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Endometriosis: a high-risk population for major chronic diseases?

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BACKGROUND: Despite an estimated prevalence of 10% in women, the etiology of endometriosis remains poorly understood. Over recent decades, endometriosis has been associated with risk of several chronic diseases, such as cancer, autoimmune diseases, asthma/atopic diseases and cardiovascular diseases. A deeper understanding of these associations is needed as they may provide new leads into the causes or consequences of endometriosis. This review summarizes the available epidemiological findings on the associations between endometriosis and other chronic diseases and discusses hypotheses for underlying mechanisms, potential sources of bias and methodological complexities.

METHODS: We performed a comprehensive search of the PubMed/Medline and ISI Web of Knowledge databases for all studies reporting on the associations between endometriosis and other diseases published in English through to May 2014, using numerous search terms. We additionally examined the reference lists of all identified papers to capture any additional articles that were not identified through computer searches.

RESULTS: We identified 21 studies on the associations between endometriosis and ovarian cancer, 14 for breast cancer, 8 for endometrial cancer, 4 for cervical cancer, 12 for cutaneous melanoma and 3 for non-Hodgkin's lymphoma, as well as 9 on the links between endometriosis and autoimmune diseases, 6 on the links with asthma and atopic diseases, and 4 on the links with cardiovascular diseases. Endometriosis patients were reported to be at higher risk of ovarian and breast cancers, cutaneous melanoma, asthma, and some autoimmune, cardiovascular and atopic diseases, and at decreased risk of cervical cancer.

CONCLUSIONS: Increasing evidence suggests that endometriosis patients are at higher risk of several chronic diseases. Although the underlying mechanisms are not yet understood, the available data to date suggest that endometriosis is not harmless with respects to women's long-term health. If these relationships are confirmed, these findings may have important implications in screening practices and in the management and care of endometriosis patients.

Key words: asthma / autoimmune diseases / cancer / cardiovascular diseases / endometriosis

Introduction

Endometriosis, defined as the presence of endometrial tissue outside of the uterus, is the third leading cause of gynecologic hospitalization in the USA (Eskenazi and Warner, 1997) and one of the main causes of infertility in women. Cyclical bleeding from ectopic endometrial implants leads to the development of inflammation, scarring and adhesions, which produce debilitating pain and symptoms (such as chronic pelvic pain, fatigue, dysmenorrhea, dyspareunia, dysuria or dyschezia (Nnoaham *et al.*, 2011)). Unfortunately, there is delayed diagnosis, and treatment options are poor (Ballweg, 1987). Despite an estimated prevalence of 10% in women (Nnoaham *et al.*, 2011), substantial associated costs (Simoens *et al.*, 2011a, b) and considerable adverse impacts on quality of life (Nnoaham *et al.*, 2011), the etiology of endometriosis remains largely unknown.

There is evidence for the involvement of female hormones, local inflammation and disruption of immunologic processes in endometriosis (Missmer and Cramer, 2003), although it is unclear whether immune dysfunction is a cause or a consequence of the disease (Herington *et al.*, 2011). Familial aggregation of endometriosis additionally suggests a genetic contribution to the disease (Montgomery *et al.*, 2008), and some genetic factors have been identified in genome-wide association studies (Rahmioglu *et al.*, 2014). Recent evidence also suggests that environmental toxicants (such as phthalates, bisphenol A or organochlorinated pollutants) may play a role in the development of endometriosis (Buck Louis *et al.*, 2013; Porpora *et al.*, 2013). However, the only factors that have been robustly associated with endometriosis to date reflect increased exposure to menstruation (i.e. earlier menarche, shorter menstrual cycles and nulliparity) (Missmer and Cramer, 2003) and a low body mass index (Vigano *et al.*, 2012). Modifiable risk factors remain to be identified to help primary prevention of endometriosis.

While little is understood about the causes of the disease, endometriosis has been associated with several types of cancer, autoimmune diseases, asthma/atopic diseases or cardiovascular diseases over recent decades, suggesting that endometriosis patients may represent a high-risk group for these chronic diseases. A deep understanding of the associations between endometriosis and other chronic disease outcomes may thus extend our knowledge and provide new leads into the causes or consequences of endometriosis. Also, given the prevalence of endometriosis, the development of targeted prevention and early detection guidelines for these chronic diseases may have a significant public health impact (Missmer, 2009).

This review summarizes the available epidemiological findings on the associations between endometriosis and major chronic diseases, and discusses hypotheses for underlying mechanisms, potential sources of bias and methodological complexities.

Methods

We performed a comprehensive search of the PubMed/Medline and ISI Web of Knowledge databases for all epidemiological studies reporting on the associations between endometriosis and other diseases published up to May 2014. The search terms included 'endometriosis' in combination with the following terms: 'cancer', 'breast cancer', 'ovarian cancer', 'endometrial cancer', 'melanoma', 'skin cancer', 'colorectal cancer', 'lymphoma', 'thyroid cancer', 'autoimmune disease', 'systemic lupus erythematosus', 'Sjögren's syndrome', 'scleroderma', 'multiple sclerosis', 'rheumatoid arthritis', 'inflammatory bowel disease', 'celiac disease', 'asthma', 'allergy', 'atopic disease', 'cardiovascular disease', 'myocardial infarction', 'atherosclerosis', 'angina'. We additionally examined the reference lists of all identified papers to capture any additional articles that were not identified through computer searches.

We summarized the current literature on the topic, and based on the retrieved publications and the experience of our group on this topic, we identified and discussed hypotheses for underlying mechanisms, potential sources of bias, and methodological complexities related to the exploration of such associations.

Results

Cancer

While endometriosis is generally regarded as a benign condition, evidence suggests a potential link with some cancers. The disease has even been suggested to share some characteristics with malignant tumors, such as local and distant invasion, abnormal tissue growth, dysfunction of target organs and genetic damage (Garry, 2001). The epidemiological studies that have investigated the link between endometriosis and cancer are reviewed below.

Gynecological cancers

Of all neoplasms, ovarian cancer has been the most consistently associated with endometriosis. This association was first identified by Sampson in 1925 (Sampson 1925) and has been observed in a number of clinical case series reporting a high rate of endometriosis in ovarian cancer patients (Somigliana *et al.*, 2006; Heidemann *et al.*, 2014). Among the 21 epidemiological studies that have investigated endometriosis in relation to ovarian cancer risk to date (Fig. 1), 20 reported a positive association (including 16 which reported statistically significant findings) (Brinton *et al.*, 1997, 2004, 2005; Venn *et al.*, 1999; Ness *et al.*, 2000, 2002; Cottreau *et al.*, 2003; Borgfeldt and Andolf, 2004; Modugno *et al.*, 2004; Melin *et al.*, 2006, 2007; Kobayashi *et al.*, 2007; Merritt *et al.*, 2008; Nagle *et al.*, 2008; Rossing *et al.*, 2008; Aris, 2010; Gemmill *et al.*, 2010; Bodmer *et al.*, 2011; Pearce *et al.*, 2012; Buis *et al.*, 2013) (Table I). Most of these reports were based on a case–control or a retrospective cohort design, or were focused on specific

