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Early life factors for endometriosis: a systematic review

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BACKGROUND: Despite its high prevalence and health burden, many aspects of endometriosis remain unclear, including risk factors and the underlying biological mechanisms. Exposures during early life, including *in utero*, are thought to play an important role in the subsequent onset of the condition. To date, however, much of the evidence from studies on early life exposures and diagnosed endometriosis appears mixed and difficult to assess.

OBJECTIVE AND RATIONALE: This study aims to provide a systematic review of the epidemiologic evidence on early life factors associated with the subsequent diagnosis of endometriosis. *In utero* and early life exposures have previously been linked to a range of adult health outcomes, including infertility.

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SEARCH METHODS: A systematic review of case–control, cross-sectional and cohort studies was conducted using the search terms 'endometriosis'[MeSH] AND ('risk factors'[MeSH] OR 'protective factors'[MeSH]) AND ('*in utero*', 'fetal', 'neonatal, 'perinatal', 'developmental origins', 'early life', 'childhood' OR 'life course') in Embase, PubMed and Scopus databases. The review included articles published in English until 10 June 2018 with original data from studies with diagnosed endometriosis. The quality of primary studies was evaluated using the Newcastle–Ottawa Scale by both authors independently. Due to the degree of inconsistency in the measurements and study methods, a qualitative assessment of findings was undertaken rather than meta-analysis.

OUTCOMES: The search retrieved 70 records without duplicates that contained 20 records on human case–control, cross-sectional or cohort studies, from which 11 papers/studies were selected based on their assessment score. The majority of studies found that women born with low birthweight (<2.5 kg or <5.5 lb) were more likely to be diagnosed with endometriosis. For other early life factors, the evidence is mixed or limited, with further research needed on the association of endometriosis with preterm birth, *in utero* exposure to diethylstilbestrol and to maternal smoking, passive smoking in early life, and infant formula feeding (compared with breastfeeding).

WIDER IMPLICATIONS: While the weight of evidence points to low birthweight as a risk factor for diagnosis of endometriosis, future research is warranted on this and other key early life exposures where the findings are mixed to provide more robust evidence and for insights on potential causal pathways. Such research, however, needs to address current methodological issues, such as the use of prospective data from large population-based studies, better diagnostic methods to confirm disease free status, more consistent definitions of variables and consideration of potential biological mechanisms to guide the analyses. The improvements will advance the future synthesis of evidence to support clinically relevant risk assessment for a more timely diagnosis and treatment of endometriosis.

Key words: early life / endometriosis / *in utero* / protective factors / risk factors / systematic review

Introduction

Endometriosis is an oestrogen-dependant chronic gynaecological disorder where tissue that resembles endometrium (the lining of the uterus) occurs outside of the uterus, typically in the pelvic area (Zondervan *et al*., 2018). Indicators of the condition include chronic pelvic pain, dysmenorrhea (painful menstruation with heavy bleeding), dyspareunia (painful intercourse) and infertility (Missmer and Cramer, 2003; Zondervan *et al*., 2018). Endometriosis can also lead to psychological, physical and social difficulties (Ferreira *et al*., 2016) and carries a high economic burden from both direct and indirect health costs (Simoens *et al*., 2007).

Reliable diagnosis of endometriosis currently requires surgical visualisation, most commonly via laparoscopy. As a result, the prevalence of the disease in the general population is difficult to quantify as it can vary by diagnostic method and may be underestimated due to undiagnosed disease. Based on estimates of pelvic pain and subfertility, less than 2% of women of reproductive age have moderate or severe endometriosis and the prevalence of the disease at all stages is reported as 5–10% (Shafrir *et al*., 2018; Zondervan *et al*., 2018, As-Sanie *et al*., 2019). Community based studies, however, report a wider range of prevalence for diagnosed endometriosis, for example from 4% of women in a large French cohort study (Farland *et al*., 2017) to 11–11.5% for three studies of women in the USA and Australia (Leibson *et al*., 2004; Buck Louis *et al*., 2011; Australian Institute of Health and Welfare, 2019). The prevalence of endometriosis is typically much higher for studies that recruit women with gynaecological or reproductive problems, for example in a Belgian study of women with infertility (with or without pelvic pain) reporting that 47% were diagnosed with endometriosis via laparoscopy (Meuleman *et al*., 2009). A recent systematic review of 15 studies of adolescents found that overall 65% of girls undergoing laparoscopic investigation were diagnosed with endometriosis, including 75% of those with chronic pelvic pain resistant to treatment (Janssen *et al*., 2013).

The high prevalence of endometriosis among young women suggests the onset of the disease might be earlier than anticipated. Research that focuses on potential factors in early life, including *exposures in utero*, and during childhood may provide insights on the aetiology of endometriosis (Buck Louis, 2012; Hudelist *et al*., 2012; Suvitie *et al*., 2016). In the developmental origin of adult diseases approach, environmental exposures in early life stages, such as due to maternal exposures and behaviour, can affect the risks of chronic conditions in later life (Barker, 1998; Kuh *et al*., 2003; Parazzini *et al*., 2012). The foetal life stage is a critical or sensitive window, especially in relation to the timing of exposure to hormones essential for healthy development. This may be understood in terms of the cells in the foetus that are subject to adverse *in utero* exposures being vulnerable to the disturbance of epigenetic mechanisms. These can then lead to altered gene expression that persists through subsequent cell cycles. Such changes may alter hormone exposures that lead to suboptimal development and susceptibility to various diseases in adolescence and adulthood (Gluckman *et al*., 2010; Mishra *et al*., 2015; Fleming *et al*., 2018). In conceptualising diseases such as endometriosis as potentially arising from a complex set of processes, however, researchers need to consider both critical windows of exposure and resultant structural changes, such as birth defects, and environmental exposures during sensitive windows of development linked with functional deficits (Buck Louis, 2012).

