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Risk of cardiovascular outcomes among women with endometriosis in the United Kingdom: a retrospective matched cohort study

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Objective To describe the prevalence and incidence of endometriosis and to estimate the risk of cardiovascular outcomes in women with endometriosis.

Design Population-based cohort study using The Health Improvement Network database.

Setting UK primary care.

Population Women aged 16–50 years were followed from 1995 to 2018.

Methods Adjusted hazard ratios (aHR) for cardiovascular outcomes comparing women with endometriosis with those without endometriosis were estimated using multivariable Cox regression models. Prevalence and incidence of endometriosis were estimated using annual (1998–2017) sequential cross-sectional and cohort studies, respectively.

Main outcome measure The primary outcome was composite cardiovascular disease (CVD) including, ischaemic heart disease (IHD), heart failure (HF) and cerebrovascular disease. Secondary outcomes were arrhythmia, hypertension and all-cause mortality.

Results In all, 56 090 women with endometriosis and 223 669 matched controls without endometriosis were included in the analysis of cardiovascular risk. Compared with women without endometriosis, the aHR for cardiovascular outcomes among women with endometriosis were: composite CVD 1.24 (95% CI 1.13–1.37); IHD 1.40 (95% CI 1.22–1.61); cerebrovascular disease 1.19 (95% CI 1.04–1.36); HF 0.76 (95% CI 0.54–1.07); arrhythmia 1.26 (95% CI 1.11–1.43); hypertension 1.12 (95% CI 1.07–1.17) and all-cause mortality 0.66 (95% CI 0.59–0.74). The incidence of endometriosis was 12.3 per 10 000 person-years in 1998 and 11.5 per 10 000 person-years in 2017. The prevalence of endometriosis increased from 119.7 per 10 000 population in 1998 to 201.3 per 10 000 population in 2017.

Conclusion Endometriosis is associated with an increased risk of cardiovascular outcomes. Young women with endometriosis are a potential target for CVD risk assessment and prevention.

Keywords Arrhythmia, cardiovascular disease, endometriosis, hypertension, stroke.

Tweetable abstract Endometriosis is associated with increased risk of cardiovascular outcomes: a UK retrospective matched cohort study.

Background

Cardiovascular disease (CVD) is a leading cause of death and disability worldwide.[1] CVD risk in young women is under-perceived by both medical personnel and the women themselves.[2] Age- and sex-stratified data have shown that while CVD mortality has steadily decreased in older adults

(>55 years), the decrease has slowed in younger adults (<55 years), notably in women.[3] Attention has shifted towards investigating sex-specific risk factors for CVD to account for the differential risk between the sexes. Female sex-specific risk factors for CVD, including adverse pregnancy outcomes, polycystic ovary syndrome and premature menopause, are well documented in the literature. However, the association between endometriosis and CVD is under-studied.

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Endometriosis is the abnormal presence and growth of endometrium-like (the inner layer of the uterus) epithelium and stroma in places outside the endometrium and myometrium. It is a public health problem that affects an estimated 176 million women globally or 5–10% of women in the reproductive age group.[4] The standard for the diagnosis of endometriosis is laparoscopic visualisation, ideally accompanied by histological confirmation.[5] In the UK and several other countries, the average diagnostic delay for endometriosis is 7 years.[6] The exact cause of endometriosis is unclear. Several theories, including retrograde (backflow) menstruation, transformation of peritoneal mesothelial cells into endometrial cells (coelomic metaplasia) and lymphatic and vascular spread have been postulated.[7] Ectopic endometrial tissues undergo cyclical proliferation, secretion and sloughing.[8] The result is chronic inflammation and fibrosis. Chronic inflammation triggers endothelial dysfunction and initiates premature atherosclerosis.[9] Moreover, among people with chronic inflammatory disorders, the relative risk of atherosclerotic CVD is greatest in young women.[10] Beyond chronic inflammation, there is increased production of reactive oxygen species from oxidative stress, a known trigger of cardiac arrhythmia.[11]

Given the chronic inflammatory nature of endometriosis, coupled with diagnostic delays, young women with endometriosis may be predisposed to an increase in cardiovascular risk. Using primary care data from the UK, this study aims to investigate the association between endometriosis and cardiovascular risk, as well as to describe the incidence and prevalence of endometriosis among women of reproductive age in the UK.

Methods

Study design
To estimate yearly endometriosis prevalence, sequential cross-sectional studies were carried out on 1 January each calendar year from 1998 to 2017. Annual incidence rates were calculated by conducting a series of yearly cohort studies over the same period.

A population-based retrospective cohort study was carried out to assess the risk of long-term cardiovascular outcomes. Women with a diagnosis of endometriosis (exposed) and matched controls from the general population with no diagnosis of endometriosis (unexposed), were identified between 1 January 1995 and 31 December 2018. The rates of cardiovascular outcomes were compared in the exposed and unexposed groups.

