

Risk for and consequences of endometriosis: a critical epidemiologic review

Shafrir AL,^{1,2,*} Farland LV,^{3,4,*} Shah DK,⁵ Harris HR,⁶ Kvaskoff M,^{7,8} Zondervan K,^{9,10} Missmer SA^{1,2,4,11}

1. Division of Adolescent and Young Adult Medicine, Department of Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA
2. Boston Center for Endometriosis, Boston Children's and Brigham and Women's Hospitals, Boston, MA, USA
3. Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
4. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
5. Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA, USA
6. Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
7. CESP, Fac. de médecine - Univ. Paris-Sud, Fac. de médecine - UVSQ, INSERM, Université Paris-Saclay, Villejuif Cedex, France.
8. Gustave Roussy, Espace Maurice Tubiana, Villejuif Cedex, France
9. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK
10. Endometriosis CaRe Centre, Nuffield Dept of Obstetrics & Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
11. Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, Grand Rapids, MI, USA

*Contributed equally as first authors.

Corresponding author and to whom requests for reprints should be made:

Amy L. Shafrir
Boston Children's Hospital
1 Autumn Street, 5th Floor
Boston, MA 02115
Email: amy.shafrir@childrens.harvard.edu
Phone: 617-355-4127

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Abstract

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Endometriosis affects approximately 10% of reproductive aged women. Characteristics that have been robustly associated with endometriosis include earlier age at menarche, shorter menstrual cycle length, and leaner body size associated with greater risk, while greater parity has been associated with lower risk. Relationships with other potential characteristics, including physical activity, dietary factors, and lactation, have been less consistent, partially due to the need for rigorous data collection and longitudinal study design. Critical methodologic complexities include the need for a clear case definition, valid selection of comparison/control groups, and consideration of diagnostic bias and reverse causation when exploring demographic characteristics, medical history, and lifestyle factors. Reviewers and editors must demand detailed description of rigorous methods to facilitate comparison and replication to advance our understanding of endometriosis.

Keywords: endometriosis, epidemiology, study design, incidence, risk factors, co-morbidities

Endometriosis Prevalence and Incidence

Accurate measurement of the incidence and prevalence of endometriosis is complicated by the current requirement for surgical visualization to establish a definitive diagnosis. Factors influencing referral for / acceptance of surgery and access to surgical expertise create a biased sample among those who achieve a diagnosis. Prevalence estimates vary considerably among different populations, ranging from approximately 2-4% among asymptomatic women seeking tubal ligation [1–3] to 5-50% among infertile women [4–8] and 5-21% among women hospitalized for pelvic pain [4–8]. However, the actual prevalence of endometriosis is likely underestimated among women undergoing an elective tubal ligation, and, conversely, is likely overestimated among women undergoing surgery/hospitalization for pain symptoms and/or infertility. Most recently, the ENDO study enrolled 495 women undergoing laparoscopy/laparotomy between 2007 and 2009 and 131 women from the general population to estimate the incidence of endometriosis. Approximately 41% of women scheduled to undergo laparoscopy were found to have surgically-visualized endometriosis compared with approximately 11% of women from the general population visually diagnosed using magnetic resonance imaging [9].

Based on prevalence estimates of pelvic pain and subfertility in the general population, the estimated overall prevalence of endometriosis is 10%, and approximately 2% for undiagnosed symptomatic disease [10]. Few studies have investigated endometriosis incidence and prevalence among adolescents. The reported prevalence of visually-confirmed endometriosis among adolescents with pelvic pain ranges from 25-100%, with an average of 49% among

adolescents with chronic pelvic pain and 75% among adolescents unresponsive to medical treatment [11].