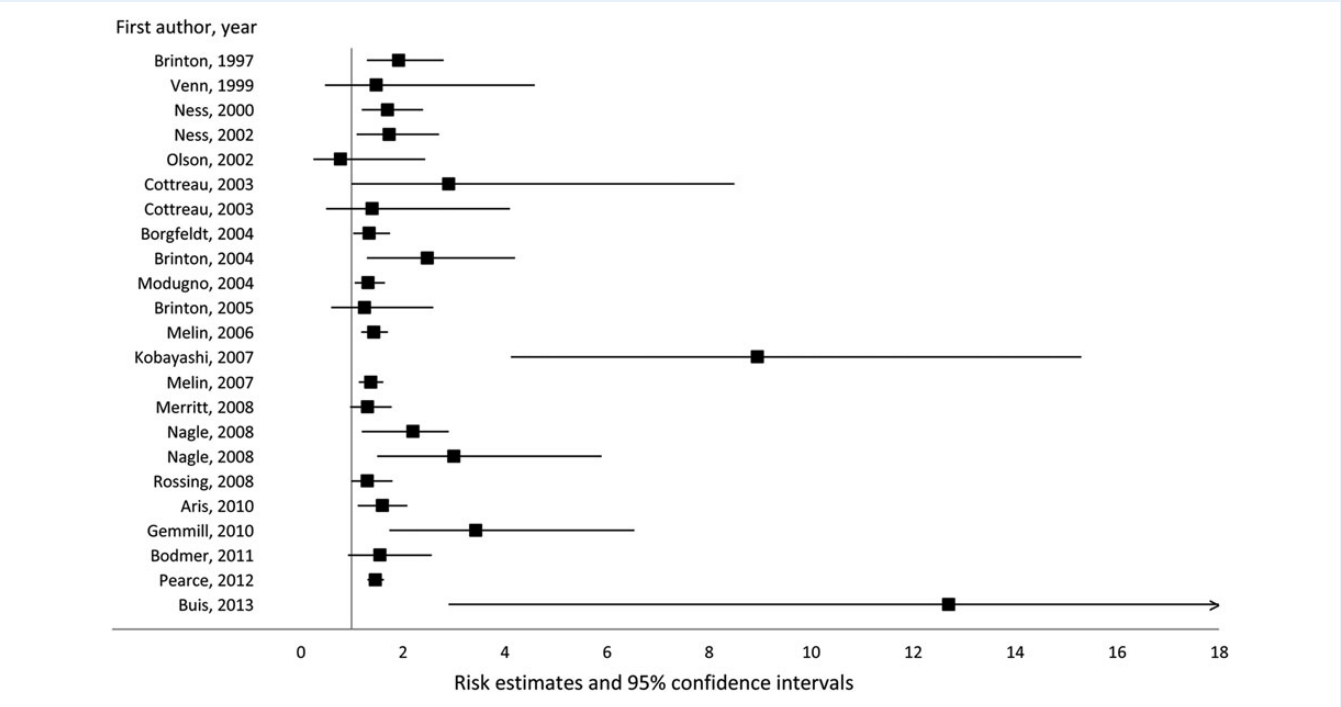

Figure 1 Association between endometriosis and ovarian cancer risk.

populations (i.e. cohort of endometriosis patients, or cohort of women evaluated for infertility). The sole study reporting no association was based on a cohort of post-menopausal women (Olson *et al.*, 2002).

The reports suggesting a positive association include two large pooled analyses of case–control studies on ovarian cancer, which include the published analyses in individual studies and have overlapping analysis populations. Ness *et al.* pooled the data from eight case–control studies that ascertained 3678 ovarian cancer cases over 1989–1999 and observed a pooled odds-ratio (OR) of 1.73 (95% confidence interval (CI) = 1.10–2.71) for ovarian cancer risk in relation to self-reported endometriosis (Ness *et al.*, 2002). Pearce *et al.* used data from the Ovarian Cancer Association Consortium in a pooled analysis of 13 case–control studies that included 7911 invasive ovarian cancer cases and 1907 borderline ovarian tumors ascertained over 1992–2008, constituting the largest evaluation of the association to date (Pearce *et al.*, 2012). The analysis produced a pooled OR of 1.46 (95% CI = 1.31–1.63) for self-reported endometriosis in relation to invasive ovarian cancer risk. In that report, subtype analyses suggested 2-fold increased risks of endometrioid or low-grade serous subtypes, and a 3-fold increased risk of clear-cell ovarian cancer, but no significantly increased risk of mucinous or high-grade serous tumors, and there was no significant association between endometriosis and borderline ovarian cancer risk.

Recently, a meta-analysis evaluated the associations between endometriosis and risk and prognosis of ovarian cancer in studies published between 1990 and 2012 (Kim *et al.*, 2014). In case–control or two-arm studies, the RR was 1.27 (95% CI = 1.21–1.32), and the standardized incidence ratio (SIR) was 1.80 (95% CI = 1.28–2.53) in single-arm cohort studies. A significant positive association was observed regardless of study design, assessment of endometriosis, quality score of study or number of adjustment factors. Interestingly, ovarian cancer associated with endometriosis was associated with better overall survival and early-stage, low-grade ovarian cancer, although progression-free ovarian cancer survival did not differ according to the presence of endometriosis.

Findings for other gynecological cancers have been conflicting. While most studies suggest a modest positive association between endometriosis and the risk of breast cancer (albeit only three reported significant positive associations) (Moseson *et al.*, 1993; Brinton *et al.*, 1997; Schairer *et al.*, 1997; Borgfeldt and Andolf, 2004; Melin *et al.*, 2006, 2007), four observed no clear association (Venn *et al.*, 1999; Weiss *et al.*, 1999; Olson *et al.*, 2002; Bertelsen *et al.*, 2007) and four reported an inverse relation (Baron *et al.*, 2001; Brinton *et al.*, 2005; Gemmill *et al.*, 2010; Matta *et al.*, 2013) (Fig. 2). None of the available studies evaluated heterogeneity of the findings according to breast cancer type, hormone receptor status or molecular subtype.

Regarding endometrial cancer, the main issue in previous investigations was the low number of cases, which offered little statistical power to adequately explore its relation with endometriosis. Most studies (with numbers of endometrial cancer cases ranging from 12 to 97) observed no association (Brinton *et al.*, 1997, 2005; Venn *et al.*, 1999; Melin *et al.*, 2007), while two studies (including one with 454 cases (Zucchetto *et al.*, 2009)) reported increased endometrial cancer risk in women with endometriosis (Melin *et al.*, 2006; Zucchetto *et al.*, 2009), in contrast to one report suggesting a significantly inverse association (Borgfeldt and Andolf, 2004) (Fig. 3).

While statistical power was even lower for cervical cancer in previous studies, all of the available investigations to date, all from Sweden, have reported decreased risks in women with endometriosis (Brinton *et al.*, 1997; Borgfeldt and Andolf, 2004; Melin *et al.*, 2006, 2007) (of note, data from two of these studies (Brinton *et al.*, 1997; Melin *et al.*, 2006)

Table I Epidemiological studies exploring the associations between endometriosis and cancer.

