GYNECOLOGY

Associations between endometriosis and common symptoms: findings from the Australian Longitudinal Study on Women's Health

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BACKGROUND: Endometriosis has been linked to higher rates of a variety of symptoms; however, the findings from longitudinal studies are scarce and inconsistent.

OBJECTIVE: This study aimed to examine the association between endometriosis and common symptoms in a prospective cohort study.

STUDY DESIGN: This study included 7606 women born from 1973 to 1978 using data from the Australian Longitudinal Study on Women's Health that were collected every 3 years from 2009 to 2018. We identified women with endometriosis based on self-reported incidence from each survey and linked administrative health data. At each survey, women also completed a checklist on the presence of 24 symptoms. Generalized estimating equations for multinomial responses were used for analyses.

RESULTS: Women with endometriosis had significantly more menstrual symptoms than those without endometriosis with an adjusted odds ratio (95% confidence interval) of 3.61 (3.11—4.19) for severe period pain, 2.40 (2.10—2.74) for heavy menstrual bleeding, 1.76 (1.52—2.03) for irregular bleeding, and 1.52 (1.32—1.76) for premenstrual tension. They also had higher odds of mental health problems with adjusted odds ratios of 1.67 (1.39—2.01) for depression and 1.59 (1.24—2.03) for anxiety and higher odds of allergies and nonspecific symptoms with adjusted odds of 1.62 (1.40—1.89) for allergies or hay fever or sinusitis, 1.79 (1.56—2.05) for severe tiredness, 1.56 (1.35—1.81) for sleep difficulty, and 1.77 (1.37—2.18) for palpitations. There was also a strong association with other forms of pain with an adjusted odds ratio of 1.76 (1.53—2.04) for backpain, 1.50 (1.29—1.74) for headaches or migraines, and 1.65 (1.41—1.93) for stiff or painful joints. Women with endometriosis also had increased odds of developing bowel and urinary symptoms with an adjusted odds ratio (95% confidence interval) of 1.67 (1.35—2.08) for constipation, 1.46 (1.12—1.90) for hemorrhoids or piles, 1.25 (1.03—1.52) for indigestion or heartburn, 2.80 (1.71—4.58) for urine burn or stings, and 1.37 (1.03—1.82) for vaginal discharge or irritation. The association between each symptom and endometriosis was similar whether endometriosis was surgically confirmed or clinically suspected. No association was found between endometriosis and the risk for skin problems, leaking urine, or breathing difficulty.

CONCLUSION: This study suggests that women with endometriosis are more likely to report not only menstrual symptoms but are also at an increased risk for mental health problems, other pain symptoms, bowel and urinary symptoms, and nonspecific symptoms, such as severe tiredness and difficulty sleeping.

Key words: bowel symptoms, endometriosis, menstrual symptoms, mental health problems, pain symptoms, urinary symptoms

Introduction

Endometriosis is a chronic gynecologic disorder characterized by the presence of endometrium-like tissue outside the uterus.[1] In Australia, 1 in 9 women (11.4%) are diagnosed with endometriosis by the age of 44 years.[2] Endometriosis has a substantial impact on women's lives, leading to increased hospitalizations, diminished work productivity, and a reduced quality of life.[3–6]

The nonspecific nature and normalization of the symptoms of endometriosis often means that there is a marked delay in the diagnosis of endometriosis between the onset of symptoms and diagnosis with several studies reporting an average delay of 7 to 11 years.[7–11] This delay in diagnosis leads to untreated endometriosis-related symptoms, hospitalizations, increased healthcare resource utilization, and potentially reduced success using assisted reproductive technologies.[12–14]

A growing body of evidence suggests that women with endometriosis are more likely to suffer from chronic pelvic pain, dysmenorrhea, heavy menstrual bleeding, dysuria, dyspareunia, dyschezia, and fatigue.[15–17] These symptoms have a detrimental impact on women's somatic, sexual, mental, and social well-being.[18,19] A recent meta-analysis conducted by Van Barneveld et al[20] showed that depression and anxiety were primarily linked to chronic pain among women with endometriosis.[20] Other meta-analyses also revealed that endometriosis was associated with an increased risk for depression,[21] migraine headache,[22] allergic disorders,[23] and irritable bowel syndrome.[24] However, most studies to date were limited to cross-sectional or descriptive studies only.

This study aimed to examine the association between endometriosis and common symptoms using data from a nationally representative, population-based longitudinal cohort study of Australian women of reproductive age.

Materials and Methods

Study design and participants

This study used data from the Australian Longitudinal Study on Women's Health (ALSWH), an ongoing, large,

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AJOG at a Glance

Why was this study conducted?

Endometriosis may cause a wide range of symptoms through immunologic and inflammatory mediators; however, the findings from longitudinal studies are limited.

Key findings

Women with endometriosis were more likely to report not only menstrual symptoms, but they also had an increased risk for mental health problems, other pain symptoms, bowel and urinary symptoms, and nonspecific symptoms, such as severe tiredness and difficulty sleeping.

What does this add to what is known?

This study conducted a comprehensive investigation of the association between endometriosis and a wide range of symptoms using data from a nationally representative longitudinal study of Australian women.

population-based prospective cohort study. The ALSWH commenced in 1996 with more than 40,000 women recruited from 3 age cohorts, namely the younger cohort (born 1973−1978), the mid-age cohort (1946−1951), and the older cohort (1921−1926). The participants were randomly selected from the National Universal Health Insurance Database (Medicare), which includes all Australian citizens and permanent residents. Eight consecutive surveys were conducted through postal or online questionnaires every 3 years from 1996 to 2018 with an overall response rate of approximately 80%. Full details of the ALSWH study, including the study design, recruitments, and response rate, have been published elsewhere.[25−27] The ALSWH study was approved by the human research ethics committees at the University of Queensland and the University of Newcastle. Informed consent was obtained from all women for each survey after an explanation of the nature of the study.

This study analyzed data from women in the cohort born from 1973 to 1978 (aged 18−23 years in 1996) who provided comprehensive information about their symptoms and risk factors. Of the 14,247 women who responded to the baseline survey in 1996, 13,501 women (95%) provided consent for the linkage of survey data with their administrative health records (Figure 1). In this study, we used the women who provided consent for data linkage and who also completed the symptoms checklists in the surveys from 2009 to 2018 for a final effective sample of 7606.

Assessment of the diagnosis of endometriosis

Information on endometriosis incidence among the 1973 to 1978 cohort of the ALSWH study was obtained from the women's self-reported surveys and their administrative health records. The incidence of endometriosis was first assessed in 2000 in survey 2 using the following question: "Have you ever been told by a doctor that you have: Endometriosis?" In surveys 3 to 8, women were asked, "In the last 3 years, have you ever been diagnosed or treated for: endometriosis?" Data from the women's self-reported surveys were combined with 3 administrative health records, including the Medicare Benefits Schedule (MBS), the Pharmaceutical Benefits Scheme (PBS), and the Admitted Patient Data Collections (hospital data), to identify women with endometriosis. Detailed information on the methods of case ascertainment and the specific codes used to identify endometriosis in each data source are published elsewhere.[2] Overall, of the total number of endometriosis cases identified, 40%, 20%, 4%, and 1% of cases were identified from the ALSWH survey, hospital, PBS, and MBS data alone, respectively. The remaining 35% of cases were identified through various combinations of the 4 data sources.[2]

The study further categorized endometriosis into surgically confirmed and clinically suspected endometriosis using the 4 longitudinal sources of data. Surgically confirmed endometriosis was identified for women who had a diagnosis of endometriosis recorded in the MBS or hospital data. Women with self-reported endometriosis in the ALSWH surveys only or those who had only been prescribed a restricted medication for endometriosis (based on PBS data) were classified as having clinically suspected endometriosis.