Data source
The health improvement network (THIN) is a database that contains anonymised electronic health records contributed by 787 general practices in the UK using VISION

software. THIN covers approximately 6.2% of the UK population.[12] Registered practices contributing to the database are representative of the UK population.[13] VISION software is an electronic health record system that is used to collect patient data by the participating practices. THIN contains data on patient demographics, medical diagnoses, lifestyle characteristics and prescriptions.

Practice eligibility criteria
Practices were eligible for inclusion from the later of the dates on which the practice met acceptable mortality reporting and 1 year after the practice began to use the VISION software system, to ensure data reporting quality and sufficient time for recording important information. Acceptable mortality reporting is a quality assurance standard that ensures practices consistently record data.[14]

Study population
For incidence and prevalence, female patients aged 16–50 years registered with an eligible practice for ≥1 year before cohort entry (to ensure documentation of all important baseline covariates) were eligible for inclusion. For the cardiovascular outcomes study, adult women aged 16–50 years at baseline were included in the study. The study period was 1 January 1995 to 31 December 2018. Participants entered the study at the latest of their 16th birthday, study start date (1 January 1995) or 1 year after joining the practice.

Exposure
Women with the exposure (endometriosis) were matched with up to four women without a diagnosis of endometriosis, randomly selected from a pool of eligible women. The exposed and unexposed groups were matched by age (±1 year), local health authority and body mass index (BMI; ±2 kg/m^2). The exposure (endometriosis) was identified using the relevant diagnostic (Read) codes (Table S1). Our study included both surgically confirmed and coded endometriosis cases, and physician-assigned codes based on clinical suspicion. Information to distinguish surgically confirmed cases from cases diagnosed on clinical suspicion was not available. Restricting cases to surgically confirmed cases alone may lead to selection bias. Although emerging evidence suggests that the clinical diagnosis of endometriosis is more reliable than previously thought,[15] there is potential for misclassification bias.

Follow-up period
The date of diagnosis of endometriosis served as the index date for newly diagnosed patients (incident) whereas for patients with pre-existing endometriosis the date the patient became eligible to take part in the study was assigned as the index date. Unexposed patients were

assigned the same index date as their corresponding exposed patient to mitigate immortal time bias. Each exposed participant and matched controls were followed up from the index to the exit date. The exit date was the earliest of (1) the outcome, (2) death, (3) study end date or (4) date of leaving the general practice or when the general practice stopped contributing to the database.

Outcomes

The primary outcomes were the incident diagnosis of any the following individual cardiovascular conditions: heart failure, cerebrovascular disease and ischaemic heart disease (IHD). Secondary outcomes were the incident diagnosis of arrhythmia or hypertension, and mortality. Participants with a diagnosis of any outcome of interest at baseline were omitted from the corresponding analysis. Outcomes were defined using the relevant clinical (Read) codes.

Study covariates

The study included the following potential confounders: age, Townsend deprivation quintile, smoking status, lipid-lowering medication (current users, with a record of a prescription within 60 days before the index date), BMI, contraceptive use (current users, i.e. those prescribed hormonal contraceptives for the last 365 days before cohort entry), alcohol use, history of pre-eclampsia, history of gestational diabetes mellitus, polycystic ovary syndrome (PCOS), pregnancy loss (miscarriage and stillbirths), preterm births, early menopause, premature ovarian insufficiency, pelvic inflammatory disease (PID), migraine, hysterosalpingo-oophorectomy and connective tissue disorders.

For each of the covariates, the most recently recorded variable before study entry was used. BMI in kg/m^2 was categorised as normal or underweight $<25 kg/m^2$, overweight $25–30 kg/m^2$, obese $>30 kg/m^2$, or missing for those with missing or implausible values. The self-reported smoking status was categorised as current smoker, ex-smoker, never smoker or missing. Alcohol use was categorised as current drinker, non-drinker and ex-drinker. A record of a prescription for lipid-lowering medication was used as a proxy for elevated cholesterol levels. Current users were defined as those with lipid-lowering medication for the last 60 days before cohort entry.

Analysis

Prevalence and incidence

For annual point prevalence, the proportion of eligible females with any record ever of endometriosis was calculated on 1 January each year from 1998 to 2017. Crude incidence rates every year from 1998 to 2017 were calculated by dividing the number of newly diagnosed females (numerator) by the total number of person-years at risk (denominator) for the given year. In addition, crude incidence rates by Townsend deprivation quintiles and age categories (18–25, 26–30, 31–35, 36–40, 41–45 and 46–50 years) were estimated.

Cardiovascular outcomes

Participant characteristics at baseline were reported using the appropriate descriptive statistics: categorical variables were reported using proportions while mean (standard deviation) or median (interquartile range; IQR) were used in reporting continuous variables. For each exposure group, the crude incidence rates of cardiovascular outcomes were calculated. Univariable and multivariable Cox proportional hazards models were used to estimate the crude and adjusted hazard ratios (aHR) and 95% CI of incident cardiovascular conditions among women with endometriosis compared with those without endometriosis. In the multivariable models, adjustments were made for age, smoking status, hormonal contraceptive use, lipid-lowering medication, BMI, alcohol use, PCOS, migraine and connective tissue disorders. For each model, the proportional hazards assumption was initially checked using the Schoenfeld residual test followed by a graphical confirmation using the log-log survival curves.