Studies	Geographic location	Study period	Design	Endometriosis number and ascertainment	Cancer cases	Risk estimates (RR, OR or SIR and 95% CI)	Comments
Ovarian cancer							
Brinton *et al.* (1997)	Sweden	1969–1989	Retrospective cohort	20 686 Clinical records	29	1.92 (1.3–2.8)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Venn *et al.* (1999)	Australia	1986–1996	Retrospective cohort	– Clinical records	13	1.48 (0.48–4.59)	Cohort of women referred to an IVF clinic
Ness *et al.* (2000)	US	1994–1998	Case–control	151 Self-report	767	1.7 (1.2–2.4)	
Ness *et al.* (2002)	Multiple	1989–1999	Pooled analysis of case–control studies	90 Self-report	3678	1.73 (1.10–2.71)	
Olson *et al.* (2002)	US	1986–1998	Prospective cohort	1392 Self-report	188	0.78 (0.25–2.44)	Cohort of post-menopausal women Age-adjusted estimate
Cottreau *et al.* (2003)	Multiple	1989–1999	Case–control	249 Self-report	1373	2.9 (1.0–8.5) 1.4 (0.5–4.1)	In danazol users In lupron or nafarelin users
Borgfeldt and Andolf (2004)	Sweden	1969–1997	Case–control	28 163 Clinical records	81	1.34 (1.03–1.75)	
Brinton *et al.* (2004)	US	1965–1999	Retrospective cohort	1919 Clinical records	45	2.48 (1.3–4.2)	Cohort of women evaluated for infertility
Modugno *et al.* (2004)	US	1993–2001	Case–control	361 Self-report	2098	1.32 (1.06–1.65)	
Brinton *et al.* (2005)	US	1965–1999	Retrospective cohort	– Clinical records	45	1.25 (0.6–2.6)	Cohort of women evaluated for infertility
Melin *et al.* (2006)	Sweden	1969–2000	Retrospective cohort	64 492 Clinical records	122	1.43 (1.19–1.71)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Kobayashi *et al.* (2007)	Japan	1985–2002	Prospective cohort	6398 Clinical records	46	8.95 (4.12–15.3)	Cohort of women with clinically documented endometriomas
Melin *et al.* (2007)	Sweden	1958–2002	Retrospective cohort (update)	63 630 Clinical records	134	1.37 (1.14–1.62)	Cohort of women hospitalized for endometriosis
Merritt *et al.* (2008)	Australia	2002–2005	Case–control	211 Self-report	1576	1.31 (0.97–1.78)	Increased risks observed for endometrioid (1.85, 1.02–3.38) and clear cell (2.66, 1.31–5.44) subtypes, but not with mucinous or serous types
Nagle *et al.* (2008)	Australia	2002–2005	Case–control	118 Self-report	142 endometrioid 90 clear cell	2.2 (1.2–3.9) 3.0 (1.5–5.9)	

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Table I *Continued*

Studies	Geographic location	Study period	Design	Endometriosis number and ascertainment	Cancer cases	Risk estimates (RR, OR or SIR and 95% CI)	Comments
Rossing *et al.* (2008)	US	2002–2005	Case–control	175 Self-report	812	1.3 (1.0–1.8)	Association with endometrioid and clear cell invasive subtypes combined (2.8, 1.7–4.7) but not with other subtypes, and with invasive (1.5, 1.1–2.1) but not borderline tumors
Aris (2010)	Canada	1997–2006	Cross-sectional	2521 Computerized patients' records	292 Identified from cancer registry	1.6 (1.12–2.09)	Endometriosis-associated ovarian cancer was mostly of the endometrioid (24.4%, $P = 0.007$) and clear-cell types (21.9%, $P = 0.003$)
Gemmill *et al.* (2010)	US	1998	Cross-sectional	– Self-report of a surgical diagnosis	–	3.43 (1.74–6.54)	Cohort of patient members of the Endometriosis Association
Bodmer *et al.* (2011)	UK	1995–2009	Case–control	88 Recorded diagnosis from National General Practitioner Database	1161 Recorded diagnosis from National General Practitioner Database	1.55 (0.93–2.57)	
Pearce *et al.* (2012)	Multiple locations	1992–2008	Pooled analysis of case–control studies	1556 Self-report	7911 invasive 1907 borderline	1.46 (1.31–1.63)	Associations with clear-cell (3.05, 2.43–3.84), endometrioid (2.04, 1.67–2.48) and low-grade serous (2.11, 1.39–3.20) tumors, but not with mucinous, high-grade serous or borderline tumors
Buis *et al.* (2013)	The Netherlands	1980–2007	Retrospective cohort	3657 Clinical records	19	12.7 (2.9–55.5)	Cohort of women with subfertility problems
Breast cancer							
Moseson *et al.* (1993)	US	1977–1981	Case–control	747 Self-report	354	1.7 (0.6–5.1)	
Brinton *et al.* (1997)	Sweden	1969–1989	Retrospective cohort	20 686 Clinical records	297	1.27 (1.1–1.4)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Schairer *et al.* (1997)	Sweden	1965–1987	Retrospective cohort	5 Clinical records	295	3.2 (1.2–8.0) in those with hysterectomy indicated for endometriosis treatment 1.7 (0.7–4.1) in those with oophorectomy indicated for endometriosis treatment	Cohort of women who underwent gynecological surgery

Venn *et al.* (1999)	Australia	1986–1996	Retrospective cohort	– Clinical records	143	1.04 (0.71–1.54)	Cohort of women referred to an IVF clinic
Weiss *et al.* (1999)	US	1990–1992	Case–control	96 Self-report of surgical diagnosis	2173	1.14 (0.7–1.8)	
Baron *et al.* (2001)	US	1990–1994	Case–control	541 Self-report	5659	0.8 (0.7–1.0)	
Olson *et al.* (2002)	US	1986–1998	Prospective cohort	1392 Self-report	1795	0.96 (0.75–1.23)	Cohort of post-menopausal women
Borgfeldt and Andolf (2004)	Sweden	1969–1997	Case–control	28 163 Clinical records	427	1.10 (0.98–1.23)	
Brinton *et al.* (2005)	US	1965–1999	Retrospective cohort	– Clinical records	292	0.78 (0.6–1.1)	Cohort of women evaluated for infertility
Melin *et al.* (2006)	Sweden	1969–2000	Retrospective cohort	64 492 Clinical records	1288	1.04 (0.98–1.09)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Bertelsen *et al.* (2007)	Denmark	1978–1998	Retrospective cohort	1978 Clinical records	16 983	0.97 (0.85–1.11)	Inverse associations in women with <40 years of age at endometriosis diagnosis; but positive association in those ≥ 50 years at endometriosis diagnosis
Melin *et al.* (2007)	Sweden	1958–2002	Retrospective cohort (update)	63 630 Clinical records	1465	1.08 (1.02–1.13)	Cohort of women hospitalized for endometriosis
Gemmill *et al.* (2010)	US	1998	Cross-sectional	– Self-report of a surgical diagnosis	–	0.54 (0.32–0.90)	Cohort of patient members of the Endometriosis Association
Matta *et al.* (2013)	Puerto Rico	2006–2012	Case–control	80 Self-report of a surgical diagnosis	385	0.5 (0.3–0.9)	
Endometrial cancer							
Brinton *et al.* (1997)	Sweden	1969–1989	Retrospective cohort	20 686 Clinical records	12	1.09 (0.6–1.9)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Venn *et al.* (1999)	Australia	1986–1996	Retrospective cohort	– Clinical records	12	0.91 (0.13–6.49)	Cohort of women referred to an IVF clinic
Olson *et al.* (2002)	US	1986–1998	Prospective cohort	1392 Self-report	–	1.20 (0.57–2.53)	Cohort of post-menopausal women
Borgfeldt and Andolf (2004)	Sweden	1969–1997	Case–control	28 163 Clinical records	39	0.58 (0.42–0.81)	
Brinton *et al.* (2005)	US	1965–1999	Retrospective cohort	– Clinical records	39	0.82 (0.3–1.9)	Cohort of women evaluated for infertility
Melin *et al.* (2006)	Sweden	1969–2000	Retrospective cohort	64 492 Clinical records	92	1.19 (0.96–1.46)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)