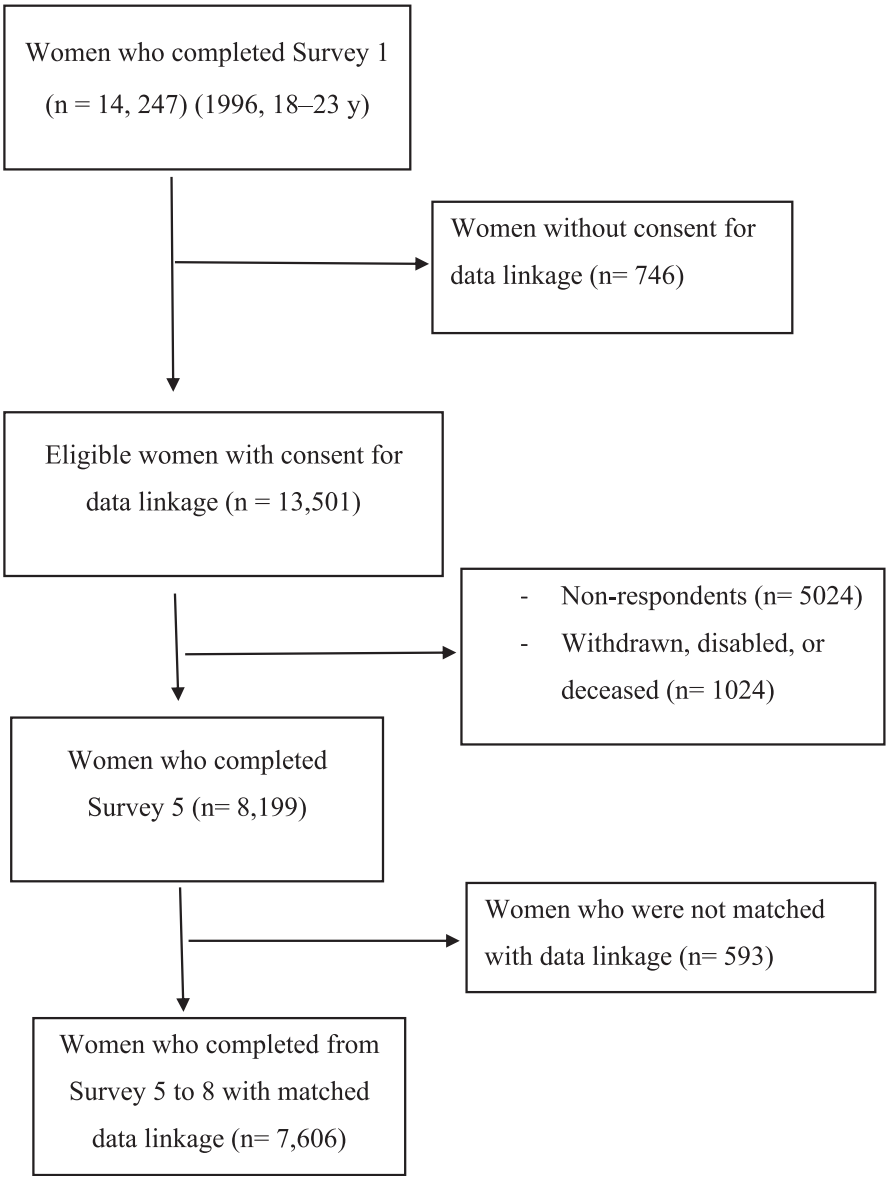
Assessments of outcomes

Data on women's symptoms were obtained from the self-reported surveys from the ALSWH study. For this study, data from surveys conducted in 2009, 2012, 2015, and 2018, which included a comprehensive checklist of common symptoms, were used. In each survey, the women were asked whether they had experienced symptoms of the following 24 conditions in the past 12 months: allergies or hay fever or sinusitis, headaches or migraines, severe tiredness, indigestion or heartburn, breathing difficulties, stiff or painful joints, back pain, problems with one or both feet, difficulty sleeping, depression, anxiety, other mental health problems, palpitations, premenstrual tension, irregular periods, heavy menstrual bleeding, severe period pain, skin problems, urine burns or stings, leaking urine, vaginal discharge or irritation, constipation, hemorrhoids or piles, and other bowel problems. Response options were never, rarely, sometimes, and often. However, women's responses as never and rarely were merged and considered as a reference group for the current analyses.

Assessments of confounders

Several potential confounders were selected based on their known association with endometriosis and women's symptoms from previous literature, including sociodemographic factors (women's age, residence, marital status, education, and income), lifestyle (smoking, alcohol intake, and physical

FIGURE 1
Flow diagram of sample for the association between endometriosis and common symptoms



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activity), and body mass index (BMI), parity, and contraceptive use (combined oral contraceptives and progestogen-only contraception, including implants and intrauterine devices).

Information on residence was categorized as urban and rural or remote.[28] The physical activity was assessed using total metabolic equivalent (MET) values based on frequency and duration of walking and moderate- and vigorous-intensity activity and categorized as sedentary (<40 MET min/wk), low (<600 MET min/wk), moderate (600 to 1200 MET min/wk), and high (≥1200 MET min/wk).[29] Smoking status was categorized as never smoker, ex-smoker, and current smoker.[30] Alcohol intake was categorized as nondrinker, low-risk drinker (≤14 drinks/wk), risky drinker (15−28 drinks/wk), and high-risk drinker (>28 drinks/wk).[31] However, because only a few women were high-risk drinkers (0.9%), this category was combined with the risky drinker group. BMI was categorized as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2).

Statistical analyses

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC), and Stata software, version 17 (StataCorp, College Station, TX). Baseline characteristics and symptoms of women with and without endometriosis were described using Pearson's chi-square tests and *t* tests, presented as percentages (%) for categorical variables and means±standard deviations (SDs) for continuous variables. Generalized estimating equations (GEEs) with multinomial logistic regression models were used to examine the association between endometriosis and the incidence of each symptom over the 4 time points. We analyzed the data using the following 3 levels of adjustment: first, adjusting for time (survey); then for survey and sociodemographic and lifestyle factors and BMI; and finally adding factors for parity and contraceptive pills. Sociodemographic and lifestyle factors and BMI were treated as time-varying covariates in the analyses. Women's symptoms were regarded as outcomes that could vary over time. We stratified the analyses to estimate the odds of experiencing each symptom and whether they had surgically confirmed or clinically suspected endometriosis. We performed 3 sensitivity analyses. The first was conducted on the association between endometriosis and the odds of urine burn or stings to observe whether the association was affected by urinary tract infections (UTIs) or not. We performed a further sensitivity analysis after imputing missing data on outcomes based on the last observation carried forward to assess the influence of excluded participants from missing outcomes. An additional sensitivity analysis was conducted to examine the odds of mental health outcomes among women with endometriosis in comparison with those without endometriosis conditions associated with pain (such as

migraines or headaches) and those without endometriosis conditions characterized by diagnostic delays owing to normalization, dismissal, and stigma (including severe tiredness and bowel problems).

Results

A total of 1149 endometriosis cases (15.1%) were identified among the 7606 women from 2009 to 2018. A total of 9 years of follow-up data were included. Of these, 565 were categorized as surgically confirmed and 584 as clinically suspected endometriosis (Figure 1). A higher percentage of endometriosis was observed among women who lived in urban areas, those who were sedentary, and those who were underweight. Parous women were less likely to be diagnosed with endometriosis (Table 1).

In this study, 6048 women were excluded from the analysis for reasons such as nonresponse, withdrawal, disability, or being deceased for any of the surveys. The included participants, in comparison with the excluded ones, were less likely to be married, educated, smokers, and drinkers (Supplemental Table 1). In contrast, they exhibited higher levels of physical activity and maintained a healthy weight.

Table 2 presents the percentage of women, with or without a diagnosis of endometriosis, who reported each symptom in the 2009 survey. A significantly greater percentage of symptoms overall was reported among women with endometriosis than among those without endometriosis. Women with endometriosis were more likely to report a range of symptoms than other women, including menstrual, mental, bowel, urinary, and other nonspecific symptoms.