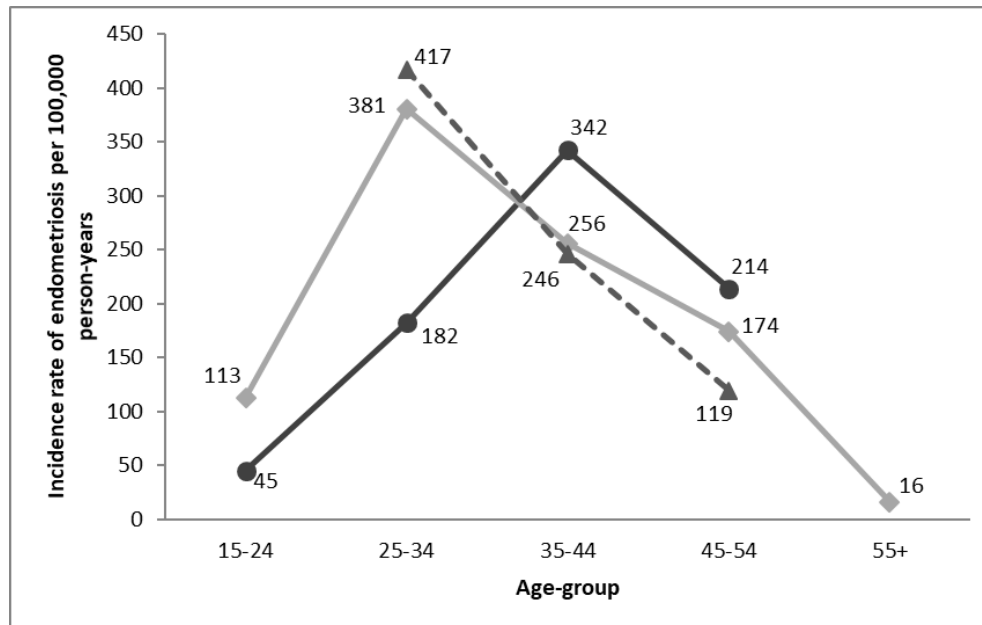


Figure 1: Age-specific incidence rates of endometriosis among women in Rochester, Minnesota and across the US. The darker solid line with circles is adapted from Houston et al. [12] and is based on histologically-confirmed endometriosis during the 1970s. The lighter solid line with diamonds is adapted from Leibson et al [13] and is based on clinically diagnosed endometriosis during the 1990s. The dashed line with triangles is adapted from Missmer et al. [14] and is based on surgically-confirmed endometriosis in the 1990s.

Information on the incidence of endometriosis in the general population is limited. Two studies have reported the age-specific incidence of endometriosis diagnosis among white women in Rochester, Minnesota (Figure 1). Houston et al. [12] reported an overall incidence of histologically-confirmed endometriosis of 160.4/100,000 person-years among women aged 15-49 years between 1970 and 1979, with a peak between ages 35-44 years (342.3/100,000 person-years). In this same geographic region, Leibson et al. [13] observed an overall incidence rate of clinically diagnosed endometriosis of 187/100,000 person-years among women aged >15 years from 1987 to 1999, with a peak in incidence between ages 25-34 years (380.6/100,000 person-

years). Similar incidence patterns to Leibson et al. [13] were observed in the Nurses' Health Study II (NHSII) (Figure 1). The NHSII is a prospective cohort of 116,429 U.S. female nurses aged 25-42 at enrollment in 1989. Between 1989 and 1999, the incidence rate of laparoscopically-confirmed endometriosis was 298/100,000 person-years [14]. While the incidence peaked at ages 25-34 (417/100,000 person-years), the decrease in incidence was more modest for women without a history of infertility, declining only after age 44 years (p-trend<0.0001) [14].

Methodologic Issues in Endometriosis-focused Study Design

The key methodologic issues for endometriosis discovery – whether clinical, population, or bench science - include choosing a valid (1) endometriosis case definition and (2) comparison group, and (3) defining the appropriate etiologic window to capture the exposures, outcomes, and disease progression to address the study aims [10,15–17]. In general, case-control studies of endometriosis tend to be more vulnerable to bias due to control selection and recall; however, these issues can occur in all study designs.

Endometriosis Case Definition

There are multiple pathways through which a person with endometriosis may be diagnosed or mis/un-diagnosed (Figure 2). Some women are diagnosed due to pelvic pain, while others are diagnosed at the time of an infertility evaluation or diagnosed incidentally for unrelated pelvic surgical procedures (such as appendectomy or tubal ligation). The wide variation in both symptoms, surgically visualized presentation and pathologic findings makes selection of an appropriate case definition for endometriosis both critical and challenging.