Continued

Table I *Continued*

Studies	Geographic location	Study period	Design	Endometriosis number and ascertainment	Cancer cases	Risk estimates (RR, OR or SIR and 95% CI)	Comments
Melin *et al.* (2007)	Sweden	1958–2002	Retrospective cohort (update)	63 630 Clinical records	97	1.14 (0.93–1.39)	Cohort of women hospitalized for endometriosis
Zucchetto *et al.* (2009)	Italy	1992–2006	Case–control	11 Self-report	454	4.03 (1.04–15.52)	
Cervical cancer							
Brinton *et al.* (1997)	Sweden	1969–1989	Retrospective cohort	20 686 Clinical records	11	0.72 (0.4–1.3)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Borgfeldt and Andolf (2004)	Sweden	1969–1997	Case–control	28 163 Clinical records	23	0.57 (0.37–0.90)	
Melin *et al.* (2006)	Sweden	1969–2000	Retrospective cohort	64 492 Clinical records	51	0.64 (0.47–0.84)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Melin *et al.* (2007)	Sweden	1958–2002	Retrospective cohort (update)	63 630 Clinical records	49	0.71 (0.53–0.94)	Cohort of women hospitalized for endometriosis
Cutaneous melanoma							
Wyshak *et al.* (1989)	US	1981	Cross-sectional	9 Self-report	18	3.9 (1.2–12.4)	
Frisch *et al.* (1992)	US	–	Case–control	– Self-report	71	1.1 (0.5–2.3)	
Holly *et al.* (1995)	US	1981–1986	Case–control	– Self-report	452	0.9 (0.5–1.4)	
Brinton *et al.* (1997)	Sweden	1969–1989	Retrospective cohort	20 686 Clinical records	35	1.0 (0.7–1.5)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Wyshak and Frisch (2000)	US	–	Cross-sectional (update)	– Self-report	62	OR = 2.6, $P = 0.3$ in red-haired	
Young *et al.* (2001)	Australia	1980–1990	Retrospective case-cohort	3 Clinical records	14	0.62 (0.16–2.41)	
Olson *et al.* (2002)	US	1986–1998	Prospective cohort	1392 Self-report	–	0.67 (0.25–1.80)	Cohort of post-menopausal women
Brinton *et al.* (2005)	US	1965–1999	Retrospective cohort	– Clinical records	42	2.06 (1.0–4.4)	Cohort of women evaluated for infertility
Melin *et al.* (2006)	Sweden	1969–2000	Retrospective cohort	64 492 Clinical records	186	1.16 (1.00–1.33)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Kvaskoff *et al.* (2007)	France	1990–2002	Prospective cohort	5949 Self-report of diagnosis or treatment through specific procedures	363	1.62 (1.15–2.29)	

Melin *et al.* (2007)	Sweden	1958–2002	Retrospective cohort (update)	63 630 Clinical records	217	1.23 (1.07–1.40)	Cohort of women hospitalized for endometriosis
Gemmill *et al.* (2010)	US	1998	Cross-sectional	– Self-report of a surgical diagnosis	–	3.81 (2.60–5.56)	Cohort of patient members of the Endometriosis Association
Non-Hodgkin's lymphoma							
Brinton *et al.* (1997)	Sweden	1969–1989	Retrospective cohort	20 686 Clinical records	28	1.79 (1.2–2.6)	Cohort of women hospitalized for endometriosis Data included in Melin *et al.* (2007)
Olson *et al.* (2002)	US	1986–1998	Prospective cohort	1392 Self-report	243	1.67 (0.97–2.87)	Cohort of post-menopausal women
Gemmill *et al.* (2010)	US	1998	Cross-sectional	– Self-report of a surgical diagnosis	–	0.84 (0.14–3.37)	Cohort of patient members of the Endometriosis Association

CI, confidence interval; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio.

were included in the most recent historical cohort on this topic (Melin *et al.*, 2007)).

Other cancers

Among non-gynecological cancers, cutaneous melanoma has been the most studied in relation to a history of endometriosis. Out of the 12 studies that explored this topic, seven suggested a positive association (Wyshak *et al.*, 1989; Wyshak and Frisch, 2000; Brinton *et al.*, 2005; Melin *et al.*, 2006, 2007; Kvaskoff *et al.*, 2007; Gemmill *et al.*, 2010), while 5 studies reported no clear relation between endometriosis and cutaneous melanoma risk (Frisch *et al.*, 1992; Holly, Cress and Ahn, 1995; Brinton *et al.*, 1997; Young *et al.*, 2001; Olson *et al.*, 2002) (Fig. 4). Only three studies to date have assessed endometriosis in relation to non-melanoma skin cancers (basal-cell carcinoma and squamous-cell carcinoma), none of which detected evidence of an association (Wyshak *et al.*, 1989; Brinton *et al.*, 1997; Melin *et al.*, 2006).

Explorations of endometriosis in relation to other types of cancer have been sparse. Two cohort studies have reported a higher risk of non-Hodgkin's lymphoma in women with endometriosis (Brinton *et al.*, 1997; Olson *et al.*, 2002), while a cross-sectional study among patient members of the Endometriosis Association observed no association (Gemmill *et al.*, 2010). Women with endometriosis were reported to be at increased risk of brain cancer in three studies (Melin *et al.*, 2006, 2007; Claus *et al.*, 2011), of endocrine cancers in two studies (Melin *et al.*, 2006, 2007), and of thyroid or kidney cancer in one study (Melin *et al.*, 2007). However, other studies showed no association between endometriosis and any of these or other cancers (Brinton *et al.*, 1997, 2005; Olson *et al.*, 2002).

Autoimmune diseases

Women have been shown to have a higher prevalence than men of several autoimmune diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), scleroderma, multiple sclerosis (MS) and rheumatoid arthritis (RA) (Tiniakou *et al.*, 2013). While part of this female preponderance has been proposed to reflect sex differences in genetic and environmental exposures (Quintero *et al.*, 2012; Tiniakou *et al.*, 2013), it has also led to the hypothesis that female hormones have a fundamental role in the pathogenesis of these diseases (Pennell *et al.*, 2012). Consistently, estrogens and prolactin have been shown to act as immune stimulants, while androgens are immune suppressors, and experimental studies show that each of these hormones promotes specific immunologic events in different types of autoimmune diseases (Quintero *et al.*, 2012). Women with endometriosis have been demonstrated to exhibit altered immune surveillance, with depressed cell-mediated immunity (high T-, B-, and natural killer cell counts but decreased activity) and heightened humoral immune response (high serum levels of IgG, IgA, IgM autoantibodies, and anti-endometrial antibodies) (Nothnick, 2001), abnormalities which are also observed in autoimmune diseases (Eisenberg *et al.*, 2012).