As shown in Figure 2, a significant positive association was observed between the odds of women's symptoms overall and endometriosis after adjustment for important potential confounders, including sociodemographic, lifestyle, and reproductive factors. However, no significant associations were found between endometriosis and the odds of leaking urine, skin problems, and breathing difficulty. In the current

TABLE 1
Baseline women's characteristics according to endometriosis cases

Women's characteristics	All women (n=7606)	Endometriosis		*P* value[a]
		Yes (n=1149)	No (n=6457)	
Women's age (y), mean (SD)	33.7 (1.5)	33.7 (1.5)	33.7 (1.5)	.53
Area of residence, n (%)[b]				.07
Urban	4220 (55.5)	15.8	84.1	
Rural or remote	3196 (42.0)	14.3	85.7	
Marital status, n (%)[b]				.25
Married	4720 (62.1)	14.7	85.3	
De facto or separated or divorced	1586 (20.9)	15.3	84.7	
Single	1272 (16.7)	16.6	83.4	
Educational status, n (%)[b]				.52
Up to year 12 or equivalent	1586 (20.9)	15.3	84.7	
Trade or apprenticeship o certificate o diploma	1972 (25.9)	15.9	84.1	
University or higher degree	3891 (51.2)	14.8	85.2	
Able to manage income, n (%)[b]				.29
It is impossible or difficult all the time	923 (12.1)	17.2	82.8	
It is difficult some of the time	2129 (28.0)	14.7	85.3	
It is not too bad	2957 (38.9)	14.9	85.1	
It is easy	1566 (20.6)	15.1	84.9	
Smoking status, n (%)[b]				.49
Never smoked	4529 (59.6)	15.2	84.8	
Ex-smoker	1954 (25.7)	14.4	85.6	
Current smoker	1105 (14.5)	16.0	84.0	
Alcohol intake, n (%)[b]				.75
Nondrinker	900 (11.8)	15.6	84.4	
Rarely drinker	1833 (24.1)	14.6	85.4	
Low-risk drinker	4508 (59.3)	15.3	84.7	
Risky drinker	334 (4.4)	13.8	86.2	
Physical activity, n (%)[b]				.25
Sedentary, <40 MET min/wk	954 (12.5)	17.3	82.7	
Low, 40 to <600 MET min/wk	2700 (35.5)	14.9	85.1	
Moderate, 600 to <1200 MET min/wk	1663 (21.9)	14.6	85.4	
High, ≥1200 MET min/wk	2054 (27.0)	14.9	85.1	
Body mass index, n (%)[b]				.19
Underweight, <18.5 kg/m^2	182 (2.4)	20.3	79.7	
Healthy weight, 18.5 to <25 kg/m^2	3858 (50.7)	15.2	84.8	
Overweight, 25 to <30 kg/m^2	1912 (25.1)	14.9	85.1	
Obese, ≥30 kg/m^2	1524 (20.4)	14.3	85.7	

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023. *(continued)*

TABLE 1
Baseline women's characteristics according to endometriosis cases
(continued)

Women's characteristics	All women (n=7606)	Endometriosis		*P* value[a]
		Yes (n=1149)	No (n=6457)	
Parity, n (%)[b]				<.0001
Nulliparous	2731 (35.9)	18.3	81.7	
Parous	4849 (63.7)	13.3	86.7	
Combined oral contraceptives, n (%)[b]				.07
Yes	1690 (22.2)	13.8	86.2	
No	5839 (76.8)	15.6	84.4	
Only progestogen, n (%)[b]				.75
Yes	269 (3.5)	14.5	85.5	
No	7260 (95.4)	15.2	84.8	
Oral contraceptives unknown type, n (%)[b]				.52
Yes	122 (1.6)	13.1	86.9	
No	7407 (97.4)	15.2	84.8	

The data for n=7606 women are presented. Values are presented as mean (standard deviation) or as the number (percentage) of women for the baseline women's characteristics.

MET, metabolic equivalent; *SD*, standard deviation.

[a] *P* values were determined using Pearson chi-square tests or *t* tests; [b] Missing values are as follows: area of residence, n=190; marital status, n=28; educational status, n=157; manage on income, n=31; smoking status, n=18; alcohol intake, n=31; physical activity, n=235; body mass index, n=130; parity, n=26; combined oral contraceptives, n=77; only progestogen, n=77; oral contraceptives unknown type, n=77.

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study, women without endometriosis and who never or rarely experienced symptoms were used as reference groups. The strongest effect size was observed for the association between endometriosis and the odds of severe period pain, followed by urine burn or stings and heavy menstrual bleeding.

A strong positive association was found between endometriosis and the odds of menstrual symptoms at *P*<.0001 (Supplemental Table 2). Women with endometriosis were more likely to report severe period pain, heavy menstrual bleeding, irregular period, and premenstrual tension than those without endometriosis (adjusted odds ratio [AOR], 3.61; 95% confidence interval [CI], 3.11−4.19; AOR, 2.40; 95% CI, 2.10−2.74; AOR, 1.76; 95% CI, 1.52−2.03; and AOR, 1.52; 95% CI, 1.32−1.76, respectively).

Women with endometriosis were also more likely to report mental health symptoms (*P*<.0001). Women with endometriosis had increased odds of depression, anxiety, and other mental problems (AOR, 1.67; 95% CI, 1.39−2.01; AOR, 1.59; 95% CI, 1.24−2.03; and AOR, 1.66; 95% CI, 1.22−2.26, respectively).

A further sensitivity analysis revealed that individuals with pain-related conditions other than endometriosis, specifically migraine or headaches (AOR, 1.42; 95% CI, 1.14−1.78) and painful or stiff joints (AOR, 1.40; 95% CI, 1.10−1.40), had a higher likelihood of experiencing depression than women with endometriosis (Supplemental Table 3). In addition, women who had conditions other than endometriosis that are often associated with a delayed diagnosis because of societal normalization, dismissal, and stigma (eg, constipation), were more inclined to report mental health issues, including depression (AOR, 1.88; 95% CI, 1.54−2.30) and anxiety (AOR, 1.81; 95% CI, 1.39−2.35), than those with endometriosis.

Women with endometriosis were more likely to report somatic and allergic symptoms. Comparing women with endometriosis with those without, the AORs (95% CIs) were 1.79 (1.56−2.05) for severe tiredness, 1.76 (1.53−2.04) for backpain, 1.50 (1.29−1.74) for allergies or hay fever or sinusitis, 1.62 (1.40−1.89) for headaches or migraines, 1.65 (1.41−1.93) for stiff or painful joints, and 1.33 (1.12−1.59) for feet problems. Endometriosis was also associated with a 77% and 56% greater likelihood of palpitations (95% CI, 1.37−2.18) and sleep difficulty (95% CI, 1.35−1.81), respectively.

The likelihood of constipation, hemorrhoids or piles, and indigestion or heartburn was increased by 67%, 46%, and 25%, respectively. Women with endometriosis were more likely to report urine burn or stings and vaginal discharge or irritation than those without endometriosis (AOR, 2.80; 95% CI, 1.71−4.58; and AOR, 1.37; 95% CI, 1.03−1.82, respectively).

The association between each symptom and endometriosis was similar whether endometriosis was surgically confirmed or clinically suspected endometriosis (Supplemental Figure) with higher odds of having all symptoms except for indigestion or heartburn, breathing difficulties, and vaginal discharge or irritation in surgically confirmed endometriosis and breathing difficulties and vaginal discharge or irritation in clinically suspected endometriosis.