Sensitivity analysis

Hysterectomy, treatment with gonadotropin-releasing hormone (GnRH) agonists, PID, PCOS and adverse pregnancy outcomes are linked to higher CVD risk.[16–18] Sensitivity analyses for composite CVD outcomes were, therefore, conducted restricting analysis to: (1) women without a record for hysterectomy or oophorectomy, (2) women without PID, (3) women without adverse pregnancy outcomes; (4) women with incident endometriosis (exposure) and their corresponding matched controls; (5) Women with a current (within the last 1 year before cohort entry) prescription for GnRH were excluded.

Statistical significance was set at $P < 0.05$. All analyses were conducted using STATA version 14.2 (StataCorp, College Station, TX, USA).

Missing data

Missing data and implausible patient characteristics were assigned to a separate missing category and included in the regression model.

Results

Incidence and prevalence

The annual incidence of endometriosis among UK women aged 16–50 years was 12.3 per 10 000 person-years in 1998 and 11.5 per 10 000 person-years in 2017 (Table S2). Overall, the annual incidence of endometriosis remained relatively stable throughout the 20 years of follow up

(Figure 1). The annual prevalence of endometriosis gradually increased from 119.7 per 10 000 population in 1998 to 201.3 per 10 000 population in 2017 (Figure 1) (Table S3). Women in the 26–35 years age bracket had the highest incidence of endometriosis: 16.1 per 10 000 person-years for the 26–30 years age group and 15.1 per 10 000 person-years for the 31–35 years age group (Figure 1) (Table S4). There was a linear decrease in the incidence of endometriosis from the least deprived to the most deprived Townsend deprivation quintile (Figure 1). Women in the least deprived Townsend quintile had the highest incidence of endometriosis (13.9 per 10 000 person-years) whereas those in the most deprived Townsend quintile had the lowest incidence of endometriosis (10.4 per 10 000 person-years) (Table S5).

Cardiovascular risk

Table 1 presents the baseline characteristics of patients with a diagnosis of endometriosis and matched controls without a diagnosis of endometriosis. A total of 279 759 women aged 16–50 years were included in the analysis of cardiovascular risk. The exposed group was composed of 56 090 (20.1%) women with a diagnosis of endometriosis and the unexposed group included 223 669 (79.9%) controls matched for age, BMI and health authority. Baseline demographic, lifestyle, medical and reproductive characteristics were similar between the two groups. At baseline, the median ages in the exposed and unexposed groups were 36.7 years (IQR 30.9–42.5 years) and 36.7 years (IQR 30.8–42.4 years), respectively; while 14.2% of women in the exposed group and 14.0% of women in the unexposed group were obese. Women with endometriosis compared with those without endometriosis were more likely to have connective tissue disorders (1.1% versus 0.7%), history of miscarriage (12.2% versus 9.3%), PCOS (5.9% versus 2.3%), PID (10.1% versus 3.0%), migraine (30.2% versus 22.4%), a current prescription for GnRH agonist (4.4% versus 0.1%) and a current prescription for combined oral contraceptive (7.0% versus 5.6%).

Cardiovascular diseases

Between 1995 and 2018, 574 (1.03%) and 1676 (0.75%) composite CVD events were recorded among women with and without endometriosis, respectively (Table 2). The crude incidence rate of composite CVD was 1.60 per 1000 person-years among women with endometriosis and 1.36 per 1000 person-years among women without endometriosis. The crude hazard ratio of composite CVD among women with endometriosis compared with those without was 1.16 (95% CI 1.06–1.28; $P = 0.002$). In the adjusted model (demographic, lifestyle characteristics, hypertension, diabetes mellitus and reproductive history) endometriosis was associated with a higher risk of composite CVD (aHR 1.24; 95% CI 1.14–1.37; $P < 0.001$) (Table 2, Figure 2).

On analysis of individual CVD subtypes, comparing women with endometriosis and those without endometriosis, the unadjusted hazard ratio of IHD was 1.26 (95% CI 1.09–1.44; $P = 0.001$). In the adjusted model, endometriosis was associated with a 40% higher risk of IHD (aHR 1.40; 95% CI 1.22–1.61; $P < 0.001$) (Table 2, Figure 2). The crude hazard ratio of cerebrovascular disease was 1.13 (95% CI 0.99–1.29; $P = 0.067$) in women with endometriosis compared with those without endometriosis. In the adjusted model, the association between endometriosis and CVD was significant (aHR 1.19; 95% CI 1.04–1.36; $P = 0.010$) (Table 2 Figure 2). For heart failure, in the crude model, women with endometriosis compared with those without endometriosis had lower heart failure risk (HR 0.71; 95% CI 0.50–0.99; $P = 0.044$). In the adjusted model, there was no association between endometriosis and risk of heart failure (aHR 0.76; 95% CI 0.54–1.07; $P = 0.115$) (Table 2 figure 2).