Many aspects of endometriosis and its aetiology remain unclear (Lessey & Young, 2012). A strong genetic component is well established, with the overall heritability or latent risk estimated at 51% (Treloar *et al*., 1999) and women whose mothers or sisters have the condition being at 7-fold increased risk of endometriosis (Moen & Magnus, 1993). The underlying mechanisms at work, including Sampson's theory of retrograde menstruation, remain a subject of debate. The characteristics of the menstrual cycle, such as a history of dysmenorrhea and shorter cycle length (Wei *et al*., 2016), might be early indicators of increased risk of endometriosis. Along these lines, however, a meta-analysis by Nnoaham *et al*. (2012) found only a

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modest increased risk for endometriosis among women with early menarche (≤12 years across the studies examined), after restricting the analysis to those studies with more rigorous control of confounders. Several individual studies have also investigated early life factors linked with childhood development and subsequent diagnosed endometriosis, including preterm birth, low or high birthweight, type of primarily feeding of infants and bodyweight during childhood, as well as *in utero* exposures to smoking and diethylstilbestrol (DES), a synthetic form of oestrogen used in the past to prevent miscarriages and pregnancy complications (Missmer *et al*., 2004; Nagle *et al*., 2009; Benagiano and Brosens, 2014; Upson *et al*., 2015). The mixed findings, however, have resulted in varying conclusions and to date no systematic review on early life factors and endometriosis has been undertaken.

This systematic review aims to synthesis evidence on early life factors, from *in utero* exposures through to childhood, and the risk of diagnosed endometriosis. A better understanding of early life factors could inform strategies for earlier diagnosis and targeted prevention of endometriosis.

Methods

Search strategy

A comprehensive search of Embase, PubMed and Scopus databases was performed to identify relevant studies. Medical Subject Heading (MeSH) terms ('risk factors' OR 'protective factors') were combined with ('endometriosis') AND ('*in utero*', 'fetal', 'neonatal, 'perinatal', 'developmental origins', 'early life', 'childhood' OR 'life course'), where the term 'endometriosis' was restricted to the title and the other search terms to the title and abstract search. Terms for specific types of early life exposures were not included in a search in order to avoid pre-empting the focus of candidate studies and obtain as wide a range of potential risk or protective factors as possible. Articles published in English from January 2000 to June 2018 were included. The search retrieved 99 articles: 13 from Embase, 29 from PubMed and 57 from Scopus. The Preferred Reporting Items for Systematic Review (PRISMA) guidelines were followed (Liberati *et al*., 2009). (For completeness, a subsequent search was conducted that included the term 'prenatal', but this did not produce any additional papers that met the review selection criteria.)

Types of studies

This review was limited to published papers categorised into one of three study design types: case–control studies typically set in an operative or clinical context that compared women with an endometriosis diagnosis (cases) with those who did not (controls); cross-sectional studies that had a single collection of observational data from participants; and cohort studies that used repeat observational data, typically from a community-based sample. Animal studies, conference abstracts, reviews and descriptive articles were excluded.

Data extraction

Information about first author's last name, year of publication, country and name of study, sample size, age range of participants, reporting method, study design, method of confirmation of endometriosis, type of endometriosis and relevant findings (parameter estimates) were extracted for each study.

Assessment of study quality

The quality of studies was evaluated by modified versions of the Newcastle–Ottawa Scale (NOS) for observational studies, provided in the Supplementary Data (Wells *et al*., 2000). Quality of assessment was performed independently by authors K.O. and G.M. Studies were assessed for case–control, cross-sectional or cohort study design according to the following scale: 0 indicated the lowest quality, and 9 the highest quality (or 8 for cross-sectional studies) (Supplementary Data). It should be noted that the assessment was undertaken not in terms of endometriosis as an outcome, but rather of *diagnosed endometriosis*. This distinction is made due to the need for invasive techniques (laparoscopy or other surgery) as the gold standard to confirm the absence of endometriosis. Thus, it is not feasible to confirm disease-free status of community-based controls in case–control studies (Selection Criteria 4) or of participants in cross-sectional and cohort studies (Outcome Criteria 1) until a non-invasive technique for reliable diagnosis of all types of endometriosis is available. It is currently possible, however, for studies to meet these criteria in terms of confirming *the absence of an endometriosis diagnosis* using record linkage (such as hospital records). In addition, cohort studies meet Selection Criteria 4 on the confirmed absence of outcome at the time of the exposure where they investigate early life exposures before endometriosis diagnosis occurs, but it would not currently be met by those studies evaluating adult exposures or exposures after menarche (without comprehensive linkage to hospital records of endometriosis diagnosis).

Results

Study selection process

Figure 1 shows a flowchart of the study selection process. The database search identified 99 records, of which 29 were duplicates. Of the 70 remaining records, 50 studies were excluded after title and abstract screening for study type (e.g. animal studies). The remaining 20 records, with one additional study (Missmer *et al*., 2004) identified from other sources, were assessed for eligibility by full-text reading. As a result, 11 studies were selected for inclusion: five case–control studies (Nagle *et al*., 2009; Somigliana *et al*., 2011; Borghese *et al*., 2015; Upson *et al*., 2015; Vannuccini *et al*., 2016), two cross-sectional studies (Buck Louis *et al*., 2007; Wolff *et al*., 2013) and four cohort studies (Missmer *et al*., 2004; Vitonis *et al*., 2010; Kvaskoff *et al*., 2013; Farland *et al*., 2017).