Comment

Principal findings

In this study, a comprehensive investigation of the association between endometriosis and a wide range of symptoms was performed using data from a nationally representative longitudinal study of Australian women. We found a significant positive association between

TABLE 2
Baseline women's symptoms according to endometriosis cases

Women's symptoms	All women (n=7606)	Endometriosis		*P* value[a]
		Yes (n=1149)	No (n=6457)	
Allergies or hay fever or sinusitis, n (%)[b]				.001
Never or rarely	4341 (57.1)	52.9	58.4	
Sometimes	2046 (27.0)	28.7	26.9	
Often	1153 (15.2)	18.5	14.7	
Headaches or migraines, n (%)[b]				<.0001
Never or rarely	3590 (47.2)	40.8	48.7	
Sometimes	2891 (38.0)	40.0	37.9	
Often	1079 (14.2)	19.3	13.4	
Severe tiredness, n (%)[b]				<.0001
Never or rarely	3819 (50.2)	43.9	52.1	
Sometimes	2448 (32.2)	36.0	32.0	
Often	1237 (16.3)	20.1	15.8	
Breathing difficulties, n (%)[b]				.44
Never or rarely	6870 (90.3)	91.1	92.4	
Sometimes	488 (6.4)	7.1	6.5	
Often	90 (1.2)	1.5	1.2	
Stiff or painful joints, n (%)[b]				.001
Never or rarely	5642 (74.2)	72.7	76.2	
Sometimes	1313 (17.3)	18.0	17.5	
Often	498 (6.6)	9.3	6.2	
Back pain, n (%) [b]				<.0001
Never or rarely	4176 (54.9)	49.7	56.7	
Sometimes	2339 (30.8)	32.8	30.9	
Often	989 (13.0)	17.5	12.4	
Problems with one or both feet, n (%) [b]				.59
Never or rarely	6418 (84.4)	85.0	86.1	
Sometimes	702 (9.2)	10.1	9.3	
Often	348 (4.6)	4.9	4.6	
Indigestion or heartburn (%) [b]				.46
Never or rarely	6079 (80.0)	80.3	81.8	
Sometimes	989 (13.0)	14.3	13.1	
Often	382 (5.0)	5.4	5.1	
Constipation, n (%)[b]				<.0001
Never or rarely	6100 (80.2)	77.0	82.2	
Sometimes	1095 (14.4)	17.3	14.1	
Often	294 (3.9)	5.7	3.6	

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023. *(continued)*

endometriosis and common symptoms overall. As expected, women with endometriosis had an increased risk for menstrual symptoms, but they also were shown to be at increased risk for mental health, bowel, urinary, pain, and other nonspecific symptoms. However, no significant association was observed between endometriosis and the risk for skin problems, leaking urine, or breathing difficulty.

Results in the context of what is known

The strong association between a diagnosis of endometriosis and menstrual symptoms is consistent with the findings of Ballard et al[16] and Mahmood et al.[32] Endometriosis may affect menstrual symptoms through inflammation and vasoconstriction. Endometriotic lesions induce increasing prostaglandins and leukotrienes production, which are key drivers of menstrual pain. Prostaglandins also cause vasoconstriction, myometrial contractility, and uterine ischemia, which could affect menstrual and bowel symptoms.[33–36]

Our findings that women with endometriosis were at higher risk for depression, anxiety, and other mental problems are in line with those of previous cohort studies from the United States[37] and Taiwan.[38] A possible explanation for this association might be that it is a consequence of endometriosis-associated pain. Chronic endometriosis-associated pain plays an important role in the development of depression and anxiety among women with endometriosis.[39,40]

Endometriosis was also significantly associated with an increased risk for bowel symptoms. An association between endometriosis and gastrointestinal disorders has also been reported in Sweden,[41] Germany,[42] the United Kingdom,[43] and Taiwan.[44] Endometriosis may be linked to bowel disorders through alteration of gut microbiota. For example, Svensson et al[45] showed an association between endometriosis and gut microbiota, predominantly Bacilli, Clostridia, Bacteroidia, and Gammaproteobacter.[45]

Women with endometriosis were more likely to experience urine burn or

TABLE 2
Baseline women's symptoms according to endometriosis cases *(continued)*

Women's symptoms	All women (n=7606)	Endometriosis		*P* value[a]
		Yes (n=1149)	No (n=6457)	
Hemorrhoids or piles, n (%)[b]				.007
Never or rarely	6598 (86.7)	86.1	88.6	
Sometimes	690 (9.1)	10.1	9.1	
Often	187 (2.5)	3.7	2.3	
Other bowel problems, n (%)[b]				<.0001
Never or rarely	6717 (88.3)	87.4	90.4	
Sometimes	499 (6.6)	7.0	6.6	
Often	253 (3.3)	5.6	3.0	
Leaking urine, n (%)[b]				.86
Never or rarely	6661 (87.6)	89.4	89.0	
Sometimes	639 (8.4)	8.5	8.6	
Often	177 (2.3)	2.1	2.4	
Urine burn or stings, n (%)[b]				.001
Never or rarely	7091 (93.2)	93.0	95.2	
Sometimes	342 (4.5)	5.9	4.4	
Often	41 (0.5)	1.2	0.4	
Vaginal discharge or irritation, n (%)[b]				.11
Never or rarely	6496 (85.4)	85.1	87.3	
Sometimes	796 (10.5)	12.2	10.4	
Often	176 (2.3)	2.8	2.3	
Premenstrual tension, n (%)[b]				<.0001
Never or rarely	5005 (65.8)	62.5	67.5	
Sometimes	1724 (22.7)	22.7	23.0	
Often	770 (10.1)	14.8	9.5	
Irregular period, n (%)[b]				<.0001
Never or rarely	6078 (79.9)	76.4	82.2	
Sometimes	799 (10.5)	11.0	10.6	
Often	597 (7.8)	12.6	7.2	
Heavy menstrual bleeding, n (%)[b]				<.0001
Never or rarely	5864 (77.1)	66.1	80.6	
Sometimes	990 (13.0)	17.1	12.5	
Often	624 (8.2)	16.8	6.9	
Severe period pain, n (%)[b]				<.0001
Never or rarely	5909 (77.7)	62.4	81.8	
Sometimes	993 (13.1)	17.9	12.4	
Often	589 (7.7)	19.7	5.8	

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stings and vaginal discharge. Little evidence was found in the literature on the association between endometriosis and the risk for urinary symptoms. Our finding is in agreement with that of Gabriel et al[46] who reported a positive association between endometriosis and a higher risk for dysuria. In a national case-control study conducted in the United Kingdom, Ballard et al[16] showed that women with endometriosis had an increased risk for vaginal discharge, however, they found no association between endometriosis and risk for dysuria.[16] The association might be a consequence of an alteration in the pelvic innervation that was caused by an endometriotic lesion. For example, Miller and Fraser[47] showed that pelvic innervation was altered among women with endometriosis with a greater density of sensory C and A delta nerve fibers detected within endometriotic lesions; this change in pelvic sensation might potentially influence the urinary system.

Other symptoms that are associated with endometriosis and that were also found in our study and previous reports are headaches or migraines,[48–52] severe tiredness,[53–55] allergies,[56–59] sleep difficulty,[54,60,61] and back and lower extremities pain.[62,63]

The association between endometriosis and risk for urine burn or stings remained statistically significant after further adjustment for UTI. However, the effect estimate was slightly reduced. Consistent results were also observed for the association between endometriosis and the risk for each symptom in a further analysis of outcomes and confounders after imputing missing data.

When compared with women with endometriosis, individuals who experienced pain-related conditions, particularly migraine or headaches and painful or stiff joints, other than endometriosis were found to have a higher likelihood of experiencing depression. Women who have a condition other than endometriosis that is linked to a delay in diagnosis as a consequence of normalization, dismissal, and stigma were more prone to reporting mental health issues, including depression and anxiety. Pain-

TABLE 2
Baseline women's symptoms according to endometriosis cases *(continued)*

Women's symptoms	All women (n=7606)	Endometriosis		*P* value[a]
		Yes (n=1149)	No (n=6457)	
Skin problems, n (%)[b]				.13
Never or rarely	5935 (78.0)	77.8	79.7	
Sometimes	966 (12.7)	13.1	12.9	
Often	575 (7.6)	9.2	7.4	
Difficulty sleeping, n (%)[b]				.01
Never or rarely	4886 (64.2)	61.9	65.8	
Sometimes	1797 (23.6)	25.0	23.8	
Often	814 (10.7)	13.1	10.5	
Depression, n (%)[b]				<.0001
Never or rarely	5933 (78.0)	74.0	80.1	
Sometimes	1050 (13.8)	17.3	13.4	
Often	508 (6.7)	8.7	6.4	
Anxiety, n (%)[b]				.003
Never or rarely	6780 (89.1)	87.8	90.9	
Sometimes	539 (7.1)	9.1	6.9	
Often	175 (2.3)	3.1	2.2	
Other mental problems, n (%)[b]				.06
Never or rarely	7201 (94.7)	95.4	96.7	
Sometimes	149 (2.0)	2.7	1.9	
Often	109 (1.4)	2.0	1.4	
Palpitations, n (%)[b]				<.0001
Never or rarely	6641 (87.3)	85.2	89.4	
Sometimes	695 (9.1)	11.6	8.9	
Often	145 (1.9)	3.1	1.7	

The data for n=7606 women are presented. Values are presented as column percentage (%).