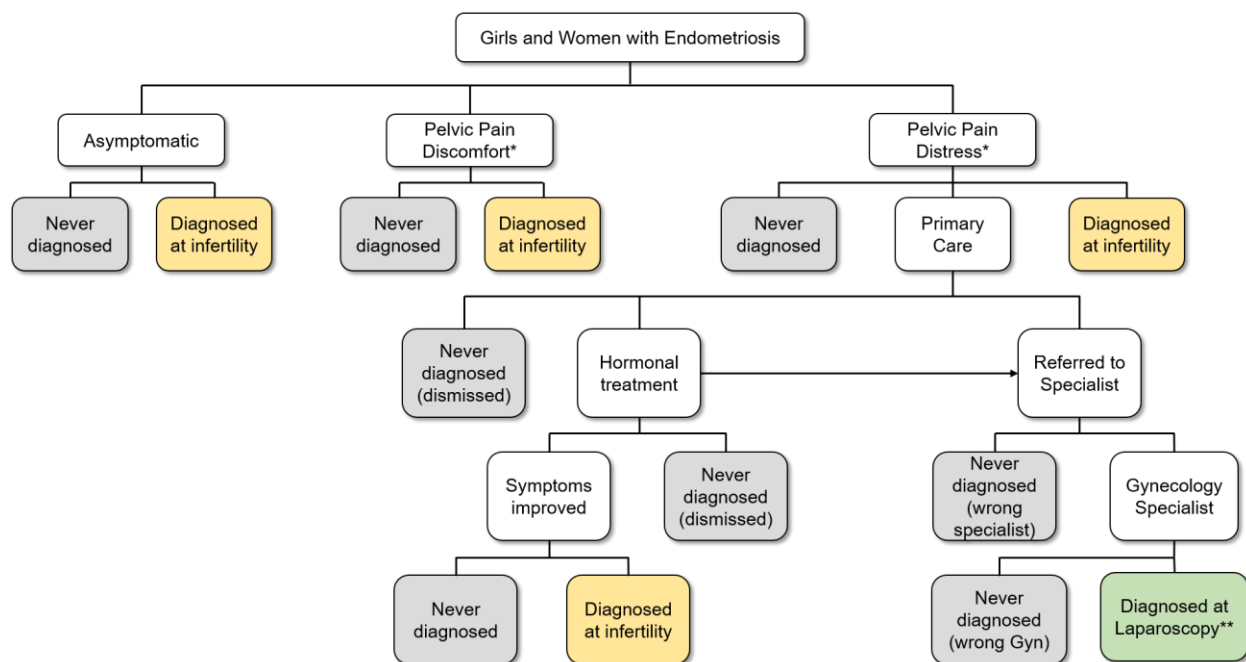


Figure 2. Pathways to surgical endometriosis diagnosis. Given the current requirement for surgical visualization for a definitive diagnosis, women can reach a surgical diagnosis of endometriosis through multiple pathways including through laparoscopy for an infertility evaluation (yellow boxes) or due to pain symptoms (green box). Women with endometriosis may also never reach a surgical diagnosis (gray boxes).

*Pelvic pain discomfort and pelvic pain distress terminology attributed to Deborah Bush of Endometriosis New Zealand. Discomfort categorizes pelvic pain considered to be “normal,” or of too low impact to warrant referral for surgical evaluation.

**Endometriomas and deep endometriosis may also be diagnosed through radiologic methods. Any of these paths could include sporadic incidental diagnoses during other surgeries such as appendectomy, cholecystectomy, or tubal ligation.

Laparoscopy remains the gold standard for diagnosing endometriosis [18,19]. The accuracy of self-reported endometriosis varies among populations [14,20]. However, women who undergo laparoscopy for a definitive diagnosis due to pain symptoms may differ in pathophysiology, symptomatology, and risk factor profiles from (1) women whose symptoms are managed less invasively through anti-inflammatory treatments or oral contraceptives (OCs) and from (2) women with ‘asymptomatic’ endometriosis identified through infertility evaluation or incidental visualization. These differences may introduce selection bias when surgical confirmation is used

as a case definition, as those who have access to laparoscopy may be more frequent users of the medical system or have more severe symptoms compared with women who do not undergo a laparoscopy. This issue of selection bias is particularly important for “adolescent” endometriosis given that only those with the most severe symptoms will undergo surgery. Similarly, studies that only include women whose endometriosis was diagnosed as part of an infertility evaluation may under-sample women with pelvic pain [21], as these women may never have come to laparoscopic diagnosis if they had not attempted pregnancy and if they did not have access to an infertility evaluation [22,23].

Thus, various endometriosis case definitions can be considered including diagnosis based on symptoms, laparoscopic confirmation due to pelvic pain, infertility or unrelated surgery, or visualization through imaging techniques. Surgically evaluated cases can be further subdivided based on the revised American Society for Reproductive Medicine (rASRM) disease staging system. However, it is important to note that rASRM stage does not correlate with endometriosis symptoms nor with prognosis [24]. While many case definitions are valid given the aims of a study, clear reporting of the chosen endometriosis case definition [25] in published studies is extremely important for interpretation, comparison, and validation of study findings.