Characteristics of studies and participants

The main characteristics of the primary studies are presented in Table I, with the covariates used for adjustment in the statistical analyses listed in Table II. The assessment scores ranged from three out of eight points for a cross-sectional study (Buck Louis *et al*., 2007) to six out of nine for two case–control studies (Borghese *et al*., 2015; Upson *et al*., 2015) and the two cohort studies using the data from the Nurses' Health Study II (NHS II) (Missmer *et al*., 2004; Vitonis, *et al*., 2010) (Supplementary Tables S1–S3). As the analysis of Wolff *et al*. (2013)

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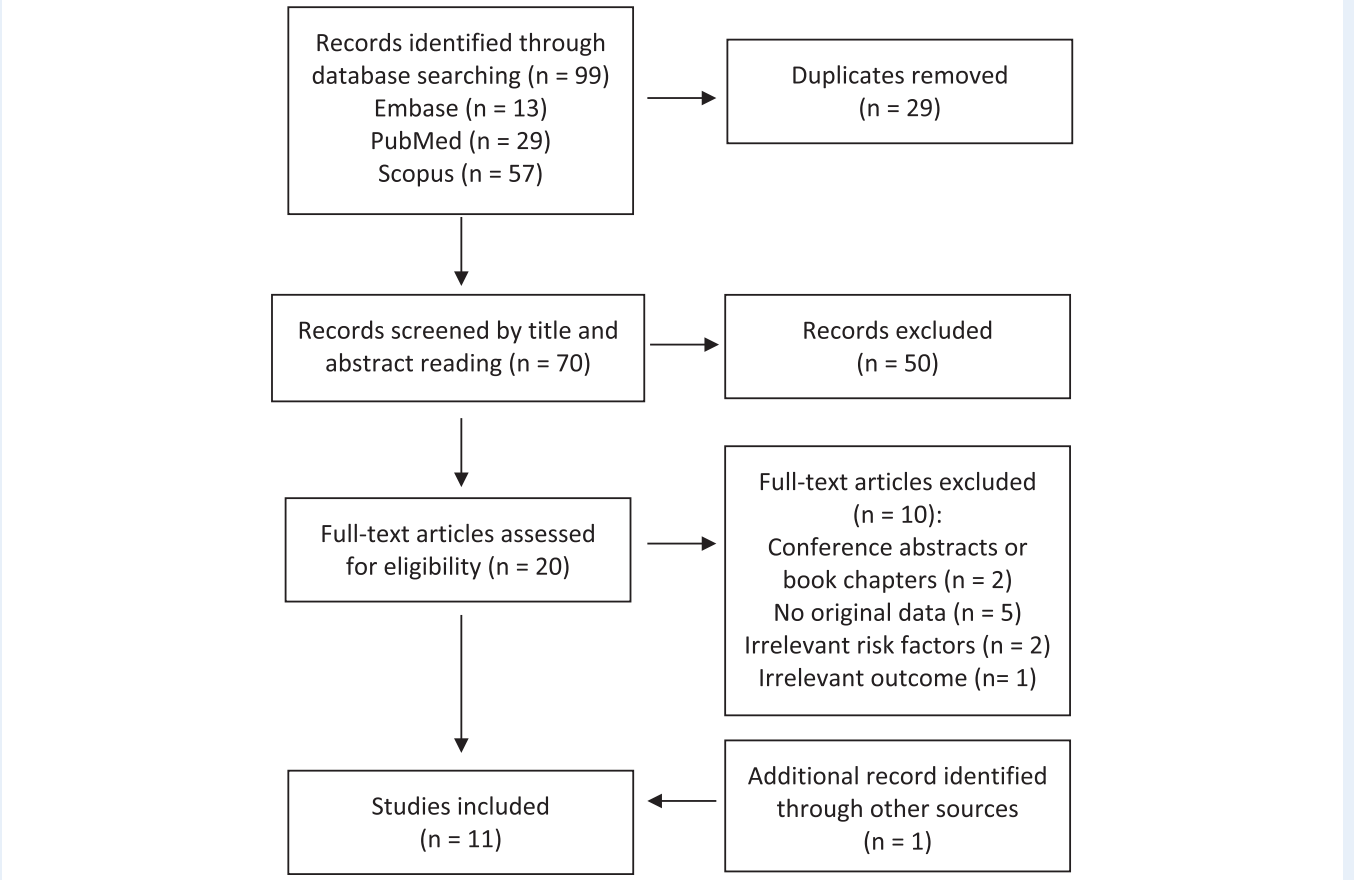

Figure 1 PRISMA flowchart of the study selection process in a systematic review of early life factors for endometriosis. PRISMA: Preferred Reporting Items for Systematic Review.

was done separately for the operative and population samples in this study, each was given a separate score (both five out of eight). The number of participants across studies varied significantly: from a small sample of 84 for Buck Louis *et al.* (2007) to 1037 participants for the case–control study of Upson *et al.* (2015) and to over 60 000 participants in each of the four cohort studies. As noted in Table I, all studies were conducted in high income countries, mostly in the USA (five studies), France (three studies) and Italy (two studies). Endometriosis was diagnosed mainly via laparoscopy or surgery, with Wolff *et al.* (2013) relying on pelvic MRI for diagnosis in their population sample. All of the studies provided information about endometriosis diagnosis in the reference group (controls), but two case–control studies (Nagle *et al.*, 2009; Upson *et al.*, 2015) and all of the cohort studies were unable to confirm their disease-free status.