[a] *P* values were determined using the Pearson chi-square test; [b] Missing values are as follows: allergies or hay fever or sinusitis, n=66; headaches or migraines, n= 46; severe tiredness, n=102; breathing difficulties, n=158; stiff or painful joints, n=153; back pain, n=102; problems with one or both feet, n=138; indigestion or heartburn, n=156; constipation, n=117; hemorrhoids or piles, n= 131; other bowel problems, n=137; leaking urine, n=129; urine burns or stings, n=132; vaginal discharge or irritation, n=138; premenstrual tension, n=107; irregular periods, n=132; heavy menstrual bleeding, n=128; severe period pain, n=115; skin problems, n=130; difficulty sleeping, n=109; depression, n=115; anxiety, n=112; other mental health problems, n=147; and palpitations, n=125.

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023.

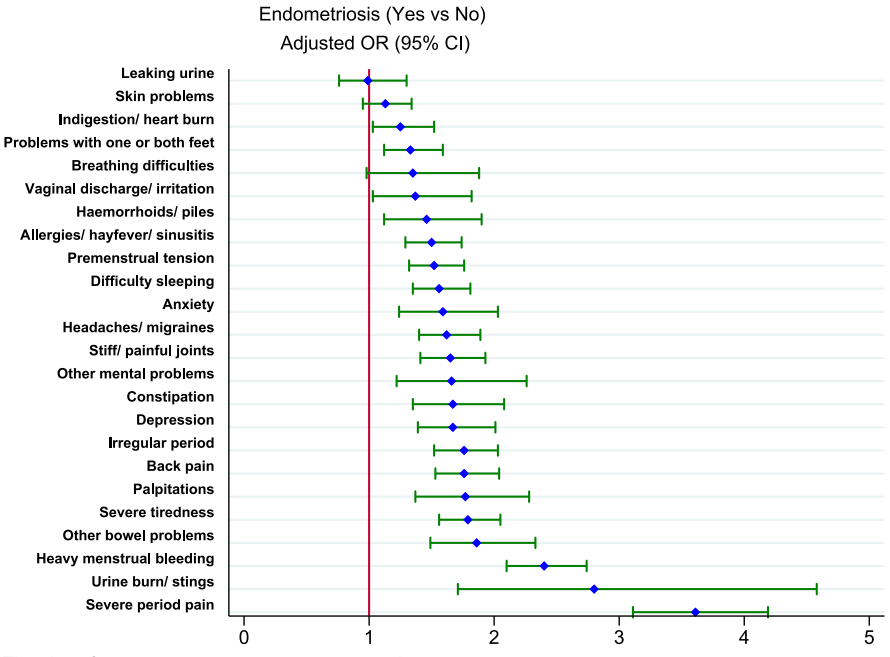
related conditions, such as migraines or headaches and painful joints, may have a notable impact on physical and emotional well-being. These conditions can disrupt sleep patterns, affect daily functioning, and limit social activities, potentially leading to the development of depression.[64,65] Women who face delays in receiving a proper diagnosis for their condition may experience additional emotional distress.[66,67] The normalization of symptoms, dismissal from healthcare providers, or societal stigma can prolong the process of diagnosing the condition and make individuals feel disregarded or invalidated. This prolonged period of uncertainty and the absence of proper medical validation may increase the risk of experiencing mental health issues. The observed mental health outcomes may not be exclusive to endometriosis but could be shared by other conditions involving pain or other diagnostic delays. This observation may provide a valuable understanding of the unique mental health challenges faced by individuals with endometriosis when compared with other groups.

To evaluate symptoms experienced by women, this study employed data obtained from the ALSWH surveys conducted between 2009 and 2018, covering the age range of 31 to 45 years. These surveys were selected because of their inclusive checklist of commonly occurring symptoms. However, endometriosis cases were identified using 4 different sources of data. The average age at which endometriosis was first diagnosed was 32 years. The youngest reported age at diagnosis was 18 years, whereas the oldest was 45 years. It is important to note that the data in this study may not be entirely representative of individuals with endometriosis who were diagnosed at a younger age, such as adolescents who experienced early-onset of the disease.

Potential explanations

Endometriosis may cause a wide range of symptoms through immunologic and inflammatory mediators.[68] Endometriotic lesions induce excess production of proinflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor-alpha), chemokines, and prostaglandins, which play a critical role in the development of menstrual, somatic, mental, urinary, and bowel symptoms.[33,69,70] Elevated proinflammatory cytokines in endometriosis may impair the brain-blood barrier and neuroendocrine system, subsequently affecting mental health.[71–74] These proinflammatory mediators can also activate primary afferent meningeal nociceptive neurons that induce inflammation of the trigeminovascular system, and potentially cause headaches or migraine attacks.[75] Furthermore, they might have a potential to trigger nonspecific symptoms, including fatigue and sleep disturbances.[70,76,77] The proinflammatory cytokines could stimulate the synthesis of regulated activation,

FIGURE 2
Association between endometriosis (yes vs no) and each symptom (often vs never/rarely)



The data for n=7606 women are presented.

CI, confidence interval; *OR*, odds ratio.

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023.

normal T-cell expressed and secreted, and monocyte chemotactic protein-1 in endometriotic lesions that induce histamine-releasing factor production.[78,79] The histamine-releasing factor induces interleukin-4 and interleukin-13 production that could favor a Th2 response and the development of allergic diseases.[80,81] The hypothalamic-pituitary-adrenal axis might be altered among women with endometriosis because of a higher level of stress−−this leads to nonspecific symptoms, including fatigue and chronic pain.[82,83] Central sensitization plays a role in the development and maintenance of chronic pain experienced by women with endometriosis.[35,84] Endometriosis-related pain can be complex and involve various factors, such as inflammation, pelvic adhesions, and nerve involvement, which can contribute to peripheral sensitization. With prolonged exposure, persistent peripheral sensitization can trigger alterations in the central nervous system and lead to the development of central sensitization. This can lead to widespread pain and the cooccurrence of symptoms commonly associated with chronic overlapping pain conditions, including fatigue, sleep disturbance, and bowel disorders.[85,86]

Clinical implications

This study underscores that women diagnosed with endometriosis have a greater risk for experiencing a wide range of symptoms than those without endometriosis. This highlights the importance of early diagnosis and treatment of endometriosis to reduce the risk for associated symptoms and complications. Women with endometriosis should also be encouraged to proactively manage their symptoms, such as through lifestyle changes, medications, or surgery, to improve their quality of life and prevent further complications.

Research implications

Future research should explore the potential causal pathways between endometriosis and the associated symptoms. Further exploring the underlying pathways in these association may inform the development of targeted intervention strategies with the potential to enhance women's health. Further research is also needed to elucidate the specific mechanisms through which central sensitization contributes to the association between endometriosis and women's symptoms.

Recently, evidence has been gathered on the role of shared genetic etiology, that is, genetic correlation, between endometriosis and depression and gastrointestinal disorders,[87] migraine,[88] menstrual characteristics,[89] irregular period, and pain.[90] Further studies would be required to discern if the association between these symptoms and endometriosis are the consequence of direct causation or shared underlying etiologic factors.