Comparison / control group

A similar challenge in endometriosis research exists when attempting to define a valid comparison group. This is of particular importance in case-control studies, as controls must represent the exposure distribution of the population that gave rise to the cases, and sampling

must be independent of the exposure. Strategies for control selection will depend on the hypothesis to be tested. Often women undergoing pelvic surgery for reasons other than endometriosis (e.g. tubal ligation, hysterectomy, or laparoscopy) are included as the control group in an effort to prevent the inclusion of undiagnosed cases among the controls. However, these highly selected women represent a biased sample of those from the underlying population, e.g. tubal ligation controls are multiparous and not a valid control for case women diagnosed during an infertility evaluation [10] (Figure 3). Additionally, inclusion of controls undergoing surgery for a pathology other than endometriosis may lead to an erroneously null association if the pathology is related to the exposure of interest, for example environmental toxin exposure or body size.

Ideal situation



Controls selected from women with tubal ligation

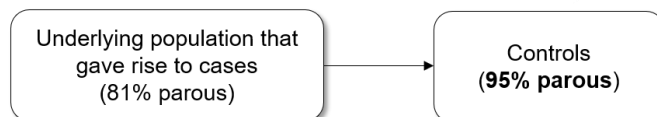


Figure 3. Potential for selection bias in case-control studies of endometriosis. Selection bias may arise when utilizing women undergoing tubal ligation as the control group in a case-control study. This is an example of bias introduced if parity is related to the exposure under study (e.g. body size, breastfeeding duration, miRNA profile, or epigenetic profile). Numbers are based on data from the NHSII.

Fertility status also presents a challenge in studies of endometriosis as women who seek a medical evaluation for infertility differ on important demographic, lifestyle, and access to healthcare factors from infertile women who do not access these services. Failure to account for

these differences may lead to selection bias or hinder generalizability [22], particularly when exposures of interest, such as menstrual cycle characteristics, body size, or hormonal milieu, are correlated with both endometriosis and infertility.

Onset of Endometriosis Symptoms

To understand the relationship with modifiable risk factors, epidemiologic studies should ideally focus on incident rather than prevalent cases of disease. However, the exact time of disease onset is unknown for endometriosis, as a symptom “threshold” must typically be reached before evaluation is sought. In the case of endometriosis, the literature reports delays averaging seven-years from symptom onset to surgical diagnosis [21]. As a result, most epidemiologic investigations are estimating the incidence of endometriosis *diagnosis* as opposed to the true disease onset. The temporal relationship between exposure and disease must therefore be interpreted critically when considering modifiable risk factors or biomarkers that are interpreted as having a role in disease etiology but may actually change as a consequence of endometriosis symptoms – resulting in reverse causation (Figure 4).

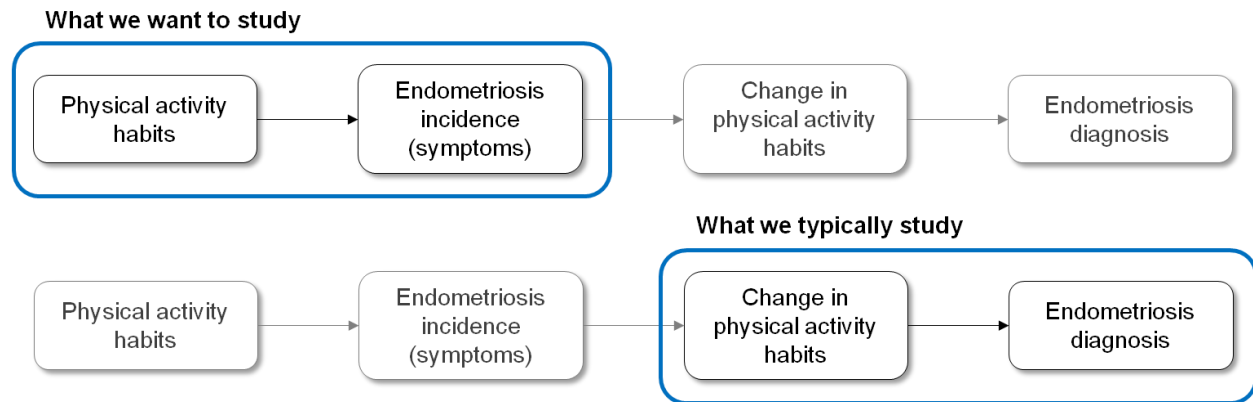


Figure 4. Example of potential for reverse causation in epidemiologic studies. If endometriosis symptoms have an impact on physical activity habits, then analyses of physical activity and prevalent endometriosis will typically be assessing this changed physical activity level in relation to endometriosis diagnosis as opposed to physical activity levels before symptoms and the true incidence of endometriosis.