Arrhythmias

The crude incidence rate of arrhythmia was 0.92 per 1000 person-years and 0.72 per 1000 person-years among women with endometriosis and those without endometriosis, respectively. The unadjusted hazard ratio comparing women with endometriosis and those without was 1.26 (95% CI 1.11–1.44; $P < 0.001$). In the adjusted model, endometriosis was associated with a 26% higher risk of arrhythmia (aHR 1.26; 95% CI 1.11–1.43; $P = 0.001$) (Table S6, Figure S1).

Hypertension

The crude incidence rate of hypertension was 6.99 per 1000 person-years and 6.52 per 1000 person-years among women with endometriosis and those without endometriosis, respectively. Comparing women with endometriosis to those without, the crude hazard ratio was 1.06 (95% CI 1.01–1.11; $P = 0.016$). In the adjusted model (demographic, lifestyle characteristics and diabetes mellitus, reproductive history, connective tissue disorders and migraine), endometriosis was associated with a higher risk of hypertension (aHR 1.12; 95% CI 1.07–1.17; $P < 0.001$) (Table S6, Figure S1).

Mortality

The crude mortality rates were 0.90 and 1.46 per 1000 person-years in women with and without endometriosis, respectively. The fully adjusted hazard ratio was 0.66 (95% CI 0.59–0.74; $P < 0.001$) in women with endometriosis compared with those without (Table S6).

Sensitivity analysis

Tables S7, S8 and Figure S2 provide the results of various restricted analyses on the association between
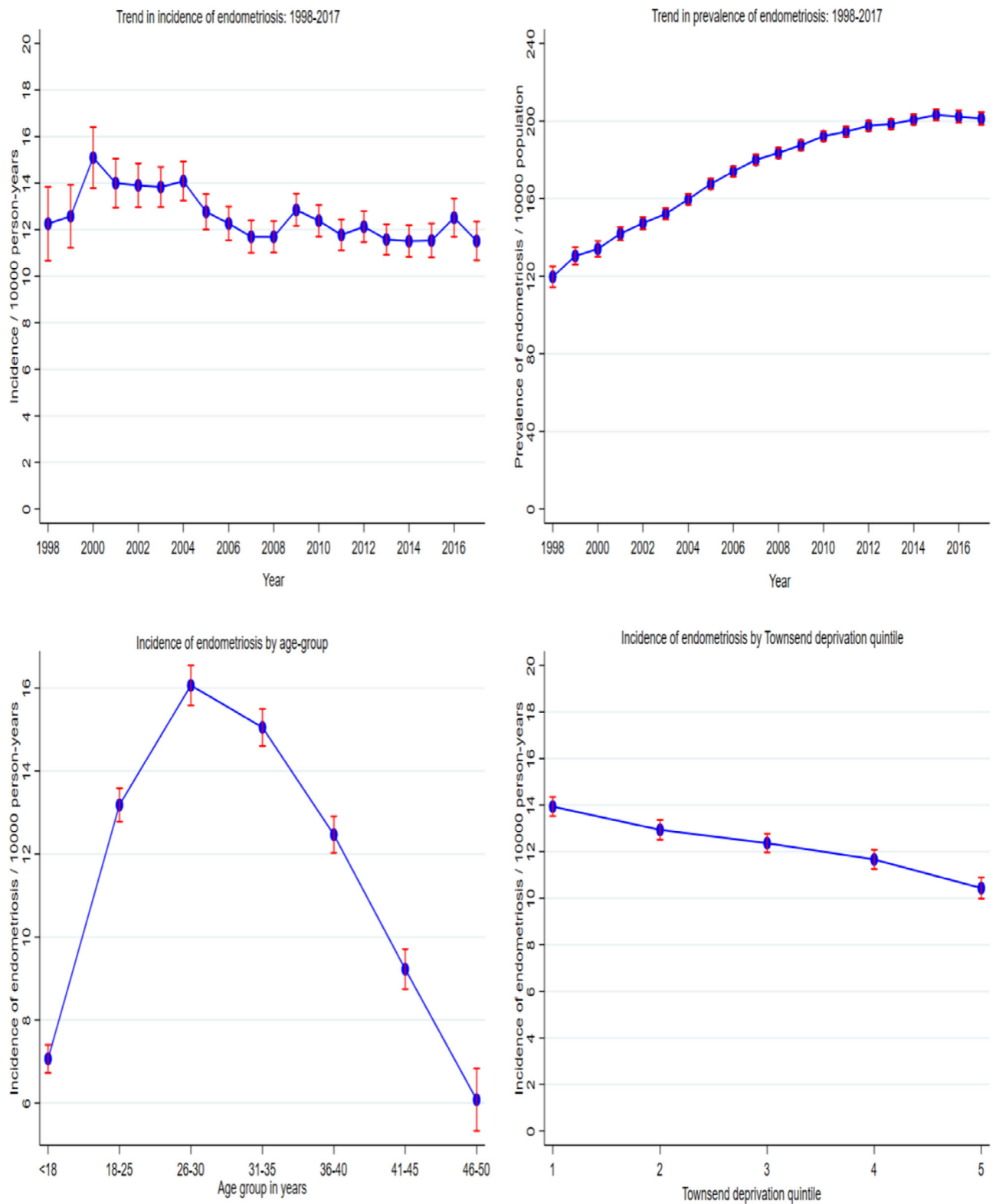
Figure 1. The incidence and prevalence of endometriosis among UK women: 1998–2017.