Few studies have evaluated the co-morbidity of endometriosis with autoimmune diseases (Table II). A cross-sectional survey conducted among patient members of the Endometriosis Association first reported higher than expected rates of SLE, MS, RA and SS than in the general female US population (Sinaii *et al.*, 2002). While the latter study relied on self-reported diagnosis of autoimmune diseases, a later Spanish case–control study based on clinical record information reported no

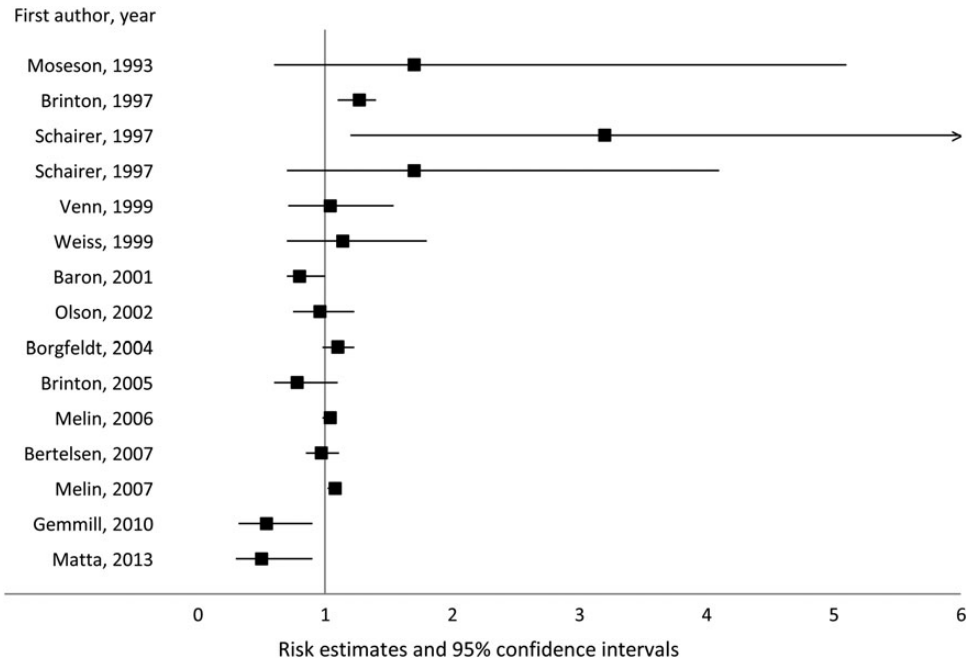

Figure 2 Association between endometriosis and breast cancer risk.

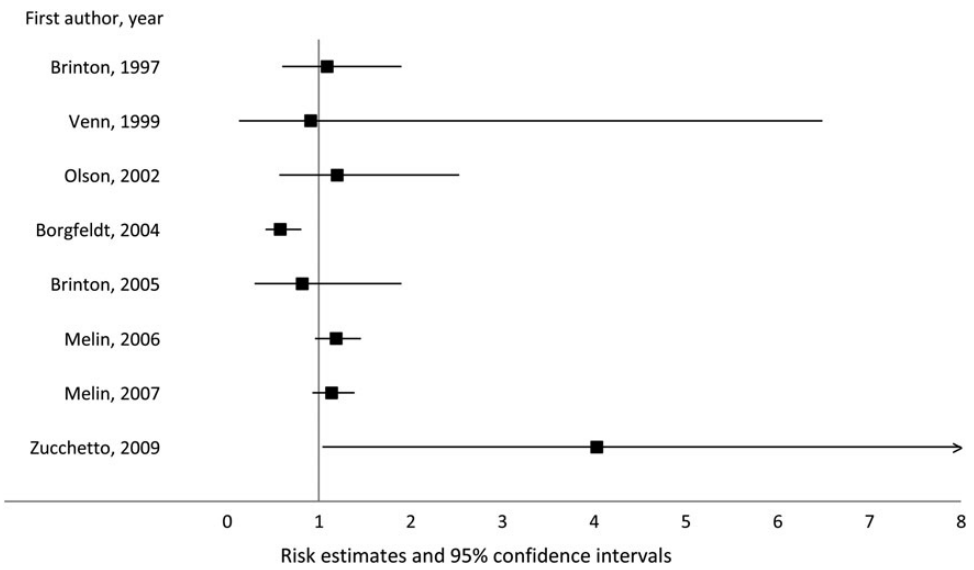

Figure 3 Association between endometriosis and endometrial cancer risk.

significant association between endometriosis and risk of SLE or SS (Matorras *et al.*, 2007). However, the most recent and largest report to date, based on a retrospective cohort relying on clinical records ($n = 37\,661$), observed a significant increased risk of SLE (SIR = 1.6; $n = 54$ cases), SS (SIR = 1.6; $n = 86$ cases) and MS (SIR = 1.2; $n = 130$ cases) in Denmark (Nielsen *et al.*, 2011). When the analyses were restricted to surgically verified endometriosis, associations were attenuated, except for MS, for which the association was slightly strengthened and statistically significant. The same group also reported significantly increased risks of inflammatory bowel diseases (ulcerative colitis (SIR = 1.5; $n = 228$ cases) or Crohn's disease (SIR = 1.6; $n = 92$ cases)), and these relations were stronger when restricted to surgically verified endometriosis (Jess *et al.*, 2012). Three studies evaluated the association between endometriosis and celiac disease: two case–control studies, based on low numbers of celiac disease cases ($n = 3$ and $n = 7$, respectively), reported either a statistically significant positive association (OR = 3.8) (Aguiar *et al.*, 2009) or a non-significant higher occurrence of celiac disease among endometriosis patients (2.2%) compared with

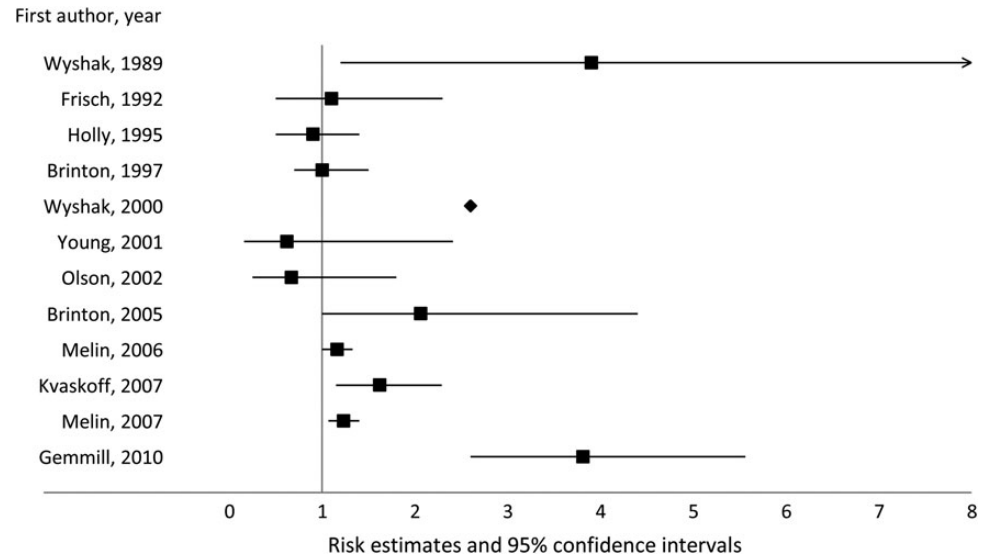

Figure 4 Association between endometriosis and cutaneous melanoma risk.

controls (0.8%) (Santoro *et al.*, 2014). A large Swedish cohort study, based on registry and population registers, confirmed a significantly positive association between celiac disease and endometriosis (HR = 1.39, 1.14–1.70) (Stephansson *et al.*, 2011). Finally, no association was observed between endometriosis and risk of autoimmune thyroid disorders, hypo- or hyperthyroidism in a Brazilian cross-sectional study (Petta *et al.*, 2007).