Birthweight and birth characteristics

Six studies (Missmer *et al.*, 2004; Somigliana *et al.*, 2011; Wolff *et al.*, 2013; Borghese *et al.*, 2015; Upson *et al.*, 2015; Vannuccini *et al.*, 2016) investigated the relationship between birthweight and subsequent endometriosis diagnosis (Table III). Three of these studies (Missmer *et al.*, 2004; Borghese *et al.*, 2015; Vannuccini *et al.*, 2016) found evidence that women with low birthweight were more likely to be diagnosed with endometriosis than those in the reference group. For Vannuccini *et al.* (2016), low birthweight (<2.5 kg) was associated with 3-fold increased likelihood of endometriosis diagnosis in univariate analysis (odds ratio (OR) = 2.9; 95% CI = 1.4–6.1) compared with the reference birthweight of ≥2.5 kg, but this result was attenuated after adjusting for key covariates, including maternal history of endometriosis and preterm birth (adjusted odds ratio (aOR) not provided in the original paper). Borghese *et al.* (2015) found that low birthweight (≤2.5 kg) increased the overall likelihood of endometriosis diagnosis (aOR = 1.7; 95% CI = 1.04–2.62) compared with the reference birthweight of >2.5 to ≤4.0 kg. Additional findings from this study show this association mainly reflected an increased likelihood of a diagnosis of deep infiltrating endometriosis (aOR = 1.8; 95% CI = 1.1–2.9; not shown), whereas no associations were evident for diagnosis of endometrioma or superficial endometriosis. The analysis of Wolff *et al.* (2013), which had null results for both the operative and population samples, examined the effect of every unit decrease in birthweight. Of the remaining two studies that were unable to detect evidence, Somigliana *et al.* (2011) defined low birthweight (less than 3.0 kg) higher than the other studies. No evidence of an association for high birthweight with endometriosis diagnosis was identified in any of the studies (Missmer *et al.*, 2004; Somigliana *et al.*, 2011; Borghese *et al.*, 2015; Upson *et al.*, 2015; Vannuccini *et al.*, 2016).

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Table I Characteristics of primary studies for early life exposures.

First author, year	Quality of study[1]	Country	Type of study	Number of participants	Age group	Reporting method	Confirmation of endometriosis	Type of endometriosis	Prevalence/ incidence
Nagle *et al.*, 2009	5	AUS	Case–control	512	18–55	Questionnaire	Laparoscopy/ surgery	Moderate to severe	
Somigliana *et al.*, 2011	5	ITA	Case–control[6]	173	20–45	Interviews	Histologic	Stage I to IV[10]	
Borghese *et al.*, 2015	6	FRA	Case–control[6]	743	Up to 42	Interviews	Histologic	SUP, OMA, DIE[11]	
Upson *et al.*, 2015	6	USA, WREN[2]	Case–control	1037	18–49	Interviews and questionnaire	Laparoscopy/ surgery	Not specified	
Vannuccini *et al.*, 2016	5	ITA	Case–control[6]	391	21–45	Interviews	Histologic	SUP, OMA, DIE[11]	
Buck Louis *et al.*, 2007	3	USA	Cross-sectional[7]	84	18-40	Interviews	Laparoscopy/ surgery	Minimal to severe	
Wolff *et al.*, 2013	5/5	USA, ENDO[3]	Cross-sectional	473/127	18–44	Interviews	Laparoscopy/ surgery/MRI[8]	Stage I to IV[10]	40%/11%
Missmer *et al.*, 2004	6	USA, NHS II[4]	Cohort	84 446	25–42	Questionnaire	Laparoscopy/ surgery[9]	Not specified	217/100 000[12]
Vitonis *et al.*, 2010	6	USA, NHS II[4]	Cohort	87 603	25–42	Questionnaire	Laparoscopy/ surgery[9]	Not specified	218/100 000[12]
Kvaskoff *et al.*, 2013	5	FRA, E3N[5]	Cohort	75 918	40–65	Questionnaire	Laparoscopy/ surgery[9]	Not specified	3.54%
Farland *et al.*, 2017	5	FRA, E3N[5]	Cohort	61 208	40–65	Questionnaire	Laparoscopy/ surgery[9]	Not specified	3.95%

[1]Quality of study assessed by modified Newcastle–Ottawa Scale, (Supplementary Data)
[2]Women's Risk of Endometriosis Study
[3]Endometriosis, Natural History and Diagnosis study comprised two samples: one recruited from clinics (operative), which was matched to sample recruited from the population
[4]Nurses' Health Study II
[5]Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale
[6]Study selected controls from patients seeking treatment or undergoing surgery for reproductive or gynaecological issues other than endometriosis
[7]Study surveyed patients with reproductive or gynaecological problems undergoing surgery, some of whom were then diagnosed with endometriosis
[8]Main analysis based on laparoscopy/surgical confirmation in the operative cohort, pelvic MRI in the population cohort
[9]Community sample with self-report of endometriosis diagnosis via laparoscopy or surgery (but not confirmed from sources, such as clinical records)
[10]Stage I to IV: according to classification of endometriosis (American Society for Reproductive Medicine, 1997)
[11]SUP = superficial endometriosis, OMA = endometrioma, DIE = deep infiltrating endometriosis
[12]Incidence in women years
AUS: Australia, ITA: Italy, FRA: France

Of the five studies that examined preterm birth (Table III), Vannuccini *et al.* (2016) found that women with preterm birth (not explicitly defined) were four times more likely to be diagnosed with endometriosis (aOR = 4.55; 95% CI = 2.05–10.1), three studies had aOR >1 but with CI that included the null (Somigliana *et al.*, 2011; Upson *et al.*, 2015), similarly for one study with adjusted relative risk (aRR) >1 (Missmer *et al.*, 2004), and Wolff *et al.* (2013) found no association. Two studies investigated multiple birth. Missmer *et al.* (2004) found women who were one of a multiple birth were at 70% higher risk to be diagnosed with endometriosis compared with singletons (aRR = 1.7, 95% CI = 1.2–2.5), while the finding of Upson *et al.* (2015) had aOR = 1.3 (95% CI = 0.5–3.6).