Table 1. Baseline demographic, lifestyle, reproductive and medical characteristics among women with endometriosis and those without endometriosis

Characteristics	Endometriosis (n = 56 090)	Unexposed (n = 223 669)
Age (years), median (IQR)	36.7 (30.9–42.5)	36.7 (30.8–42.4)
Smoking status, n (%)		
Smokers	13 332 (23.8)	51 458 (23)
Ex-smokers	8771 (15.6)	31 100 (13.9)
Non-smokers	31 151 (55.5)	126 255 (56.5)
Missing	2836 (5.1)	14 856 (6.6)
BMI (kg/m²), n (%)		
<18.5	1645 (2.9)	5551 (2.5)
18.5–25	25 557 (45.6)	103 884 (46.4)
25–30	12 245 (21.8)	48 471 (21.7)
>30	7974 (14.2)	31 401 (14.0)
Missing	8669 (15.5)	34 402 (15.4)
Alcohol status, n (%)		
Non-drinker	9549 (17.0)	37 878 (16.9)
Drinker	35 873 (64.0)	139 609 (62.4)
Excessive drinker	1300 (2.3)	5051 (2.3)
Missing	9368 (16.7)	41 131 (18.4)
Townsend Deprivation Index, n (%)		
1 (Least deprived)	12 385 (22.1)	44 710 (20.0)
2	10 362 (18.5)	39 580 (17.7)
3	10 354 (18.5)	41 457 (18.5)
4	8567 (15.3)	37 416 (16.7)
5 (Most deprived)	5480 (9.8)	26 527 (11.9)
Missing	8942 (15.9)	33 979 (15.2)
Current statin prescription, n (%)	481 (0.9)	1889 (0.8)
Connective tissue disorders, n (%)	613 (1.1)	1643 (0.7)
Migraine, n (%)	16 950 (30.2)	50 129 (22.4)
Outcomes at baseline, n (%)		
Hypertension	1767 (3.2)	6870 (3.1)
Diabetes	573 (1.0)	2820 (1.3)
IHD	91 (0.2)	432 (0.2)
Stroke/TIA	160 (0.3)	619 (0.3)
Heart failure	16 (0.0)	93 (0.0)
Reproductive history, n (%)		
Current COC prescription	3938 (7.0)	12 584 (5.6)
Current GnRH agonists	2482 (4.4)	280 (0.1)
Nulliparity	222 (0.4)	854 (0.4)
Primiparity	392 (0.7)	1452 (0.7)
Multiparity	375 (0.7)	1398 (0.6)
Miscarriage	6836 (12.2)	20 882 (9.3)
Stillbirths	181 (0.3)	726 (0.3)
Gestational diabetes mellitus	368 (0.7)	1390 (0.6)
Pre-eclampsia	294 (0.5)	1156 (0.5)
Premature delivery	231 (0.4)	994 (0.4)

Table 1. (Continued)

Characteristics	Endometriosis (n = 56 090)	Unexposed (n = 223 669)
Placental abruption	28 (0.1)	118 (0.1)
Polycystic ovary syndrome	3327 (5.9)	5221 (2.3)
Premature ovarian insufficiency	66 (0.1)	202 (0.1)
Pelvic inflammatory disease	5649 (10.07)	6599 (3.0)
Hysterectomy/ oophorectomy	8466 (15.1)	7119 (3.2)

COC, combined oral contraceptive; GnRH, gonadotropin-releasing hormone; TIA, transient ischaemic attack.

endometriosis and composite CVD. On exclusion of women with hysterectomy and oophorectomy, the association was attenuated (fully adjusted HR 1.17; 95% 1.04–1.31; $P = 0.010$). The exclusion of women with PCOS and those with a current prescription for GnRH agonist did not materially change the effect estimates for composite CVD (HR 1.25; 95% CI 1.13–1.38; $P < 0.001$ and HR 1.25; 95% CI 1.14–1.38; $P < 0.001$, respectively). Exclusion of women with PID resulted in minimal change on the effect estimate (fully adjusted HR 1.22; 95% CI 1.10–1.35; $= P < 0.001$). Restriction of the analysis to women without adverse pregnancy outcomes strengthened the effect estimate for CVD (fully adjusted HR 1.30; 95% CI 1.18–1.45; $P < 0.001$). On restriction to incident exposure only, the increased risk was maintained but the association was no longer statistically significant (fully adjusted HR 1.21; 95% CI 0.98–1.49; $P = 0.074$).

Discussion

Main findings

This population-based retrospective cohort demonstrated that cardiovascular outcomes were increased among UK women diagnosed with endometriosis compared with those without a diagnosis for endometriosis. Specifically, endometriosis was associated with a higher risk of composite CVD, IHD, cerebrovascular disease, arrhythmia, hypertension, independent of demographic, lifestyle and reproductive confounders. No association was found between endometriosis and heart failure risk. Overall, between 1998 and 2017, the trend in the annual incidence of endometriosis was stable with only minor variations noted between the years. During the same period, there was a steady increase in the annual prevalence of endometriosis.