Asthma/allergies

Pertinent to the aberrant immunologic response and heightened inflammatory reaction in women with endometriosis, endometriosis patients also tend to be more susceptible to allergic manifestations and to allergy-related conditions such as asthma or atopic diseases than women without endometriosis (Bungum *et al.*, 2014). The first suggestion of such associations came from two early US studies from the same group, which reported higher rates of eczema, hay fever, food sensitivities and allergic reactions in endometriosis cases compared with controls (Lamb and Nichols, 1986; Nichols *et al.*, 1987) (Table III). Then, the survey of patient members of the Endometriosis Association suggested a higher proportion of reported allergies and asthma as compared with the general US female population (Sinaii *et al.*, 2002). While a later case–control study reported a similar prevalence of asthma among women with or without endometriosis (Ferrero *et al.*, 2005), a recent study found significantly higher risks of endometriosis among women with allergies (OR = 4.3), asthma (OR = 2.2), allergic rhinitis (OR = 23.3), medication (OR = 4.7) or penicillin (OR = 7.0) allergy, or with allergic disease in first-degree relatives (OR = 8.8) (Matalliotakis *et al.*, 2012). In addition, in a case–control study in Italy, Ammendola *et al.* observed a significantly higher proportion of allergies in women with endometriosis (Ammendola *et al.*, 2008). In that study, carriers of the C allele of the acid phosphatase locus 1 (ACP1) polymorphism, suggested to have a role in allergic manifestations, were at higher risk of endometriosis than those carrying other genotypes, although this gene was not reported to be associated with endometriosis in genome-wide scans (Rahmioglu *et al.*, 2014).

Cardiovascular diseases

Levels of various inflammatory factors, such as intracellular adhesion molecule 1 (ICAM-1), C-reactive protein (CRP), interleukin-1 and 6 (IL-1 and IL-6), tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF), have been shown to be elevated in the peritoneal fluid and peripheral blood of women with endometriosis (Koumantakis *et al.*, 1994; Wu *et al.*, 1998; Pizzo *et al.*, 2002; Bedaiwy *et al.*, 2006; Agic *et al.*, 2007), suggesting that endometriosis is associated with local and systemic chronic inflammation. Recent evidence also suggests higher levels of markers of oxidative stress (Van Langendonckt *et al.*, 2002; Szczepanska *et al.*, 2003; Gupta *et al.*, 2006) and higher serum levels of low-density lipoprotein in women with endometriosis (Melo *et al.*, 2010). Because inflammation, oxidative stress and an atherogenic lipid profile play key roles in the pathogenesis of coronary heart disease (CHD) (Hansson, 2005; Bonomini *et al.*, 2008), and because endometriosis and CHD may share a common genetic background (Mu *et al.*, manuscript under consideration for publication), endometriosis patients may be at increased risk of cardiovascular diseases.

Pretta *et al.* examined whether women with endometriosis ($n = 66$) had more subclinical atherosclerosis than controls ($n = 66$) by comparing their intima-media thickness and distensibility coefficient on the common carotid artery (Pretta *et al.*, 2007). While no significant difference was reported, it is important to note the small sample size and thus low power of the study. However, despite even smaller sample sizes ($n = 41$ cases/28 controls and $n = 37$ cases/31 controls, respectively), two subsequent studies showed significantly lower values of flow-mediated dilation in endometriosis patients compared with controls (Kinugasa *et al.*, 2011; Santoro *et al.*, 2012), although no significant differences were observed in common carotid intima-media thickness between groups in the second study (Santoro *et al.*, 2012). Recently, a prospective analysis of endometriosis in relation to CHD risk in the Nurses' Health Study II showed increased risks of myocardial infarction (RR = 1.52, 95% CI = 1.17–1.98; $n = 498$), angiographically confirmed angina (RR = 1.91, 1.59–2.29; $n = 891$), and coronary artery bypass

Table II Epidemiological studies exploring the associations between endometriosis and autoimmune diseases.

Studies	Geographic location	Study period	Design	Endometriosis number and ascertainment	AID cases and ascertainment	Risk estimates (RR, OR or SIR and 95% CI)
Sinaii *et al.* (2002)	US	1998	Cross-sectional	3680 Self-report of a surgical diagnosis	31 SLE 19 MS 68 RA 23 SS Self-report	SLE: 20.7 (14.3–29.9) MS: 7.1 (4.4–11.3) RA: 1.5 (1.2–1.9) SS: 23.9 (15.5–36.5)
Matorras *et al.* (2007)	Spain	1990–2004	Case–control	342 Clinical records	120 SLE 22 SS Clinical records	SLE: 0.37 (0.09–1.59) SS: 2.17 (0.48–9.90)
Petta *et al.* (2007)	Brazil	2005–2006	Cross-sectional	148 Surgically confirmed	38 AITD 5 hyperthyroidism 30 hypothyroidism Clinical records	0.52 (0.25–1.06) 0.09 (0.01–1.65) 1.49 (0.69–3.23) No difference in AITD/thyroid dysfunction risk according to endometriosis stage
Aguiar *et al.* (2009)	Brazil	2000–2003	Case–control	120 Laparoscopically confirmed	3 CeD Intestinal biopsy	3.8 (1.03–14.08)
Nielsen *et al.* (2011)	Denmark	1977–2007	Retrospective cohort	37 661 Clinical records	130 MS 54 SLE 86 SS Clinical records	MS: 1.2 (1.05–1.5) SLE: 1.6 (1.2–2.1) SS: 1.6 (1.3–2.0) In surgically verified endometriosis: MS: 1.4 (1.04–1.9) SLE: 1.1 (0.6–2.1) SS: 1.4 (0.9–2.3)
Stephansson *et al.* (2011)	Sweden	1969–2008	Prospective cohort	517 Hospital registry records	11 097 CeD Biopsy reports	1.39 (1.14–1.70) 1.35 (1.07–1.69) in women aged 16–45 years at study entry
Jess *et al.* (2012)	Denmark	1977–2007	Retrospective cohort	37 661 Clinical records	228 UC 92 CD Clinical records	IBD: 1.5 (1.4–1.7) UC: 1.5 (1.3–1.7) CD: 1.6 (1.3–2.0) In surgically verified endometriosis: UC: 1.8 (1.4–2.3) CD: 1.7 (1.2–2.5)
Santoro *et al.* (2014)	Italy	2012	Case–control	223 Laparoscopically confirmed	7 CeD Intestinal biopsy	CeD occurrence in endometriosis patients (2.2%) higher than that among controls (0.8%) ($P = 0.265$)

AI, autoimmune; AID, autoimmune disease; AITD, autoimmune thyroid disease; CD, Crohn's disease; CeD, celiac disease; CI, confidence interval; IBD, inflammatory bowel disease; MS, multiple sclerosis; OR, odds ratio; RA, rheumatoid arthritis; RR, relative risk; SIR, standardized incidence ratio; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; UC, ulcerative colitis.