Strengths and limitations

The current study has several strengths, including the nationally representative, large samples, population-based prospective cohort study design, and comprehensive information on a wide variety of symptoms and potential confounders. Women's self-reported data were combined with national administrative health records to identify women with endometriosis. We further performed a sensitivity analysis to test the robustness of the findings, including assessing the effect of missing data on the results and the role of UTI in the association between endometriosis and risk for urine burn or stings. However, this study was limited by self-reported data on women's symptoms, which might have the potential for information bias. The association between endometriosis and severe period pain showed the strongest effect size, followed by the association with urine burn or stings and heavy menstrual bleeding. However, for other symptoms, the odds ratios were generally below 2 and occasionally only slightly above 1. Although the study controlled for a wide range of potential confounders, there is a possibility of residual confounding or measurement errors that might alter the effect size. The symptoms examined may not be causal for endometriosis but rather represent

manifestations required for successful evaluation and diagnosis. The symptoms are also not unique to endometriosis but rather a consequence of the diagnostic process. Because this study is observational, it is impossible to draw causality. In this study, the association between each symptom and endometriosis was similar whether endometriosis was surgically confirmed or clinically suspected endometriosis. However, we acknowledge that there may be slight variations in the observed associations because of the different methods of diagnosis. Surgical confirmation tends to favor individuals with more severe symptoms, whereas clinical suspicion may include cases of misdiagnosis. The ALSWH survey experienced a high nonresponse rate during each follow-up, particularly between the first and third surveys. This nonresponse might potentially introduce selection bias. However, despite the dropout, our previous study indicated that attrition did not introduce any substantial biases that would affect the validity of the longitudinal study.[91]

Conclusion

Women with endometriosis often experience a broad range of not only menstrual problems, but also mental health problems, pain such as back pain and headaches, and nonspecific symptoms such as severe tiredness, sleep difficulties, and palpitations. Further studies need to be carried out to elucidate the potential biologic pathways between endometriosis and these associated symptoms. ■

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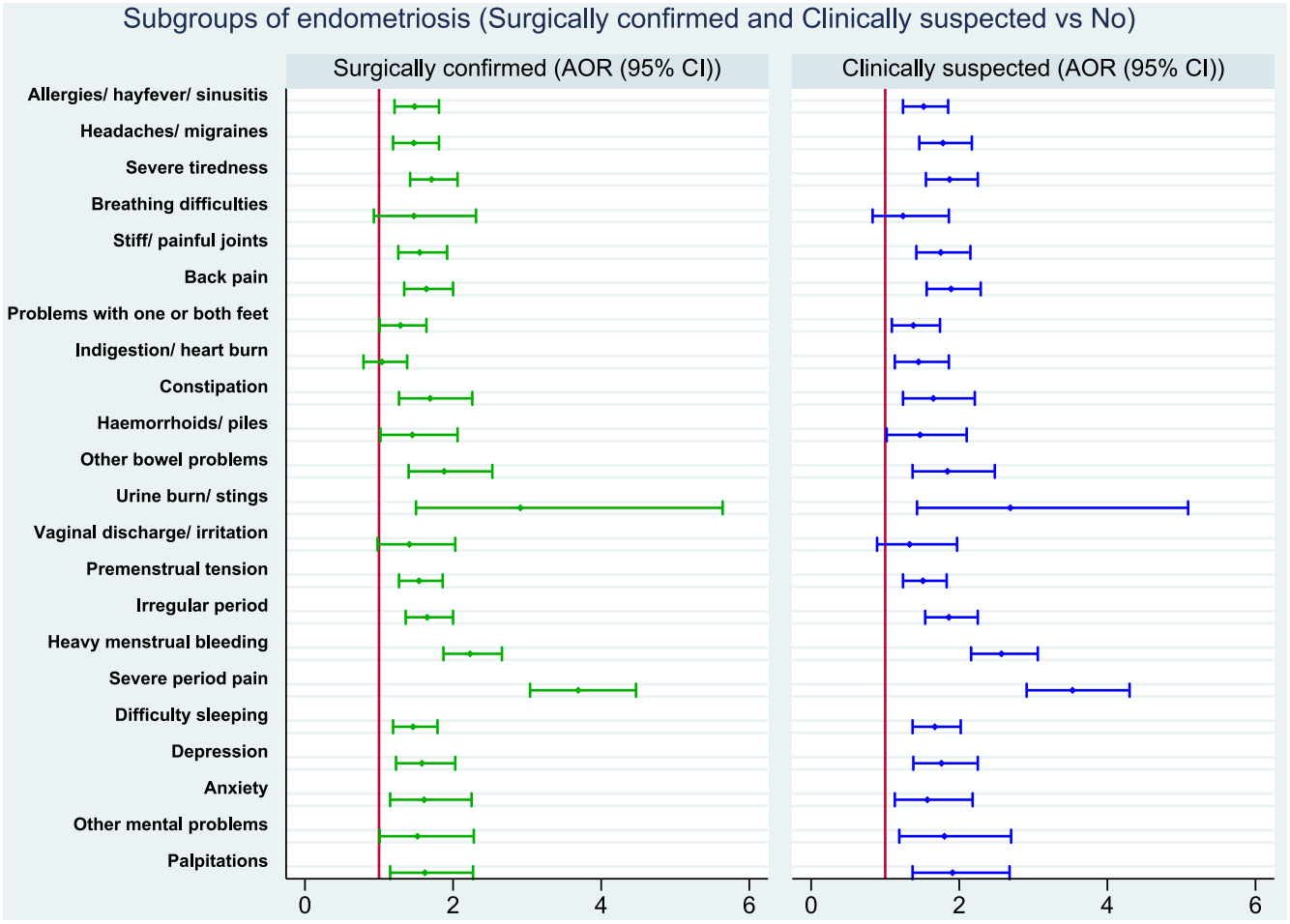
SUPPLEMENTAL FIGURE
Association between subgroups of endometriosis and each symptom (often vs never or rarely)



AOR, odds ratio; *CI*, confidence interval.

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SUPPLEMENTAL TABLE 1

Baseline characteristics for women who participated in the study (n = 7606) vs those who were excluded from analyses (n = 6048)

Women's characteristics	Women included in the analyses (n=7606)	Women excluded from the analyses (n=6048)	*P* values[a]
Women's age (y), mean (SD)	20.8 (1.5)	20.7 (1.5)	.12
Area of residence, n (%)			.82
Urban	3949 (51.9)	3129 (51.8)	
Rural or remote	3652 (48.1)	2916 (48.2)	
Marital status, n (%)			<.0001
Married	649 (8.6)	570 (9.5)	
De facto or separated or divorced	972 (12.8)	1015 (16.9)	
Single	5961 (78.6)	4420 (73.6)	
Educational status, n (%)			<.0001
Up to year 12 or equivalent	5186 (68.5)	4454 (74.2)	
Trade or apprenticeship or certificate or diploma	1317 (17.4)	1113 (18.5)	
University/higher degree	1071 (14.1)	434 (7.2)	
Able to manage income, n (%)			<.0001
It is impossible or difficult all the time	1241 (16.4)	1281 (21.3)	
It is difficult some of the time	2458 (32.4)	2069 (34.4)	
It is not too bad	2809 (37.0)	2027 (33.7)	
It is easy	1080 (14.2)	639 (10.6)	
Smoking status, n (%)			<.0001
Never smoked	4093 (55.9)	2705 (47.1)	
Ex-smoker	1082 (14.8)	917 (16.0)	
Current smoker	2144 (29.3)	2124 (37.0)	
Alcohol intake, n (%)			<.0001
Nondrinker	566 (7.5)	637 (10.7)	
Rarely drinker	2445 (32.5)	2193 (36.7)	
Low-risk drinker	4136 (54.9)	2781 (46.6)	
Risky drinker	383 (5.1)	360 (6.0)	
Physical activity, n (%)			<.0001
Sedentary, <40 MET min/wk	550 (7.2)	301 (5.0)	
Low, 40 to <600 MET min/wk	1975 (26.0)	929 (15.4)	
Moderate, 600 to <1200 MET min/wk	2863 (37.6)	3917 (64.8)	
High, ≥1200 MET min/wk	2218 (29.2)	901 (14.9)	

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023. *(continued)*

SUPPLEMENTAL TABLE 1

Baseline characteristics for women who participated in the study (n = 7606) vs those who were excluded from analyses (n = 6048) *(continued)*

Women's characteristics	Women included in the analyses (n=7606)	Women excluded from the analyses (n=6048)	*P* values[a]
Body mass index, n (%)			<.0001
Underweight, <18.5 kg/m^2	601 (8.6)	563 (11.4)	
Healthy weight, 18.5 to <25 kg/m^2	4871 (70.1)	3242 (65.7)	
Overweight, 25 to <30 kg/m^2	1065 (15.3)	768 (15.6)	
Obese, ≥30 kg/m^2	412 (5.9)	362 (7.3)	

Values are presented as mean (SD) or number (percentage) for the baseline characteristics of the included and excluded participants.