Taking into account these various methodologic challenges, we now present a review of the current discoveries regarding risk factors for endometriosis (Figure 5).

Endometriosis Risk Factors

In-Utero and Early Life Exposures

Maternal exposure to environmental toxins: Prenatal exposure to diethylstilbestrol (DES), a synthetic estrogen, has been associated with a greater risk of endometriosis in the NHSII cohort (Rate Ratio [RR]=1.8, 95% CI=1.2-2.8) [26] and also the suggestion of greater risk in a population-based case-control study in western Washington State (Odds Ratio [OR]=1.3, 95% CI=0.5-3.6) [27]. *In-utero* DES exposure, which has been linked to reproductive tract structural abnormalities and altered estrogen receptor expression, potentially influences endometriosis development through increased retrograde menstruation and immune dysfunction [26,28].

Exposure to paternal cigarette use during gestation has been associated with a non-significant reduction in the odds of endometriosis within the ENDO study (OR=0.72; 95% CI=0.43-1.19) [29]. An even stronger and statistically significant reduction in the odds of endometriosis (OR=0.22; 95% CI=0.06-0.82) was observed for self-reported prenatal cigarette exposure in a small prospective hospital-based study [30]. As current smoking appears to decrease circulating estrogen levels among women [31], these results suggest that exposure to cigarette smoke during gestation may alter circulating maternal hormone levels, highlighting the potential importance of the maternal hormonal milieu in endometriosis etiology.

Birth characteristics: While few studies have assessed birth weight and endometriosis risk, the current evidence suggests a higher risk among women born at lower birth weights compared to normal or high birth weights [26,29,32]. Compared to having a normal birth weight (defined as 7.0-8.4 pounds), women in the NHSII cohort born at lower birth weights (<5.5 pounds) had a significant greater risk of developing endometriosis later in life (RR=1.3, 95% CI=1.0-1.8) [26]. Differences in birth weight may reflect variations in the hormonal milieu within the *in utero* environment or in the adequacy of blood supply to the fetus during pregnancy. Conversely, conflicting results have been observed for the association between prematurity and endometriosis risk with some studies reporting a greater risk [27,32] and others reporting no association [26,29]. It is critical for valid interpretation for studies on birth weight to restrict analyses to full-term births only, and for studies of prematurity to adjust for birth weight. Lack of rigorous statistical analysis may underlie the inconsistent findings.

Childhood and Adolescent Exposures

Menstrual cycle characteristics: Earlier age at menarche has been consistently associated with an higher risk of endometriosis [33–35], potentially through an altered hormonal environment or earlier and increased duration of exposure to retrograde menstruation. A recent meta-analysis of 10 case-control studies calculated that endometriosis cases were 0.15 standard deviations of age (in years) younger at time of first menstrual period than controls [35]. Additionally, within the NHSII cohort shorter menstrual cycles (<26 days) during late adolescence (18-22 years) were associated with an greater rate of endometriosis compared to 26-31 day menstrual cycles [33].

Body size: The current evidence suggests an inverse association between childhood and adolescent body size and the risk of endometriosis [36–40]. In a recent nested case-control study within the French E3N cohort, 61,208 women estimated their childhood body size using Sorensen somatotypes [41]. Women reporting large compared to lean body sizes at 8 years old and at menarche had lower odds of endometriosis (OR=0.86, 95% CI=0.77-0.95 and OR=0.79, 95% CI=0.71-0.88, respectively) [39]. A similar inverse association between childhood body size and endometriosis risk was observed in the NHSII (p-trend=0.0002), and this association was independent of age at menarche and adulthood body mass index (BMI) [38]. Among endometriosis cases, a Korean hospital-based study observed that cases with smaller childhood body size were more likely to present with rASRM disease stages III/IV compared to stages I/II (p-trend=0.002) [42].

Additionally, adult height may be a surrogate for childhood exposure to growth factors. Both the NHSII cohort study and the nested case-control study within E3N noted that taller adult height was associated with a higher likelihood of endometriosis compared to shorter adult height [14,39,40]. Additionally, three case-control studies have reported greater odds of endometriosis with taller height [37,43,44].

Other Early Life Exposures: Exposure during childhood/adolescence to indoor passive smoke for several hours per day, higher physical activity proximal to menarche, and more severe or frequent sunburns during childhood/adolescence have all been associated with higher risk of endometriosis but warrant replication and additional investigation [45–47].

Adulthood Exposures

Menstrual cycle characteristics: Shorter menstrual cycles during adulthood have been consistently associated with greater endometriosis risk [33,34,44]. Less consistent evidence has accumulated relating to monthly duration of menses, regularity of menstrual cycles, heaviness of menstrual flow, and tampon use [34,44,48].

