examination Survey; Ni, nickel; ND, non-detectable samples; NDL, non-

dioxin-like; OCP, organochlorine pesticide; OR, odds ratio; OvE, ovarian endometrioma; Pb, lead; PBB, polybrominated biphenyls; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyl; PCDDs, polychlorinated-dibenzo-dioxins; PCDFs, polychlorinated-dibenzo-furans; PFBS, perfluorobutane sulfonic acid; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFDoDA, perfluorododecanoic acid; PFHpA, perfluoroheptanoic acid; PFOSA, perfluorooctane sulfonamide; PFUnDA, perfluoroundecanoic acid; PM, particulate matter; Q_1, first quartile; Q_2, second quartile; Q_3, third quartile; Q_4, fourth quartile; SES, socioeconomic status; Sb, antimony; SD, standard deviation; Sn, tin; T_1, first tertile; T_2, second tertile; T_3, third tertile; Te, tellurium, TEQ, toxic equivalent units; Tl, thallium; W, tungsten; U, uranium; Zn, zinc.

[a]Classified road segments as follows: A1: primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits; A2: primary major, non-interstate highways and major roads with access restrictions; A3: smaller, secondary roads, usually with more than two lanes.

[b]Abbreviations only provided for analytes in manuscript.

[c]Used same abbreviations as that of Louis et al (2012).

[d]MBP estimated by summing concentrations of MnBP and MiBP.

[e]Specific isomer measured not stated.

[f]Unclear how OR estimated since all values for controls were <LOD.