MET, metabolic equivalent; *SD*, standard deviation.

[a] *P* values were determined using Pearson chi-square or *t* tests.

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023.

SUPPLEMENTAL TABLE 2
Association between endometriosis and each symptom among Australian women

Women's symptoms	Endometriosis (yes vs no) Adjusted OR with 95% CI		
	Model 1[a]	Model 2[b]	Model 3[c]
Allergies or hay fever or sinusitis			
Never or rarely	1.00	1.00	1.00
Sometimes	1.18 (1.05–1.32)	1.14 (1.01–1.28)	1.13 (1.01–1.27)
Often	1.51 (1.31–1.74)	1.49 (1.29–1.73)	1.50 (1.29–1.74)
Headaches or migraines			
Sometimes	1.25 (1.13–1.39)	1.23 (1.10–1.37)	1.24 (1.11–1.38)
Often	1.69 (1.47–1.96)	1.63 (1.40–1.89)	1.62 (1.40–1.89)
Severe tiredness			
Sometimes	1.33 (1.20–1.46)	1.36 (1.22–1.50)	1.37 (1.24–1.52)
Often	1.77 (1.55–2.01)	1.75 (1.53–2.01)	1.79 (1.56–2.05)
Breathing difficulties			
Sometimes	1.45 (1.25–1.69)	1.42 (1.21–1.66)	1.40 (1.20–1.64)
Often	1.45 (1.06–1.99)	1.34 (0.97–1.86)	1.35 (0.98–1.88)
Stiff or painful joints			
Sometimes	1.13 (1.02–1.25)	1.14 (1.03–1.26)	1.13 (1.02–1.26)
Often	1.72 (1.48–2.00)	1.69 (1.45–1.98)	1.65 (1.41–1.93)
Back pain			
Sometimes	1.23 (1.12–1.36)	1.25 (1.13–1.38)	1.26 (1.13–1.39)
Often	1.76 (1.54–2.02)	1.77 (1.53–2.04)	1.76 (1.53–2.04)
Feet problems			
Sometimes	1.17 (1.04–1.32)	1.16 (1.02–1.32)	1.16 (1.02–1.32)
Often	1.37 (1.16–1.62)	1.34 (1.13–1.60)	1.33 (1.12–1.59)
Indigestion or heartburn			
Sometimes	1.22 (1.08–1.37)	1.19 (1.06–1.35)	1.19 (1.05–1.34)
Often	1.28 (1.06–1.54)	1.26 (1.04–1.54)	1.25 (1.03–1.52)
Constipation			
Sometimes	1.42 (1.27–1.59)	1.43 (1.27–1.60)	1.41 (1.26–1.58)
Often	1.78 (1.45–2.18)	1.70 (1.37–2.10)	1.67 (1.35–2.08)
Hemorrhoids or piles			
Sometimes	1.18 (1.03–1.36)	1.17 (1.01–1.36)	1.20 (1.04–1.39)
Often	1.44 (1.12–1.85)	1.41 (1.08–1.83)	1.46 (1.12–1.90)
Other bowel problems			
Sometimes	1.30 (1.13–1.50)	1.28 (1.11–1.49)	1.25 (1.08–1.45)
Often	1.94 (1.57–2.40)	1.88 (1.51–2.35)	1.86 (1.49–2.33)

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023.

(continued)

SUPPLEMENTAL TABLE 2
Association between endometriosis and each symptom among Australian women *(continued)*

Women's symptoms	Endometriosis (yes vs no) Adjusted OR with 95% CI Model 1[a]	Model 2[b]	Model 3[c]
Leaking urine			
Sometimes	1.05 (0.91–1.19)	1.02 (0.88–1.17)	1.04 (0.90–1.20)
Often	1.01 (0.78–1.29)	0.97 (0.74–1.27)	0.99 (0.76–1.30)
Urine burn or stings			
Sometimes	1.39 (1.14–1.69)	1.43 (1.17–1.74)	1.42 (1.16–1.73)
Often	2.89 (1.80–4.64)	2.83 (1.73–4.65)	2.80 (1.71–4.58)
Vaginal discharge or irritation			
Sometimes	1.18 (1.04–1.35)	1.16 (1.02–1.33)	1.16 (1.01–1.33)
Often	1.53 (1.18–2.00)	1.38 (1.04–1.82)	1.37 (1.03–1.82)
Premenstrual tension			
Sometimes	1.05 (0.95–1.16)	1.05 (0.95–1.17)	1.03 (0.93–1.15)
Often	1.59 (1.38–1.82)	1.56 (1.35–1.80)	1.52 (1.32–1.76)
Irregular periods			
Sometimes	1.25 (1.11–1.41)	1.29 (1.14–1.46)	1.28 (1.13–1.45)
Often	1.75 (1.52–2.01)	1.80 (1.56–2.08)	1.76 (1.52–2.03)
Heavy menstrual bleeding			
Sometimes	1.33 (1.19–1.48)	1.33 (1.19–1.50)	1.33 (1.18–1.49)
Often	2.34 (2.06–2.65)	2.44 (2.14–2.78)	2.40 (2.10–2.74)
Severe period pain			
Sometimes	1.74 (1.56–1.95)	1.84 (1.64–2.07)	1.80 (1.61–2.02)
Often	3.67 (3.19–4.22)	3.77 (3.25–4.37)	3.61 (3.11–4.19)
Skin problems			
Sometimes	1.11 (0.99–1.24)	1.09 (0.97–1.23)	1.07 (0.96–1.21)
Often	1.17 (0.99–1.38)	1.13 (0.95–1.35)	1.13 (0.95–1.34)
Sleep difficulty			
Sometimes	1.14 (1.03–1.25)	1.14 (1.03–1.26)	1.13 (1.02–1.26)
Often	1.55 (1.35–1.78)	1.58 (1.37–1.83)	1.56 (1.35–1.81)
Depression			
Sometimes	1.50 (1.34–1.69)	1.54 (1.36–1.74)	1.52 (1.35–1.72)
Often	1.62 (1.36–1.93)	1.70 (1.42–2.05)	1.67 (1.39–2.01)
Anxiety			
Sometimes	1.47 (1.28–1.69)	1.49 (1.29–1.72)	1.48 (1.28–1.71)
Often	1.61 (1.27–2.04)	1.62 (1.27–2.07)	1.59 (1.24–2.03)
Other mental problems			
Sometimes	1.42 (1.17–1.73)	1.44 (1.17–1.76)	1.40 (1.14–1.72)
Often	1.71 (1.28–2.28)	1.70 (1.25–2.31)	1.66 (1.22–2.26)

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023. *(continued)*

SUPPLEMENTAL TABLE 2
Association between endometriosis and each symptom among Australian women *(continued)*

Women's symptoms	Endometriosis (yes vs no) Adjusted OR with 95% CI		
	Model 1[a]	Model 2[b]	Model 3[c]
Palpitations			
Sometimes	1.49 (1.31–1.69)	1.49 (1.31–1.70)	1.47 (1.29–1.68)
Often	1.90 (1.50–2.41)	1.80 (1.40–2.32)	1.77 (1.37–2.28)

The data for n=7606 women are presented.