In utero exposures

Of the five studies that investigated maternal smoking during pregnancy (Table IV), Vannuccini *et al.* (2016) found a modest association (aOR = 1.10; 95% CI = 1.03–2.06) for *in utero* exposure to maternal smoking and endometriosis diagnosis, compared to women not exposed to maternal smoking during pregnancy. Three studies had null results, two with aOR > 1 (Wolff *et al.*, 2013, Upson *et al.*, 2015) and one with aOR <1 (Somigliana *et al.*, 2011). The fifth study, Buck Louis (2007) linked maternal smoking during pregnancy with reduced risk of endometriosis diagnosis (OR = 0.2; 95% CI = 0.06–0.6), compared with the reference group not exposed to maternal smoking. In the only study to examine links with *in utero* exposure to paternal smoking, Wolff *et al.* (2013) were unable to identify any clear association in the operative and population samples.

Regarding DES exposure (Table IV), a US cohort study has found that women exposed to DES prior to birth had almost double the risk of endometriosis diagnosis (aRR = 1.8; 95% CI = 1.2–2.8) (Missmer *et al.*, 2004), with a subsequent case–control study showing a null result but with the aOR > 1 (Upson *et al.*, 2015). No evidence for associations regarding other *in utero* exposures was identified, including maternal consumption of coffee and/or alcohol during pregnancy (Buck Louis *et al.*, 2007; Wolff *et al.*, 2013).

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Table II Exposures and covariates adjusted for in the analysis.

First author, Year	Exposure	Covariates used in the adjustment
Nagle *et al.*, 2009[1]	Lean/large body size (over/under weight categories) at 10 years.	Age at menarche, state of residence, and relative weight at 16 years
Somigliana *et al.*, 2011	Premature birth, low/high birthweight, maternal smoking[1].	Age[2], parity
Borghese *et al.*, 2015	Low/high birthweight.	Ethnicity, smoking status
Upson *et al.*, 2015	Premature birth, low/high birthweight, multiple births, maternal smoking[1], maternal DES[4] exposure[1], soy formula feeding	Age[2,3], year, maternal smoking, prematurity, birthweight, foetal number,
Vannuccini *et al.*, 2016	Premature birth, infant formula feeding	Maternal age at delivery, maternal history of endometriosis, uterine fibroids, and maternal smoking[1].
	Low birthweight, maternal smoking[1]	Not adjusted
Buck Louis *et al.*, 2007	Maternal smoking[1], caffeine intake[1] and alcohol intake[1].	Not adjusted[5]
Wolff *et al.*, 2013	Premature birth, low birthweight, maternal smoking[1], caffeine intake[1], alcohol intake[1], and DES[4] exposure, paternal smoking[1]	Clinical site, age of menarche, smoking status, BMI[4]
Missmer *et al.*, 2004	Premature birth, low birthweight, multiple birth	Age in months, calendar time (2-year questionnaire period), race, parity, and BMI[6] at 18 years
Vitonis *et al.*, 2010	Lean/large body size	Age in months, calendar time (2-year questionnaire period), birthweight, age of menarche, parity, adult BMI, oral contraceptive use.
Kvaskoff *et al.*, 2013	Time exposed to indoor passive smoke during childhood, one or more parent smoked during childhood.	Birth cohort, age of menarche, length of menstrual cycle before age 17 years, height, body shape at 20–25 years, parity
Farland *et al.*, 2017	Large body size	Age at last questionnaire, Birth cohort, age at menarche, menstrual cycle length during midlife, parity, physical activity, lifetime breastfeeding and smoking status.

[1] During pregnancy, i.e. *in utero* exposure
[2] Case controls matched by (5 year age group) and urban/rural geographic location
[3] For cases, age refers to the age at diagnosis of endometriosis (and the same time as recruitment)
[4] DES = diethylstilbestrol
[5] Adjusted for age in an additional combined analysis with women's smoking status (results not used here)

Table III Adjusted[1] association of birth characteristics with endometriosis.

First author, year	Parameter estimate[2]	Low birthweight <2.5 kg (<5.5 lb)	High birthweight >4 kg (>8.8 lb)	Preterm birth[3]	Multiple birth
Case–control					
Somigliana *et al.*, 2011	aOR (CI)	0.9 (0.5–2.0)[4]	1.2 (0.6–2.4)[6]	1.1 (0.4–2.9)	
Borghese *et al.*, 2015	aOR (CI)	1.7 (1.04–2.6)	0.5 (0.2–1.1)		
Upson *et al.*, 2015	aOR (CI)	1.0 (0.5–1.8)	1.3 (0.8–2.2)[7]	1.7 (0.9–3.1)	1.3 (0.5–3.6)
Vannuccini *et al.*, 2016	OR (CI) aOR (CI)	2.9 (1.4–6.1)		4.6 (2.1–10.1)[9]	
Cross-sectional					
Wolff *et al.*, 2013					
Operative	aOR (CI)	1.1 (0.9–1.3)[5]		1.0 (0.5–2.0)	
Population	aOR (CI)	0.8 (0.5–1.3)[5]			
Cohort					
Missmer *et al.*, 2004	aRR (CI)	1.3 (1.0–1.8)	0.9 (0.7–1.1)[8]	1.1 (0.9–1.4)	1.7 (1.2–2.5)

[1] Adjusted according to Table II
[2] aOR = adjusted odds ratio, OR = odds ratio, aRR = adjusted relative risk, CI = 95% CI
[3] Defined as being born two or more weeks early
[4] Defined as weight <3.0 kg
[5] Effect of every pound lower in birthweight
[6] Defined as weight > 3.5 kg
[7] Defined as weight ≥ 4.09 kg
[8] Defined as weight > 8.4 pounds (3.8 kg)
[9] Premature or preterm birth not defined

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Table IV Adjusted[1] association between reported *in utero* exposures and endometriosis.