Table 2. Incidence rates and hazard ratios for primary cardiovascular outcomes

|	Composite CVD		IHD		Cerebrovascular disease		Heart failure	
	Endometriosis	Unexposed	Endometriosis	Unexposed	Endometriosis	Unexposed	Endometriosis	Unexposed
Population	55 832	222 556	55 999	223 237	55 930	223 050	56 074	223 576
Events, n (%)	574 (1.03)	1676 (0.75)	279 (0.5)	753 (0.33)	294 (0.53)	881 (0.39)	41 (0.07)	195 (0.08)
Person-years	357 959.8	1 233 555	360 270.9	1 241 282	360 076.3	1 240 657	362 130.2	1 247 165
Crude incidence rate/1000 person-years	1.60	1.36	0.77	0.61	0.82	0.71	0.11	0.16
Age at outcome (years), median (IQR)	42.6 (37.5–46.8)	43.4 (39.1–47.1)	43.2 (39.4–47.1)	43.5 (40.0–46.8)	41.3 (36.3–46.6)	43.0 (38.3–47.0)	43.6 (37.0–46.7)	43.2 (39.4–47.3)
Crude HR (95% CI)	1.16 (1.06–1.28)		1.26 (1.09–1.44)		1.13 (0.99–1.29)		0.71 (0.50–0.99)	
P value	0.002		0.001		0.067		0.044	
Adjusted HR (95% CI)	1.24 (1.14–1.37)		1.40 (1.22–1.61)		1.19 (1.04–1.36)		0.76 (0.54–1.07)	
P value	<0.001		<0.001		0.010		0.115	

Adjusted for: age, Townsend deprivation quintiles, BMI, smoking status, lipid-lowering medication, alcohol use, diabetes mellitus, hypertension, connective tissue disorders, migraine, contraceptive use, parity status, PCOS.

Interpretation of findings in the context of previous literature

Among the general female population, the prevalence of endometriosis is estimated to range from 2 to 10%.[19,20] However, prevalence estimates differ based on the study setting or diagnostic criteria.[21] The prevalence estimates in our study are similar to findings from two UK studies, a community-based study[22] and a population-based study,[23] that estimated the prevalence of endometriosis at 1.4% and 1.5%, respectively. The incidence estimates from our study align with two UK-based population studies that estimated the incidence of endometriosis at 0.97 per 1000 person-years among women aged 15–55 years,[23] and 1.46 per 1000 person-years among women aged 12–54 years.[24] A Finnish study showed that women with endometriosis had lower all-cause mortality compared with the comparator group (Figure S3).[25] This is consistent with the results from our study, which found a significantly lower rate of mortality among women with endometriosis compared with matched controls. Longer survival among women with endometriosis compared with matched controls without endometriosis may explain the increased annual prevalence with a stagnant annual incidence rate of endometriosis among UK women throughout the 20 years of follow up.

Endometriosis is an estrogen-dependent condition that is common among women of reproductive age. Similar to findings in our study, a cohort study from the USA, the Nurses' Health Study II (NHS II) study found that the incidence of laparoscopically confirmed endometriosis was highest among women aged 25–29 years and decreased after the age of 40 years.[26] The incidence of endometriosis decreased linearly from the least deprived quintile to the most deprived quintile. Our findings concur with reports in previous literature that noted a higher incidence of endometriosis among women of higher socio-economic status.[27] Socio-economic status may be a proxy marker for lifestyle risk factors associated with endometriosis in the UK. Smoking and obesity, which are inversely associated with endometriosis, tend to be more prevalent among persons from more deprived socio-economic groups; whereas excessive alcohol consumption, which is associated with increased risk, is more prevalent in younger high-income earners in the UK.[28] Also, the propensity to seek medical attention among women with pelvic pain and infertility is higher among women from higher compared with lower socio-economic status groups.[29]