The participants' ages were recorded in years during each survey and treated as a continuous variable. The residence was categorized as urban and rural or remote. Marital status was categorized as married, de facto or separated or divorced, and single. Educational status was categorized based on their highest level of education completed, that is, up to year 12 or equivalent, trade or apprenticeship or certificate or diploma, and university or higher degree. The options for ability to manage the income available were easy, not too bad, difficult sometimes, and difficult always or impossible. The physical activity was assessed using total metabolic equivalent (MET) values based on frequency and duration of walking and moderate- and vigorous-intensity activity and categorized as sedentary (<40 MET min/wk), low (<600 MET min/wk), moderate (600 to 1200 MET min/wk), and high (≥1200 MET min/wk). Smoking status was categorized as never smoker, ex-smoker, and current smoker. Alcohol intake was categorized as nondrinker, low-risk drinker (≤14 drinks/wk), risky drinker (15–28 drinks/wk), and high-risk drinker (>28 drinks/wk). BMI was categorized as underweight (BMI <18.5 kg/m^2), normal weight (BMI, 18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2). Parity refers to the number of times a woman has given live birth and is categorized as nulliparous (no previous birth) and parous (one or more previous birth). Participants indicated whether they were currently using oral contraceptives (combined oral contraceptives and progestogen-only contraception, including implants and intrauterine devices) and were categorized as yes or no.

Severe tiredness was defined as a subjective feeling of extreme fatigue, exhaustion, or lack of energy that significantly affects daily functioning. Breathing difficulties was defined as any difficulties or discomfort experienced during breathing, which may include shortness of breath, wheezing, or chest tightness. Stiff or painful joints was defined as a condition in which individuals experience discomfort, limited mobility, or pain in one or more of their joints. Problems with one or both feet encompassed various foot-related issues, such as pain, swelling, deformities, and injuries. Irregular periods was defined as a condition in which a person's menstrual cycle deviates from the typical pattern or duration. Severe period pain was defined as intense or debilitating pain experienced during menstruation, often referred to as dysmenorrhea. Skin problems included a broad range of conditions that affect the skin's appearance, texture, or overall health, including rash, itching, irritation, dryness, inflammation, or the presence of bumps, sores, or lesions on the skin.

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

[a] Model 1 adjusted for time (survey); [b] Model 2 adjusted for time, age, residence, marital, education, income, smoking, alcohol intake, physical activity, and BMI; [c] Model 3 adjusted for time, age, residence, marital, education, income, smoking, alcohol intake, physical activity, BMI, parity, and oral contraceptives.

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023.

SUPPLEMENTAL TABLE 3

The odds ratios of mental health outcomes, specifically comparing women with endometriosis with those with nonendometriosis conditions associated with pain and diagnostic delay as a consequence of normalization, dismissal, and stigma

	Mental health outcomes		
Comparison groups	Depression	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Endometriosis	Never or rarely	1.00	1.00
Nonendometriosis pain-associated condition	Sometimes	1.08 (0.94–1.22)	0.96 (0.84–1.10)
	Often	1.40 (1.15–1.68)	1.14 (0.93–1.38)
Migraine or headache	Sometimes	1.16 (1.01–1.35)	1.07 (0.91–1.25)
	Often	1.72 (1.40–2.11)	1.42 (1.14–1.78)
Painful or stiff joints	Sometimes	1.20 (1.02–1.41)	0.97 (0.81–1.16)
	Often	1.91 (1.53–2.40)	1.40 (1.10–1.80)
Backpain	Sometimes	1.11 (0.96–1.29)	0.93 (0.79–1.10)
	Often	1.61 (1.30–1.98)	1.20 (0.95–1.52)
Dysmenorrhea	Sometimes	1.36 (1.13–1.63)	1.06 (0.87–1.29)
	Often	2.10 (1.58–2.58)	1.30 (0.98–1.72)
Nonendometriosis-associated normalization or stigma	Sometimes	1.43 (1.25–1.63)	1.31 (1.14–1.50)
	Often	2.18 (1.80–2.62)	1.88 (1.54–2.30)
Severe tiredness	Sometimes	1.60 (1.40–1.83)	1.46 (1.26–1.69)
	Often	2.52 (2.08–3.05)	2.21 (1.79–2.72)
Palpitations	Sometimes	1.86 (1.40–2.46)	1.76 (1.29–2.39)
	Often	5.79 (4.28–7.82)	4.29 (2.99–6.16)
Constipation	Sometimes	1.27 (1.02–1.59)	1.16 (0.91–1.47)
	Often	1.98 (1.50–2.62)	1.65 (1.20–2.28)
Other bowel problems	Sometimes	1.28 (1.02–1.61)	1.13 (0.88–1.46)
	Often	2.04 (1.52–2.74)	1.54 (1.10–2.16)
Nonendometriosis pain-associated condition	Anxiety		
	Sometimes	1.09 (0.94–1.27)	0.97 (0.82–1.14)
	Often	1.31 (1.01–1.68)	1.07 (0.81–1.39)
Migraine or headache	Sometimes	1.21 (1.02–1.43)	1.07 (0.89–1.29)
	Often	1.50 (1.14–1.98)	1.22 (0.90–1.64)
Painful or stiff joints	Sometimes	1.19 (0.98–1.45)	1.01 (0.81–1.25)
	Often	1.49 (1.08–2.04)	1.10 (0.78–1.56)
Backpain	Sometimes	1.10 (0.92–1.31)	0.93 (0.77–1.13)
	Often	1.55 (1.17–2.06)	1.15 (0.84–1.56)
Dysmenorrhea	Sometimes	1.39 (1.12–1.72)	1.10 (0.87–1.39)
	Often	2.07 (1.49–2.86)	1.56 (1.00–2.23)
Nonendometriosis-associated normalization or stigma	Sometimes	1.39 (1.20–1.62)	1.27 (1.08–1.50)
	Often	2.14 (1.67–2.74)	1.81 (1.39–2.35)

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023. *(continued)*

SUPPLEMENTAL TABLE 3

The odds ratios of mental health outcomes, specifically comparing women with endometriosis with those with nonendometriosis conditions associated with pain and diagnostic delay as a consequence of normalization, dismissal, and stigma *(continued)*

	Mental health outcomes		
Comparison groups	Depression	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Severe tiredness	Sometimes	1.51 (1.29–1.77)	1.37 (1.16–1.63)
	Often	2.06 (1.60–2.67)	1.71 (1.31–2.25)
Palpitations	Sometimes	1.88 (1.33–2.66)	1.78 (1.22–2.60)
	Often	16.39 (11.85–22.67)	13.90 (9.59–20.14)
Constipation	Sometimes	1.53 (1.20–1.95)	1.42 (1.09–1.85)
	Often	2.20 (1.54–3.13)	1.85 (1.25–2.73)
Other bowel problems	Sometimes	1.12 (0.84–1.49)	1.00 (0.74–1.36)
	Often	2.28 (1.54–3.38)	1.66 (1.10–2.55)

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio.

The comparison groups in this study consisted of 3 categories, namely women with endometriosis, women with nonendometriosis conditions related to pain (such as migraine or headache, painful or stiff joints, back pain, and dysmenorrhea), and women with nonendometriosis conditions associated with diagnostic delays owing to societal normalization, dismissal, and stigma (including severe tiredness, palpitations, constipation, and other bowel problems). Mental health outcomes with women's responses of never and rarely were merged and considered as a reference group for the analyses.

[a] Crude odds ratio adjusted for time (survey); [b] Adjusted odds ratio adjusted for time, age, residence, marital, education, income, smoking, alcohol intake, physical activity, BMI, parity, and oral contraceptives.

Gete. Associations between endometriosis and common symptoms. Am J Obstet Gynecol 2023.