First author, year	Parameter estimates[2]	Maternal smoking[2]	Maternal exposure to DES[2]	Maternal caffeine intake[2]	Maternal alcohol intake[2]	Paternal smoking[2]
Case–control						
Somigliana *et al.*, 2011	aOR (CI)	0.6 (0.2–1.9)				
Upson *et al.*, 2015	aOR (CI)	1.1 (0.8–1.5)	1.3 (0.5–3.6)			
Vannuccini *et al.*, 2016	OR (CI)	1.1 (1.03–2.06)				
Cross-sectional						
Buck Louis *et al.*, 2007	OR (CI)	0.2 (0.06–0.6)		0.7 (0.3–1.7)	0.4 (0.07–1.8)	
Wolff *et al.*, 2013						
Operative	aOR (CI)	1.2 (0.6–2.2)		1.0 (0.6–1.5)	0.8 (0.3–1.9)	0.7 (0.4–1.2)
Population	aOR (CI)			0.8 (0.2–3.0)		3.4 (0.8–15.7)
Cohort						
Missmer *et al.*, 2004	aRR (CI)		1.8 (1.2–2.8)			

[1]Adjusted according to Table II
[2]During pregnancy

Table V Adjusted[1] association between reported postnatal exposures and endometriosis.

First author, year	Parameter estimates[2]	Breastfed	Formula feeding	Passive smoke	Lean body size at 5–10 years	Large body size at 5–10 years
Case control						
Nagle *et al.*, 2009	aOR (CI)				0.9 (0.5–1.7)[6]	2.8 (1.1–7.5)[6]
Somigliana *et al.*, 2011	aOR (CI)	1.0 (0.7–1.4)				
Upson *et al.*, 2015	aOR (CI)		2.4(1.2–4.9)[2]			
Vannuccini *et al.*, 2016	OR (CI)		2.0(1.1–3.5)[3]			
Cohort						
Missmer *et al.*, 2004	aRR (CI)	0.9(0.8–1.0)				
Kvaskoff *et al.*, 2013	aOR (CI)			1.3(1.1–1.6)[4]		
	aOR (CI)			1.1(1.0-1.2)[5]		
Vitonis *et al.*, 2010	aRR (CI)				1.2 (1.1–1.4)[7]	0.9 (0.7–1.1)[7]
Farland *et al.*, 2017	aOR (CI)					0.9 (0.8–1.0)[8]

[1]Adjusted according to Table II
[2]Specified as regular soy formula feeding during infancy versus other feeding
[3]Specified as regular formula feeding during infancy versus breastfeeding
[4]Several hours per day of indoor exposure to passive smoking during childhood
[5]At least one parent smoked during childhood
[6]Relative weight at age 10 years categorised in three pre-specified categories: 'underweight', 'average weight', and 'overweight'
[7]Average of self reported body size over age 5 to 10 years based on a 9 level figure drawing: lean = 1, large ≥5
[8]Average of self reported body size at 8 years based on an 8 level figure drawing: lean = 1, large ≥3

Breastfeeding and infant formula

Of the four studies that investigated infant feeding (Table V), Missmer *et al.* (2004) found a modest association for women who had been breastfed, with lower risk of endometriosis diagnosis (aRR = 0.9; 95% CI = 0.8–1.0) compared with women who were not breastfed, but no such link was identified in Somigliana *et al.* (2011). Another Italian case–control study (Vannuccini *et al.*, 2016), however, used breastfeeding as the reference category and found that women who had infant formula (duration not specified) were twice as likely to be diagnosed with endometriosis (aOR = 1.98; 95% CI = 1.12–3.52). Upson *et al.* (2015) found that soy formula feeding was associated with increased likelihood of endometriosis diagnosis (aOR = 2.4; 95% CI = 1.2–4.9), compared with other unspecified methods (but mainly other types of formula feeding).

Passive smoking during childhood

With regard to exposure to passive smoking (Table V), the cohort study of Kvaskoff *et al.* (2013) had a modest association (aOR = 1.1,

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95% CI = 1.0–1.2) for at least one parent smoking during childhood and endometriosis diagnosis, compared with both parents not smoking. The same study found increased likelihood of endometriosis diagnosis for women who reported several hours per day of indoor exposure to passive smoking during childhood (aOR = 1.3, 95% CI = 1.1–1.6) compared with no exposure and identified a trend for increased likelihood of endometriosis diagnosis with longer duration of daily exposure to passive smoking (*P* value = 0.0008; not shown).

Body shape during childhood

In the absence of measured bodyweight during childhood, with some studies using body shape instead, findings have been described here in terms of body size categories (Table V). One cohort study (Vitonis *et al*., 2010) found that lean body size at age 5 years increased the risk of endometriosis diagnosis (aRR = 1.2; 95% CI = 1.1–1.4), compared with the middle body size category. Farland *et al*., (2017) found a modest negative association (i.e. a protective effect) with endometriosis diagnosis for 'large' body size both at 8 years (aOR = 0.9; 95% CI = 0.8–1.0) and at menarche (aOR = 0.8; 95% CI = 0.7–0.9; not shown), compared with 'lean' body size. In contrast, an Australian case–control study (Nagle *et al*., 2009) identified increased likelihood of endometriosis diagnosis for women who self-reported as being 'overweight' at age 10 years (aOR = 2.8; 95% CI = 1.1–7.5), compared with women who reported being 'average weight,' and no association was evident for lean body size.