Pregnancy and lactation: While pregnancy may be important in endometriosis etiology, it is also an important detection window for endometriosis, particularly among asymptomatic women presenting with infertility, thus rendering the evaluation of associations between pregnancy and endometriosis challenging methodologically. An inverse association between parity and

endometriosis was reported in three case-control studies [49–51] and in one cohort study regardless of time since last birth [33]. Importantly, while women with endometriosis in the NHSII cohort were found to have a two-fold higher risk of incident infertility, 83% of nurses with endometriosis were parous by the age of 40 [52]. Similar findings were reported in the ENDO study [53].

A recent analysis in the NHSII noted a lower risk of endometriosis with longer length of total breastfeeding (RR=0.92, 95% CI=0.90-0.94 for every additional 3 months of breastfeeding per pregnancy) and an even stronger inverse association for exclusive breastfeeding (RR=0.86; 95% CI=0.81-0.90) [54]. This association was partially attributed to the length of postpartum amenorrhea. Pregnancy and lactation result in hormonal changes, including increased levels of progesterone and prolactin, respectively, which may hinder implantation and/or growth of endometrial lesions. Alternatively, breastfeeding may have a positive impact on pain symptoms, thus decreasing the likelihood of surgical evaluation for endometriosis among parous women.

Body size: Extensively studied, a consistent inverse association between adult BMI and endometriosis has been observed [14,36,39,44,55]. Additionally, women with a waist-to-hip ratio, a marker of body fat distribution, of <0.60 in the NHSII had almost a three-fold higher risk of endometriosis compared to women with a waist-to-hip ratio of 0.70-0.79 (RR=2.78, 95% CI=1.38-5.60) [40]. Similar results were observed in a case-control study [56] and may be explained by a genetic link, as the same intergenic locus on 7p15.2 was associated with endometriosis and body fat distribution (waist-to-hip ratio adjusted for BMI) [57]. Peripheral fat

accumulation as opposed to visceral fat has been associated with a higher ratio of estrogens to androgens [58].

Physical activity: The relationship between physical activity and endometriosis has been inconsistent [59], potentially due to reverse causation from endometriosis symptoms affecting physical activity levels (Figure 4). In case-control studies relying on recalled physical activity levels, an approximately 40-80% decreased risk of endometriosis has been observed with regular exercise [43,44,60,61]. However, a more modest, non-significant decreased risk of endometriosis comparing women with the highest physical activity levels to the lowest was observed in the NHSII (RR=0.89, 95% CI=0.77-1.03) [62]. The prospective design of the NHSII overcomes limitations of recalled physical activity information inherent in case-control studies. Physical activity is known to influence hormone levels including lowering luteal estrogens [63] and increasing sex hormone binding globulin levels [64], which may potentially influence endometriosis development.

Dietary factors: There is limited literature on dietary factors and endometriosis risk, particularly among studies utilizing advanced nutritional epidemiologic methods. While no clear association has been observed between fish consumption and endometriosis in case-control studies, an inverse association was observed for intake of long-chain omega-3 fatty acid consumption and endometriosis in the NHSII (RR=0.88, 95% CI=0.62-0.99), with salad dressing as the primary source [65]. A similar inverse association was observed in a recent case-control study [66].

Women in the NHSII with the highest quintile of trans fat intake were at significantly greater risk

of endometriosis diagnosis compared with women in the lowest quintile (RR=1.48, 95% CI=1.17-1.88) [65], although this finding was not replicated in a recent case-control study [67]. Trans-unsaturated fat intake may be related to the pathogenesis of endometriosis through the up-regulation of inflammatory markers including IL-6 and markers of TNF system activation [68,69]. Conflicting results have been reported for fruit and vegetable intake [67,70,71], red meat consumption, saturated fat and animal fat intake [60,65–67,70,72], olive oil consumption and monounsaturated fat intake [65,70,72], phytoestrogens and soy isoflavones [73,74], dairy intake [60,67,70,75], and serum vitamin D levels [76]. Variation in study design and nutritional epidemiologic methods may underlie this lack of replication. Future studies must account for diet temporality and total caloric intake, and apply substitution and other dietary component modeling methods.