Table III Epidemiological studies exploring the associations between endometriosis and asthma and atopic diseases.

Studies	Geographic location	Study period	Design	Asthma/atopic disease number and ascertainment	Endometriosis number and ascertainment	Risk estimates (RR, OR or SIR and 95% CI) or frequency	Comments
Lamb and Nichols (1986)	US	–	Case–control	– Self-report	43	Eczema, hay fever and food sensitivities were significantly more common in women with endometriosis than controls	Only the abstract could be viewed
Nichols *et al.* (1987)	US	–	Case–control	– Self-report	88	Women with endometriosis were significantly more likely to report allergic manifestations	Only the abstract could be viewed
Sinaii *et al.* (2002)	US	1998	Cross-sectional	Allergies: 2245 Asthma: 442 Self-report	3680 Self-report of a surgical diagnosis	– 61% reported allergies versus 18% in the general female US population – 12% reported asthma versus 6% in the general female US population	
Ferrero *et al.* (2005)	US	2001–2004	Case–control	Asthma: 45 Self-report	467 Histologically confirmed	Similar prevalence of asthma in women with endometriosis (4.9%, CI = 3.1–7.3) and those without (5.3%, CI = 3.4–8.0), $P = 0.78$	Asthma patients responded to LWAQ
Ammendola *et al.* (2008)	Italy	–	Case–control	Allergy tested by prick tests	113 Laparoscopically confirmed	– Higher proportion of women with a positive prick test among endometriosis patients (45.6% versus 24.7%, OR = 2.55, 95% CI = 1.53–4.27) – Carriers of the *C allele of the ACP1 polymorphism were at higher risk of endometriosis (OR = 1.99, 95% CI = 1.15–3.41)	
Matalliotakis *et al.* (2012)	US	1996–2002	Case–control	Allergies: 328 Self-report	501 Surgically confirmed	Allergies: 4.28 (2.9–6.3) Asthma: 2.22 (1.03–4.80) Allergic rhinitis: 23.32 (9.42–57.73) Medication allergy: 4.66 (3.09–7.02) Penicillin allergy: 7.01 (3.31–14.86) First-degree relative with allergic disease: 8.82 (5.27–14.79) No significant differences according to severity of endometriosis	The 188 controls had surgical evaluation and were confirmed not to have endometriosis

ACP1, acid phosphatase locus 1; CI, confidence interval; LWAQ, Living with Asthma Questionnaire; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio.

graft surgery/coronary angioplasty procedure/stent (RR = 1.35, 95% CI = 1.08–1.69; $n = 690$) associated with endometriosis (Mu *et al.*, manuscript under consideration for publication). Endometriosis was also associated with a higher risk of any of the three CHD events combined (RR = 1.62, 95% CI = 1.39–1.89). Part of the associations was found to be statistically accounted for by endometriosis treatments that are risk factors for CHD, such as hysterectomy/oophorectomy and earlier age at surgery following endometriosis diagnosis.

Discussion

The available epidemiological evidence suggests that women with endometriosis are at higher risks of ovarian and breast cancers, cutaneous melanoma, asthma, and some autoimmune, cardiovascular and atopic diseases, and at a decreased risk of cervical cancer.

Hypotheses for underlying mechanisms

While the exact pathophysiology underlying these associations is unknown, the co-occurrence of endometriosis and other disease outcomes may reflect at least four potential explanations.

Endometriosis shares common risk factors or a common exposure profile with these outcomes

A first potential explanation is the existence of common risk factors between endometriosis and the explored disease outcomes. These risk factors could affect risk of both diseases and thus act as potential *confounders* of the association (i.e. factors associated with both the exposure and the outcome but that are *not* in the causal pathway between the exposure and the outcome; e.g. the relation between parity and Down syndrome is confounded by maternal age) or as *mediators* (i.e. factors associated with both the exposure and the outcome that *are* in the causal pathway between the exposure and the outcome and act as intermediate factors of the relation; e.g. the relation between having multiple sex partners and cervical cancer risk is mediated by the increased risk of HPV infection). They may also be unknown risk markers for endometriosis, which the association with the other disease would enable us to uncover. Multivariable modeling allowing for adjustment for multiple factors and mediation analyses may help to identify some of these factors.

Treatment for endometriosis is associated with these outcomes

Treatment for endometriosis may include hormonal treatment (oral contraceptives, gonadotrophin-releasing hormone (GnRH) agonists, medroxyprogesterone, danazol), surgical treatment (including hysterectomy), and use of analgesics. If any of these treatments were associated with the risk of the explored disease outcomes, then it would have the potential to act as a mediator of the association between endometriosis and this disease outcome. These issues can be explored through mediation analyses, and through testing for effect modification by conducting stratified analyses according to these treatments (see 'Methodological complexities' below).

In the report from our group cited in this review (Mu *et al.*, under consideration for publication), mediation analyses showed that part of the association between endometriosis and myocardial infarction and angina could be partially attributed to medical treatments for endometriosis.

Endometriosis induces a systemic change that is associated with these outcomes

It is possible that some consequences of endometriosis, such as infertility, aberrant hormonal milieu, chronic inflammation, and deficient immunologic response, as well as behavioral changes following endometriosis diagnosis (e.g. diet, physical activity), influence the long-term risk of other diseases, thus mediating the studied relationships between endometriosis and the explored disease outcomes. It is thus important to investigate this potential effect while exploring the associations between endometriosis and other diseases, which, again, may be explored through mediation or stratification analyses.

Bias

Because endometriosis and some of the explored disease outcomes (e.g. autoimmune diseases) are poorly characterized, there is potential for misclassification, which may either induce spurious associations that are only due to systematic error, or attenuate any existing association (see 'Methodological complexities' below). This bias can be minimized by selecting laparoscopically confirmed endometriosis and medically confirmed disease outcomes whenever possible. Since associations between endometriosis and the considered outcomes are likely not known from the general public, misclassification would be mostly non-differential and would thus result in an underestimation of effects. However, diagnostic, recall or other biases may also alter results in an unpredictable direction. Another bias that may be considered is the possibility that women with endometriosis may be at a higher probability of being diagnosed with one of the studied outcomes, and vice versa, because of a higher exposure to the medical system.

Methodological complexities

Temporality

Perhaps the most critical methodological aspect of evaluating the co-occurrence of endometriosis and other chronic diseases is the issue of temporality. In epidemiology, temporality is one of the criteria that support causal inference of an association. While observational studies do not allow the establishment of causal associations, prospective studies are associated with a higher level of evidence for causality, mostly because exposures are recorded prior to outcome data. However, within the context of the potential co-occurrence of endometriosis and other disease outcomes, the notion of temporality becomes more complex. We lack understanding about endometriosis initiation and progression; a mean delay of 7 years has indeed been estimated between onset of endometriosis symptoms and laparoscopic diagnosis (Nnoaham *et al.*, 2011). There is also uncertainty in the diagnosis and onset of some of the disease outcomes of interest, such as autoimmune diseases, asthma/atopic diseases, cardiovascular diseases and some slow-growing cancer diagnoses. This double imprecision, along with the potential overlapping age-specific incidence curves of endometriosis and the considered outcome, renders it difficult to evaluate the direction of the temporal association, as it is uncertain whether endometriosis precedes these disease outcomes, endometriosis and the outcome of interest occur at a similar point in time, or endometriosis represents a consequence of the altered milieu resulting from the presence of these diseases. Therefore, associations should be interpreted with caution with regards to causality.