Discussion

This paper is, to the best of our knowledge, the first systematic review of evidence regarding early life factors and the risk of endometriosis diagnosis. Due to the methodological differences across studies, including detailed study design and measurement of exposures, a meta-analysis was not performed. Instead, a narrative review and qualitative assessment was undertaken.

Main findings

Of the studies that examined birthweight, the majority found that women born with low birthweight were more likely to have diagnosed endometriosis, but further research is needed on potential causal pathways. Mixed or insufficient evidence was found for links between endometriosis diagnosis and having been born preterm, *in utero* exposure to maternal smoking or DES, exposure to passive smoking in early life and formula feeding. Similarly, mixed or insufficient evidence was available on a protective association for breastfeeding. As many of the studies had small sample sizes, were underpowered or had other methodological issues, the early life factors covered here need further investigation in large-scale studies or in combined studies that use consistent exposure categories.

Low birthweight

Low birthweight (<2.5 kg or <5.5 lb) was identified as associated with increased likelihood of endometriosis diagnosis in three of the four studies that specifically used this definition. In addition, two of these studies (Missmer *et al*., 2004; Borghese *et al*. 2015) found a linear increase in the likelihood of endometriosis diagnosis across lower birthweight categories (not shown). Based on their more detailed finding that low birthweight was linked with the development of deep infiltrating endometriosis, but not with superficial endometriosis, nor with endometrioma, Borghese *et al*. (2015) suggested that subsequent research should distinguish factors linked with different types of the disease. In Vannuccini *et al*. (2016), however, the risk associated with low birthweight did not vary according to the severity of the disease. Given the established heritability of endometriosis and potential links with pregnancy complications (such as pre-eclampsia, low birthweight, preterm birth), it is surprising that Vannuccini *et al*. (2016) is the only study to adjust for a range of key maternal characteristics and birth outcomes, including most importantly maternal history of endometriosis. As a result, the initial finding from this case–control study of low birthweight being associated with a more than 3-fold higher likelihood of endometriosis diagnosis was attenuated in the fully adjusted model, while preterm birth remained a significant risk factor. A recent large registry study from Sweden (*N* = 628 312), however, has substantially strengthened the evidence, in finding both that low birthweight was associated with increased risk of endometriosis diagnosis (adjusted hazard ratio (aHR) = 1.16; 95% CI 1.02–1.32) and a linear relationship with lower birthweight categories, after adjustment for maternal endometriosis and gestational age (Gao *et al*. 2019).

Preterm birth

Evidence in relation to preterm birth was lacking in this review with only one study finding a clear association with endometriosis diagnosis (Vannuccini *et al*., 2016) and three other null results from studies with aOR > 1. This is consistent with the lack of an association found for preterm birth in the registry data study of Gao *et al*. (2019).

Maternal smoking and passive smoke

Although evidence on exposure to maternal smoking during pregnancy was mixed, it warrants more detailed consideration in future research. Recent findings from Gao *et al*. (2019) indicate that maternal smoking early in pregnancy was associated with the risk for endometriosis diagnosis, compared with non-smokers and after adjusting for other factors including maternal endometriosis. None of the studies that examined maternal smoking during pregnancy have accounted for exposure to passive smoke during childhood, which Kvaskoff *et al*. (2013) identified as a risk factor for endometriosis, including a dose response related to increasing duration of daily exposure. One potential mechanism is that exposure to smoke during early life negatively affects the developing immune system with long-term consequences (Winans *et al*., 2011), while rates of autoimmune and endocrine disorders are known to be higher among women with endometriosis (Sinaii *et al*., 2002).

Chemical exposure *in utero*

Although mostly no longer used and unlikely to be an issue for younger women, the limited evidence from one study on the association of endometriosis diagnosis with *in utero* exposure to DES, a synthetic oestrogen, suggests that it is worth further research (Missmer *et al*., 2004). This highlights the potential issue of other sources of hormonal exposures (pharmaceutical or environmental) *in utero* that could be risk factors for endometriosis (Buck Louis, 2012). In their review, Benagiano and Brosens (2014) discuss a range of exposures, such as

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dioxins and other endocrine-disrupting chemicals, which have been previously associated with poor health outcomes, including adverse impacts on the foetal development of reproductive organs. The potential for these exposures to be linked with increased risk of developing endometriosis has been investigated in several studies. As they point out, however, accurate measurement of the chemical exposures *in utero* combined with the length of time between these and the outcome in adulthood, as well as accounting for intervening environmental factors, poses serious challenges for this research. As a result, most of the available data come from small studies or animal models with inconclusive evidence for associations with endometriosis in humans.

Infant feeding

Limited evidence is available on infant feeding. While Missmer *et al.* (2004) identified a modest protective effect for maternal breastfeeding and endometriosis diagnosis, no trend regarding breastfeeding duration was detected, nor was any association found in the subsequent study of Somigliana *et al.* (2011). These studies, however, need to be seen alongside that of Vannuccini *et al.* (2016) which found substantially increased likelihood of endometriosis diagnosis associated with (primarily dairy based) formula feeding compared with infants who were breastfed. The type of formula used may also play a role as Upson *et al.* (2015) found that soy-based formula feeding was clearly linked with increased endometriosis diagnosis compared with other methods (that is mainly other types of formula feeding rather than breastfeeding, which was not highly prevalent at the time). Further studies are needed to provide more robust evidence on the links between breastfeeding or alternatives and subsequent endometriosis diagnosis and to provide insights on potential mechanisms that currently remain to be elucidated. Vannuccini *et al.* (2016) suggests that formula feeding intake may act as an exogenous source of hormones or may promote endogenous steroid production. For instance, soy formula feeding has been previously associated with early age of menarche (age $\leq$ 11 years) (D'aloisio *et al.*, 2013), while the meta-analysis of Nnoaham *et al.* (2012) has also found some evidence of association between early age at menarche and endometriosis.