Findings from our study are comparable with findings from a narrative systematic review that examined the association between endometriosis and atherosclerotic CVD. The systematic review included two population-based studies from the US NHS II Cohort.[30,31] The findings from these studies are summarised in Figure S3. The NHS II
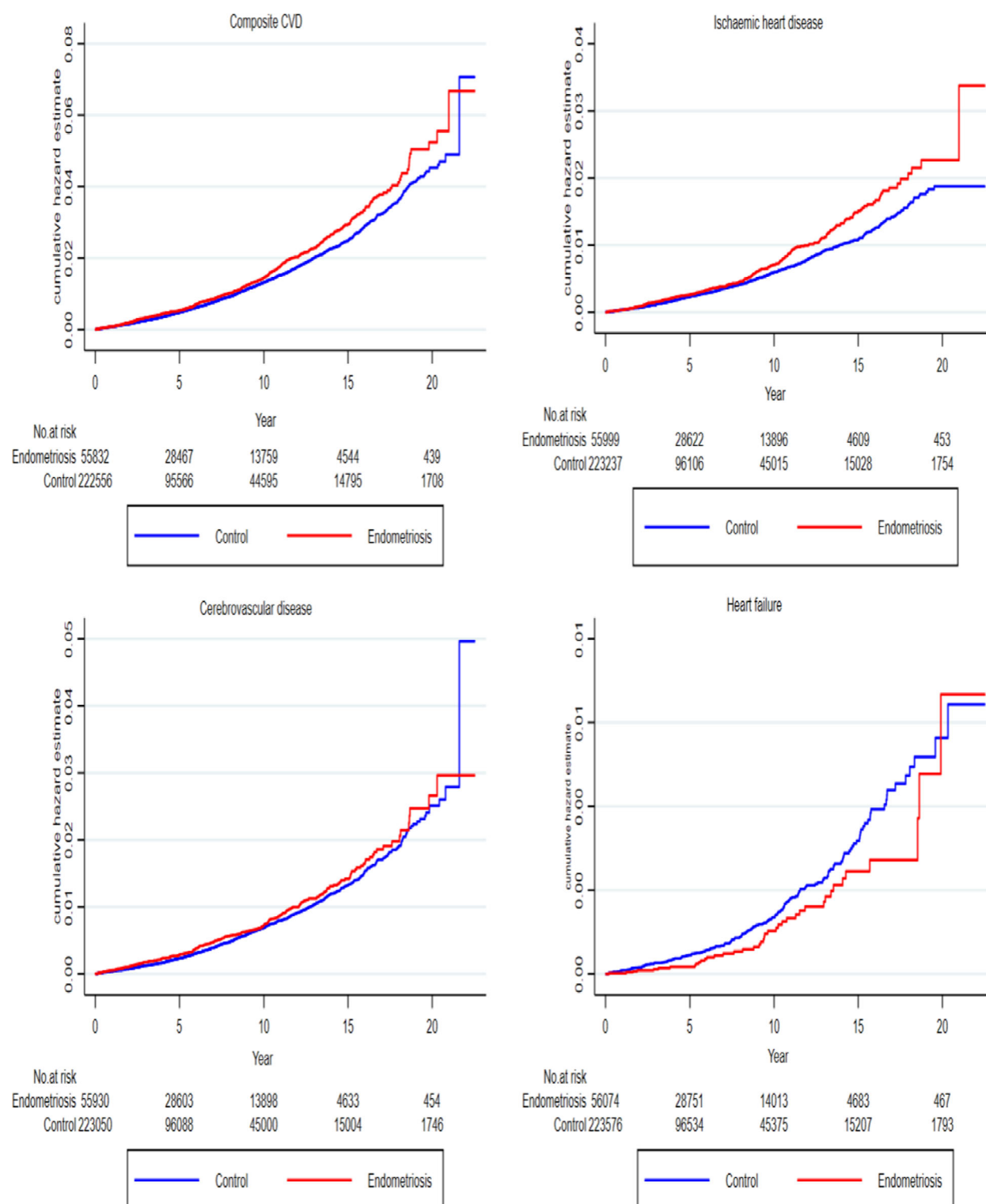
Figure 2. Cumulative hazard of primary cardiovascular outcomes among women with endometriosis (exposed) and those without endometriosis (unexposed/control).

prospective cohort studies found that women with endometriosis compared with those without endometriosis were at a higher risk of composite IHD and hypertension (Figure S3).[30,31] We adjusted for additional confounding variables, including migraine, PCOS and connective tissue disorders. This may partly explain the lower effect estimate of IHD risk in our study. The NHS II studies were limited to investigating the association between endometriosis, IHD risk and hypertension risk.[30,31] On extending the research to other CVD subtypes, we found that endometriosis was associated with increased risk of cerebrovascular disease and composite CVD. Our findings are supported by a recent population-based cohort study by Chiang et al., which found an increased risk of composite CVD including cerebrovascular events among Taiwanese women with endometriosis compared with controls (Figure S3).[32] However, we did not find any association between endometriosis and heart failure risk. The attenuation of the increased risk of composite CVD after the exclusion of women with hysterectomy supports previous reports in the literature that both ovarian conservation and oophorectomy are linked to increased CVD risk.[33] A detailed pre-operative counselling on the benefits and risks of performing hysterectomies among women with endometriosis should be emphasised. Exclusion of women with a current prescription of GnRH analogues was not associated with attenuation of CVD risk, consistent with the results from the study by Chiang et al.[32] The exclusion of women with PID did not support findings of increased risk of CVD among women with PID reported in the literature.[17,34] Further robust studies are needed because important confounding variables, including smoking, BMI and alcohol, were unaccounted for in these studies. A study by Brincat et al found that up to 10% of infertile women had endometriosis with PCOS. Exclusion of women with PCOS did not attenuate the risk of CVD, suggesting that the association between endometriosis and CVD was independent of PCOS.[35] It is not clear why, on sensitivity analyses, the exclusion of women with adverse pregnancy outcomes amplifies cardiovascular risk. Endometriosis is an enigmatic condition. It is probable that the phenotypes of endometriosis linked to increased adverse pregnancy outcomes are associated with greater localised pelvic inflammation but are less likely to be associated with systemic inflammation linked to cardiovascular complications. Restriction of the analysis to women with incident exposure and their matched controls resulted in a non-significant increase in composite CVD with fewer outcomes reported. Prospective studies with a longer duration of follow up are needed.