Dermatologic and pigmentation characteristics: A positive dose-effect relation between risk of endometriosis and skin sensitivity (OR=1.22, 95% CI=1.10-1.36 for highest vs. lowest tertile), number of moles (OR=1.59, 95% CI=1.37-1.83 for highest vs. lowest quartile), and freckling (OR=1.11, 95% CI=1.03-1.20 for highest vs. lowest tertile) was reported in the E3N nested case-control study [77]. Similarly, endometriosis risk was associated with moles on the lower legs (RR=1.08, 95% CI=1.02-1.14) and a family history of melanoma (RR=1.13, 95% CI=1.01-1.26) within the NHSII [47]. Case-control studies have observed a higher risk of endometriosis among women with blue/green eyes [36,78]. Conflicting results have been reported for the association between red hair color and endometriosis risk [47,77,79,80].

Environmental toxins: Smarr et al. [81] recently summarized the evidence on endocrine-disrupting chemicals and endometriosis risk. Endocrine-disrupting chemicals, such as polychlorinated biphenyl (PCB) and dioxin, may influence endometriosis risk through the disruption of circulating hormone levels and/or dysregulation of the immune system [82]. However, the literature has been inconsistent, perhaps due to small sample sizes, varying time windows of exposure, and differences in control populations [81]. Two retrospective cohort studies have assessed the relationship between environmental toxins and endometriosis [20,83]. In the first study, women with levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) >100 parts per trillion had a non-significant higher rate of endometriosis (RR=2.1, 95% CI=0.5-8.0) [83]. In the second study, women exposed to levels of PCBs >8 parts per billion had a greater but non-significant rate of endometriosis compared to women exposed to ≤ 5 part per billion (RR=1.68, 95% CI=0.95-2.98) [20].

Other Adulthood Exposures: Results for smoking and endometriosis risk have been conflicting, with some studies reporting an inverse association [14,44,48], and others reporting no association [14,43,50,84,85]. This variation may be due in part to differences in risk between infertile and fertile women. In the NHSII, a positive association was observed among fertile women, while an inverse association was observed among infertile women [14]. While smokers have lower estrogen levels [31], they are also exposed to higher levels of exogenous estrogen from organochlorines. A greater risk of endometriosis has been noted for both alcohol and caffeine intake in infertile populations [60,86–88]. However, case-control studies of infertile and fertile women found no associations [34,43,70,89]. In the NHSII, no association was observed for caffeine intake and an inverse association was observed between alcohol and endometriosis

[14]. A recent meta-analysis quantified no association between caffeine or coffee intake (RR=1.26; 95% CI=0.95-1.66; RR=1.13; 95% CI=0.46-2.76; respectively) [90]. Limited research has noted an association between night shift work and endometriosis risk [91,92]. Nightshift work has been shown to disrupt circadian estrogen secretion and has been associated with an elevated risk of other estrogen-dependent diseases, such as breast cancer [93,94].




Potential Increased risk		Potential Decreased risk	
<u><i>In-Utero and early life</i></u>			
	↑ <u>Consistent</u> Lower birth weight	↓ <u>Consistent</u>	
	↑ <u>Inconsistent</u> Prematurity	↓ <u>Inconsistent</u> Maternal/paternal smoking	
	↑ <u>Understudied</u> Maternal diethylstilbestrol	↓ <u>Understudied</u>	
<u>Childhood and Adolescence</u>			
	↑ <u>Consistent</u> Earlier age at menarche Lower body mass index	↓ <u>Consistent</u>	
	↑ <u>Inconsistent</u>	↓ <u>Inconsistent</u>	
	↑ <u>Understudied</u> Intense physical activity Passive smoke exposure Skin sensitivity	↓ <u>Understudied</u>	
<u>Adulthood</u>			
	↑ <u>Consistent</u> Shorter menstrual cycle length Lower body mass index	↓ <u>Consistent</u> Greater parity	
	↑ <u>Inconsistent</u> Greater height Alcohol use Caffeine intake PCB/dioxin exposure Red hair Freckling Moles Skin sensitivity	↓ <u>Inconsistent</u> Cigarette smoking Regular physical activity	
	↑ <u>Understudied</u> Heavier menstrual volume Lower waist-to-hip ratio Night shift work Red meat/saturated fat Trans fat	↓ <u>Understudied</u> Lactation Fruits and vegetables Fish and omega-3 PUFA Soy/phyto-estrogens Low-fat dairy	

Figure 5. Risk factors for endometriosis

Endometriosis and Chronic Disease Risk

A growing body of research suggests an association between endometriosis and other comorbid and chronic conditions [95,96]. However, the quality of the epidemiologic evidence, magnitude of association, and mechanism behind the association varies across different conditions. A key methodologic challenge is that women who are diagnosed with endometriosis may utilize treatments that alter their endometriosis disease (e.g. excision surgery) or that are directly related to other disease risk (e.g. exogenous hormones) or modify their lifestyle to address symptoms of endometriosis such as pain or infertility (e.g. dietary or physical activity alterations). Ideally these intermediate factors would be accounted for via formal mediation analytics. Women with endometriosis may, by the fact of their successful diagnosis, have greater access to healthcare and may also be more intensively screened than the general population, resulting in detection bias. Study design and analytic methods to address the potential impact of confounding, effect modification, mediation, bias, and reverse causation are therefore critical to incorporate when considering these associations.