Challenges for epidemiologic research on endometriosis

This review has highlighted important topics and exposures, both *in utero* and in childhood, for further research with large community-based studies. Previous reviews have also discussed the broader methodological challenges for epidemiologic research on endometriosis faced by different study designs (Holt & Weiss 2000) and specifically for case–control studies (Zondervan *et al.*, 2002). A key issue is that endometriosis requires visualisation via surgery to confirm clinical diagnosis, though the modern method of laparoscopy is less invasive than previous methods. Population-based studies can in principle select a representative sample of women from the community, but the absence of endometriosis cannot be confirmed as it is not feasible to undertake surgical diagnosis without any indications of the disease. Any consequent misclassification will lead to an underestimation of the prevalence of endometriosis in the study and will weaken (attenuate) the associations being investigated between early life and other factors and the disease (Holt & Weiss 2000). If the prevalence of endometriosis in the population is already established, however, then the degree of this misclassification can at least be estimated.

On the other hand, case–control studies on endometriosis are often conducted in the clinical setting and select the study sample from among other patients. For instance, Somigliana *et al.* (2011) used controls selected from patients with benign gynaecological conditions and without any macroscopic evidence of endometriosis at laparoscopic evaluation. A similar methodology for sample selection was applied in the study by Borghese *et al.* (2015). These studies are able to confirm the absence of endometriosis in the control group while carrying out other reproductive or related surgery. They raise questions, however, regarding the controls being representative of the underlying population from which the patients were drawn. The same early life factors that were associated with endometriosis might also be a risk factor for the other reproductive-related conditions that led to the women seeking treatment (Zondervan *et al.*, 2002). Depending on the control group of patients selected in each study, then resultant sample bias will lead to either over or underestimation of any associations.

In contrast, the case–control study of Nagle *et al.* (2009) selected controls from the Australian population using a national twin registry (matching on the basis of age band and geography). A number of potential controls were omitted due to their reporting of an endometriosis diagnosis. Since the absence of the disease could not be confirmed in the remaining controls, this study faced the same misclassification issue as described for the cohort studies. The selection strategy also assumes that being a twin does not affect the risk of endometriosis compared with the rest of the population, yet Missmer *et al.* (2004) found an adverse association for those who were one of a multiple birth. In addition, the study is not clear regarding if any of the twins were the result of IVF, which would suggest potential issues of maternal infertility that itself may be due to endometriosis, and hence an increased genetic risk for endometriosis among the offspring.

One potential way to address study design issues related to undiagnosed endometriosis among controls may be with the evidence-based algorithm recently developed by Agarwal *et al.* (2019), which combines up-to-date knowledge of typical symptoms, heritability of the disease and fast and non-surgical examinations and imaging. This approach still needs to be validated fully in future research, but if found reliable it could provide a way to substantially advance epidemiologic studies of endometriosis.

Implications for future research

In addition, this review has revealed the need to establish more harmonised definitions for risk factors, methods for reporting and analysis of results, to improve the comparability across studies of endometriosis. Given the apparent effect sizes of early life factors, and the many null results after adjusting for covariates, the relatively small sample size of the case–control studies meant that these studies may be statistically underpowered to detect such associations. Beyond increasing the sample size, more consistent study methods generally would help address this issue by enabling meta-analysis in future reviews. The typically long diagnostic delay of endometriosis adds to the problem of recall bias when measuring early life exposures, including when the source of the data is the mother's recall of her own health behaviours and other factors related to her pregnancy. Instead, developing epidemiologic studies on endometriosis using

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existing cohort studies that have comprehensive prospective data on early life exposures, together with evaluating participants with confirmed disease-free diagnosis, provides one way forward. Furthermore, replication of findings in different populations, for example in middle and low-income countries or amongst women with lower socioeconomic status, is recommended.

To strengthen the evidence base, greater attention also needs to be given to potential causal pathways that lead to the development of endometriosis. This means moving beyond simple analyses to detect associations for a narrow set of potential risk factors in early life with subsequent disease risk. For example, it is possible that an underlying common cause, such as a genetic factor or adverse *in utero* exposure, could lead to both low birthweight and endometriosis. Insights on causal pathways can be gained through statistical approaches, such as mediation analysis that enables consideration of indirect effects. For example, in identifying the potential mediating role of formula feeding on low birthweight infants (rather than those of normal weight) the subsequent high growth rates may be linked with increased risk of endometriosis. The broader strategy in these more detailed analyses aimed at unravelling the effects of specific exposures is to ensure that data are gathered on the maternal reproductive history in relation to endometriosis and infertility, *in utero* exposures to identify the potential foetal origins of disease aetiology and environmental exposures during childhood.

Conclusion

In conclusion, this systematic review finds that evidence available on early life exposures suggests that low birthweight is a risk factor for endometriosis diagnosis. Further research is warranted, however, both on this and other early life risk factors. The review has also underscored improvements needed in future studies on early life factors and endometriosis, particularly more consistent study designs and measurement methods. Future research on such factors not only will generate more robust and clinically relevant evidence on early life risk factors for endometriosis but also may provide insights on potential biological mechanisms to explain its aetiology.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Authors' roles

K.O. conducted the literature review, quality assessment and wrote the initial manuscript. G.D.M. conceived the study, conducted the quality assessment and revised the manuscript. All authors approved the submitted version.

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Conflict of interest

None to declare.

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