To the best of our knowledge, this is the first study to investigate an association between endometriosis and risk of arrhythmia. Findings in our study are supported by results from previous studies, which have demonstrated that other chronic inflammatory conditions are linked to increased arrhythmia risk.

Biological plausibility

Several biological mechanisms may explain the observed association between endometriosis and higher cardiovascular risk. First, chronic inflammation promotes endothelial dysfunction. The systemic inflammatory nature of endometriosis has been demonstrated by several studies that found increased levels of pro-inflammatory markers in the peritoneal fluid and serum of women with endometriosis.[36] Moreover, chronic inflammation may favour the development of cardiac arrhythmia, both directly through altered cardiac electrophysiology and indirectly by the accelerated development of IHD.[11]

Second, biomarkers of oxidative stress have been found to be elevated among women with endometriosis.[37] Prolonged exposure to reactive oxygen species from oxidative stress has been associated with vascular and cardiac myocyte dysfunction, which may lead to cardiac arrhythmias through cardiac fibrosis, ion-channel conduction disturbances, and early and late depolarisations.[38,39] Third, various studies have shown that endometriosis is associated with high levels of atherogenic low-density lipoproteins.[31] Fourth, the oxidation hypothesis may partly explain the association between reproductive risk factors, including endometriosis and increased CVD risk.[40] The hypothesis explains that low-density lipoprotein is not atherogenic on its own; for atherosclerosis to occur, reactive oxygen species must oxidise low-density lipoproteins leading to cell formation, a dysfunctional endothelium and finally atherogenesis.

Implications for public health and future research

Findings from this study suggest that young women with endometriosis are a potential target group for CVD prevention and, therefore, an extensive reproductive history should be taken by physicians. A multidisciplinary approach that includes gynaecologists, cardiologists and primary care physicians is needed for effective CVD risk assessment and follow up of women with endometriosis. Future research should focus on developing a non-invasive means of accurately diagnosing endometriosis, identifying phenotypes of endometriosis associated with enhanced cardiometabolic risk and assessing whether the early identification and treatment of endometriosis will translate to reduced CVD burden.

Strengths and limitations

Several limitations arose. We were unable to distinguish surgically confirmed cases from cases diagnosed through other means; cases were identified through physician-assigned diagnostic codes for endometriosis. We believe

diagnostic Read codes for endometriosis are reliable and valid for several reasons. First, a recent UK study showed that 94% of patients with a diagnosis for endometriosis in UK primary care had at least one diagnostic procedure performed, including ultrasound, magnetic resonance imaging, laparoscopy and histology, before diagnosis.[40] Therefore, the validity of the cases is likely to be high. Second, in a randomised controlled trial designed to evaluate the efficacy of leuprolide against placebo in the management of chronic pelvic pain among women with clinically diagnosed endometriosis, post-treatment laparoscopy confirmed 78% and 87% of clinically diagnosed cases in the leuprolide and placebo groups, respectively.[41] Third, in previous observational studies that used surgically confirmed endometriosis as the case definition, the inclusion of non-surgically confirmed endometriosis cases in sensitivity analyses,[29] or in stratified analyses,[23] did not lead to changes in the observed effect estimates. Furthermore, the exclusive use of laparoscopically confirmed cases may inadvertently introduce selection bias because women referred for laparoscopy may systematically differ from those not referred for laparoscopy or those who are asymptomatic.[42]

In addition, our study may be limited by the inclusion of asymptomatic patients with endometriosis in the unexposed group. The impact of including asymptomatic cases in the unexposed cohort is uncertain and may not necessarily attenuate effect estimate.[43]

In other chronic inflammatory conditions, the cardiovascular risk increases with the severity of the condition.[44] As the result of unavailability of data, stratified analysis by the severity of endometriosis could not be carried out in our study. There remains a possibility of unmeasured confounding, for instance because of factors such as dietary patterns, physical activity or breastfeeding history.

The strengths of this retrospective cohort study include large sample size, a long duration of follow up, use of a database that is representative of the UK population and the availability of data on important confounders.

Conclusion

In conclusion, this study found an association between endometriosis and a higher risk of cardiovascular outcomes. No association was found between endometriosis and risk of heart failure. Future research should focus on whether early treatment of endometriosis and primary CVD prevention strategies will be effective in reducing CVD risk among young women with endometriosis.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication

Not required.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. All relevant data are within the paper and its supporting information files.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cumulative hazard of secondary cardiovascular outcomes.

Figure S2. Forest plot hazard ratio and 95% confidence interval for sensitivity analyses.

Figure S3. Forest plot showing summary results of studies investigating the association between endometriosis and cardiometabolic outcomes including all-cause mortality.

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