Cancer: Among the most consistently demonstrated associations is that between endometriosis and clear cell and endometrioid ovarian cancer [95,97–99]. A pooled analysis of 13 ovarian cancer case-control studies reported an greater risk of clear cell (OR=3.05, 95% CI=2.43-3.84), low-grade serous (OR=2.11, 95% CI=1.39-3.20), and endometrioid ovarian cancers (OR=2.04, 95% CI=1.67-2.40) [97]. It is critical to determine if this elevated risk of ovarian cancer is associated with all phenotypes of endometriosis, or more precisely is driven primarily or solely by those with endometriomas [100,101]. Conversely, results have been conflicting for breast

cancer, with some studies reporting a modest increased risk and others reporting a null or decreased risk associated with endometriosis [95,102–104]. Breast cancer is heterogeneous in the timing of disease onset (before or after menopause), tumor hormone receptor status, and molecular subtypes, and few studies have investigated these differences [104], with the vast majority of studies investigating all breast cancers as a single outcome. Thus, some of the conflicting results may be caused by true variation in the association by breast cancer subtype.

There has been relatively limited research into the association between endometriosis and other reproductive cancers. The majority of research has suggested no association between endometriosis and endometrial cancer [95,100,105]; however, two studies reported a positive association and one study reported an inverse association [95]. While studies investigating the association between endometriosis and cervical cancer are limited, they have consistently reported an inverse association between the two conditions [95].

Seven studies investigating endometriosis and skin cancer have reported an association between endometriosis and cutaneous melanoma, although five studies have reported no association [95,106]. Very few studies have focused on non-melanoma skin cancers and suggest either a very modest or no association [95,106].

Cardiovascular conditions: Prospective data from the NHSII has suggested an association between endometriosis and cardiovascular conditions [107]. Endometriosis was associated with a

greater risk of cardiovascular disease (myocardial infarction, angiographically-confirmed angina, coronary artery bypass graft) (RR=1.62, 95% CI=1.39-1.89). About 50% of the association was attributed to the high rate of hysterectomy/oophorectomy among women with endometriosis. Limited research has also shown a greater risk of hypertension [108], hypercholesterolemia [108–110], and subclinical atherosclerosis [111] among women with endometriosis.

Immune system diseases: Research is limited with regards to endometriosis and autoimmune conditions. Some studies have suggested a higher risk of systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome among women diagnosed with endometriosis [112–116]; however, other studies reported no association [21,84,117].

Summary

While estimates of endometriosis prevalence and incidence are difficult to calculate due to the absence of a non-invasive diagnostic method, the best estimates conclude that approximately 10% of reproductive aged women are afflicted with endometriosis. Methodologic complexity associated with this disease requires application of advanced study design and statistical methodology. Many different case definitions can be utilized validly and the type of women included in comparison/control groups can vary based upon the study aims. These details are important to describe and take into account when comparing and contrasting studies.

The long delay between endometriosis symptom onset and diagnosis can lead to reverse causation, particularly for modifiable risk factors and studies based on recalled exposure

information. Overall, a greater risk of endometriosis has been consistently reported for earlier age at menarche, shorter menstrual cycle length, and lean BMI, while a lower risk has been consistently associated with greater parity. Conflicting results have been observed for physical activity both in childhood and adulthood, dietary factors, environmental toxins, lactation, night shift work, and cigarette smoking. Further research is needed into early life, childhood and adolescent exposures as risk factor profiles may differ between women diagnosed during adolescence and women diagnosed in adulthood. The phenotypic variation among women with endometriosis must be embraced, defined, and explored. Excellence in methodologic design and requirement for replication are vital to advance our understanding of risk factors for and consequences of endometriosis.

Conflict of Interest

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Research agenda

Determine the true prevalence and incidence of endometriosis

Define informative subtypes of endometriosis to advance discovery of etiologic pathways
personalized diagnostics and treatment

Determine the natural history of the disease to better define critical windows of exposure

Identify high risk groups for co-morbidities and chronic disease among women with
endometriosis

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