Misclassification

Self-reported endometriosis has a high potential to be misclassified in the general population. In nurses participating in the Nurses' Health Study II cohort, ascertainment rates for endometriosis were 96% in women reporting laparoscopically confirmed endometriosis, and 54% in those without laparoscopic confirmation (Missmer *et al.*, 2010). Since this population is health-oriented, the true ascertainment rate in those with no laparoscopic confirmation is probably lower in the general female population. Outcome misclassification is usually low with respect to cancer outcomes, which are ascertained through pathology reports or cancer registry records with often high confirmation rates. However, confirmation of autoimmune diseases has the potential to be very low. In the Nurses' Health Study II, confirmation rates were 69% for SLE and 29% for RA after examination of clinical records in those who had screened positive to the Connective Tissue Disease Questionnaire, while only 7% of the original self-reports for any SLE or RA could be confirmed (Karlson *et al.*, 2004; Costenbader *et al.*, 2007).

Another issue to be considered with regards to misclassification is the choice of the comparison group in epidemiologic studies of endometriosis (Missmer and Cramer, 2003). Because of the invasive nature of laparoscopic diagnosis, and because endometriosis may be asymptomatic, there may be a fraction of undiagnosed cases in the comparison group, whether endometriosis is evaluated as an exposure or as the outcome of interest and regardless of study design, with a dilution of the association between endometriosis and the outcome of interest as a consequence. However, it has been estimated that the community prevalence of severe/symptomatic endometriosis is likely $<2\%$ (Zondervan *et al.*, 2002), suggesting that population-based control groups in case–control or cohort studies are unlikely to contain many undiagnosed cases, and thus that the risk for this bias is low in this context. In hospital-based case–control studies, control groups selected among patients diagnosed with various conditions may represent a biased sample that is unrepresentative of the exposure distribution in the source population of cases. In addition, given the evidence reviewed above suggesting a higher risk of common chronic diseases in endometriosis patients, the inclusion of patients with other conditions in the control group has the potential to lead to biased evaluations of the associations between endometriosis and chronic disease outcomes. In retrospective cohorts, study populations are usually unrepresentative of the general female population as they are focused on a selected sample, e.g. endometriosis patients, women who underwent hysterectomy or oophorectomy, or infertile women. In addition, these samples may have particular characteristics that could either mediate or modify the amplitude of the associations between endometriosis and the considered chronic disease outcome (e.g. infertile women may have received ovarian-stimulating treatments that may be in the causal pathway of the associations under study).

Confounding and mediation

Another possible source of complexity in evaluating such associations is the potential for confounding or mediation of the relation between endometriosis and other diseases. In the assessment of co-occurrence between endometriosis and other disease outcomes, it is important to evaluate if these associations are driven by common risk factors (should they be in the causal pathway between endometriosis and these outcomes or not) rather than causal biology.

Robustness

Most previous studies exploring the relations between endometriosis and other morbidities have relied on a self-reported diagnosis of endometriosis or of autoimmune/allergic diseases, retrospective designs, or limited statistical power for rarer disease outcomes (e.g. endometrial and cervical cancers). Moreover, the studies that have assessed the associations between endometriosis and cancer to date were mostly within population historical cohorts, in which potential confounding factors or mediators of the associations could not be taken into account. Ideally, future studies should explore these relations using a prospective cohort design, large sample sizes, with laparoscopically confirmed endometriosis diagnosis and medically confirmed disease outcomes, and allowing for the assessment of temporality and potential confounders and mediators of these associations.

Very few of the reviewed studies included data on endometriosis stage (Matorras *et al.*, 2007; Ferrero *et al.*, 2005; Petta *et al.*, 2007; Pretta *et al.*, 2007; Aguiar *et al.*, 2009; Kinugasa *et al.*, 2011; Matalliotakis *et al.*, 2012; Santoro *et al.*, 2012, 2014), and such data were available on too few cases to allow stage-specific comparisons with adequate statistical power (and data were restricted to severe stages (III–IV) in one study (Kinugasa *et al.*, 2011)). Two key components on the severity scale of endometriosis are the presence of endometriomas and the presence of scarring or adhesions. It is possible that the associations between endometriosis and chronic diseases are specific to one or the other feature, which would make stage III–IV endometriosis particularly correlated with the considered comorbidities. Unfortunately, due to the paucity of data on severity, type, or location of endometriosis in the available epidemiologic studies, it is currently unknown whether the associations reviewed above involve all endometriosis cases, or if they are restricted to particular subgroups of patients.

In light of the evidence reviewed above, it is legitimate to question whether the relations between endometriosis and morbidity are unique to this condition, or if women with other gynecological disorders are at higher risk of major chronic diseases also. To our knowledge, while androgen excess disorders such as polycystic ovary syndrome (PCOS) have been associated with increased cardiovascular risk (Macut *et al.*, 2014), data seem limited to date regarding reproductive disorders other than endometriosis. Some evidence suggests that PCOS is associated with the risk of certain cancer types (Barry *et al.*, 2014; Gottschau *et al.*, 2015) and thyroiditis (Du and Li, 2013); women with uterine fibroids were reported to have a possible increased risk of cardiovascular diseases (Aksoy *et al.*, 2014; Haan *et al.*, 2015) and of overt hypothyroidism (Ott *et al.*, 2014) in emerging studies; and premature ovarian insufficiency may be associated with cardiovascular risk (Roeters van Lennep *et al.*, 2014) as well as autoimmune diseases and cancer-specific mortality (Wu *et al.*, 2014). As the research in this area develops, we suggest that the methodological issues and recommendations outlined in the present review should most generally apply to the exploration of these other gynecological conditions in relation to chronic disease risk.

Conclusion

In conclusion, increasing evidence suggests that women with endometriosis are at higher risk of a number of chronic diseases. Although the underlying mechanisms are not understood, the available data to date suggest that endometriosis is not harmless with respects to women's long-term health and may have important consequences. Whether

these mechanisms involve hormones, aberrant immune or inflammatory responses, genetic or environmental factors, a combination of these factors, or the reflection of methodological bias, needs to be investigated further. Future studies should take into account the methodological considerations involved in this type of analysis. Of note, very few of the previous studies on this topic were able to use information on stage/severity or type of endometriosis, and whether the observed associations are true for a particular type or stage of disease only is currently unknown. The ability to conduct analyses by type and stage is critical, however, to increase our understanding of endometriosis and its association with other chronic diseases. It will take large, geographically diverse, multidisciplinary collaborative efforts to disentangle these complex associations. If relationships between endometriosis and these disease outcomes are confirmed, these findings will have important implications in the management and care of endometriosis patients.

Authors' roles

M.K. and S.A.M. conceived and designed the study. M.K. drafted the original manuscript. M.K., F.M., K.L.T., H.R.H., E.M.P., L.F., and S.A.M. contributed to the interpretation of data discussed in the manuscript, revised the manuscript and approved its final version.

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Conflict of interest

None declared.

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