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Original Contribution

Depression, Anxiety, and Self-Directed Violence in Women With Endometriosis: A Retrospective Matched-Cohort Study

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The purpose of this study was to compare the incidence of mental health outcomes in women in the United States with and without documented endometriosis. In a retrospective matched-cohort study using administrative health claims data from Optum's Clinformatics DataMart from May 1, 2000, through March 31, 2019, women aged 18–50 years with endometriosis ($n = 72{,}677$), identified by *International Classification of Disease* diagnosis codes (revisions 9 or 10), were matched 1:2 on age and calendar time to women without endometriosis ($n = 147{,}251$), with a median follow-up of 529 days (interquartile range, 195, 1,164). The rate per 1,000 person-years of anxiety, depression, and self-directed violence among women with endometriosis was 57.1, 47.7, and 0.9, respectively. Comparing women with endometriosis to those without, the adjusted hazard ratios and 95% confidence intervals were 1.38 (1.34, 1.42) for anxiety, 1.48 (1.44, 1.53) for depression, and 2.03 (1.60, 2.58) for self-directed violence. The association with depression was stronger among women younger than 35 years (P for heterogeneity < 0.01). Risk factors for incident depression, anxiety, and self-directed violence among women with endometriosis included endometriosis-related pain symptoms and prevalence of other chronic conditions associated with pain. The identification of risk factors for mental health conditions among women with endometriosis may improve patient-centered disease management.

anxiety; depression; endometriosis; observational studies; safety; violence

Abbreviations: CI, confidence interval; CM, clinical modification; ICD, *International Classification of Diseases*.

Endometriosis is a common chronic gynecological condition, affecting approximately 10% of women of reproductive age (1, 2). Although some patients are asymptomatic, common clinical manifestations of endometriosis may include chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria, and infertility (3, 4). In part because of the range of symptoms, diagnosis of endometriosis is often delayed (5), resulting in delayed treatment, which negatively affects patients' quality of life (6).

Major depressive disorder and anxiety affect 10% to 20% of US adults (7, 8), with women at double the risk of men (7). Furthermore, depression and anxiety disorders are risk factors for suicidal ideation and suicide attempts (9, 10). The increased risk of depression and anxiety among endometriosis patients has been reported in several studies. (11–13) Endometriosis may be associated with mental health disorders through shared biologic pathways such as chronic inflammation or through mediation by chronic pain symptoms (14, 15). The prevalence of anxiety and depression is high in patients who suffer from other forms of chronic pain, such as chronic pelvic pain (16), low back pain (17), and migraines (18), and in a recent meta-analysis, authors suggested the association between endometriosis and depressive symptoms is mediated largely through chronic pain (19). However, the majority of existing studies looking at prevalence and incidence of mental health disorders among patients with endometriosis have several limitations, including cross-sectional design, small sample size (<50 patients), and data not being representative of the overall patient population, such as youth or inclusion of regional clinical data only (16). In addition, little is known about the risk of self-directed violence and

heterogeneity of these associations among select subgroups of patients.

Identifying women at high-risk for mental health conditions may improve patient-centered disease management and inform the selection of treatment approaches in this population. Thus, the objective of our study was to use data representative of the care provided to US patients with endometriosis to evaluate incidence of depression, anxiety, and suicide attempts after the diagnosis of endometriosis in a large sample of patients. We also identified risk factors for these mental health conditions among women with endometriosis.

METHODS

Study design and data source

We conducted a retrospective cohort study using administrative health claims from the Clinformatics Data Mart database (Optum, Inc., Eden Prairie, Minnesota) from May 1, 2000, through March 31, 2019. This database contains adjudicated, adjusted, and deidentified medical and outpatient pharmacy claims for approximately 87.4 million beneficiaries of United Healthcare, a large commercial insurance provider in the United States. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996. This study was exempt from institutional review board review because it was a retrospective analysis of deidentified administrative health care claims data.

For the primary exposure, women diagnosed with endometriosis were identified by either 1) ≥2 medical claims with *International Classification of Diseases Ninth Revision*, Clinical Modification (ICD-9-CM) diagnosis codes 617.x or *Tenth Revision* (ICD-10-CM) diagnosis codes N80.x in any position (principal or secondary) on an inpatient or outpatient claim; or 2) 1 endometriosis-related inpatient or outpatient medical claim with a laparoscopic procedure code within the previous 30 days (i.e., "laparoscopically confirmed" endometriosis). These criteria for endometriosis were used to minimize the potential for coding errors or rule-out diagnoses. The cohort entry date (index) for women with endometriosis was the date of the second claim or the date of the endometriosis claim after the laparoscopic procedure, whichever came first. In general, the distribution of the baseline characteristics between women defined using ≥2 claims of endometriosis and the laparoscopically confirmed endometriosis was not appreciably different; therefore, the primary analysis included women meeting either definition (Web Table 1) (available at https://doi.org/10.1093/aje/kwaa249).

For each woman with endometriosis, we sampled up to 2 reference patients of the same age (±1 year) without a prior diagnosis of endometriosis but who had a claim for a general medical or annual gynecological examination on the same cohort entry date as the matched exposed patient, using a risk-set sampling approach. Variable matching up to 2 reference patients can yield higher precision than 1:1 matching and retains more exposed subjects than a fixed ratio. Matching on age controlled for confounding. The reference cohort was drawn from general and gynecologic examinations because women's health may be managed by obstetrician–gynecologists or other health provider types such as internal or family medicine practitioners. Patients in the reference group had to meet the same enrollment, inclusion, and exclusion criteria. A requirement for a medical visit was used to minimize the possibility of detection bias that arises due to the increase in the number of clinical encounters associated with a new diagnosis of endometriosis, which then may lead to the discovery of other morbidities, including a mood disorder (20).

Women in both the exposed and unexposed groups were required to be health plan enrollees at least 183 days before and on the cohort entry date with a 45-day gap allowed in continuous enrollment. Patients were not eligible if, on the cohort entry date, they were younger than < 18 years or older than 50 years. Women were also excluded if they had a claim prior to any time from the start of follow-up until the date of cohort entry for depression, anxiety, self-directed violence, cancer, or hysterectomy; or a prescription claim for a filled antidepressant or antianxiety medication.

There were 3 primary outcomes of interest: incident depression, anxiety, and self-directed violence. Depression and anxiety were defined using ICD-9-CM and ICD-10-CM diagnosis codes (Web Table 2) from the medical claim (21–25). Self-directed violence was defined using ICD-9-CM and ICD-10-CM codes for suicide, suicide attempt, and intentional self-inflicted injury or self-harm from the medical claim (Web Table 2) (26, 27).

Information on participants' race/ethnicity (White, non-Hispanic; Black, non-Hispanic; Hispanic; Asian, non-Hispanic) and region of residence (West, Midwest, South, and Northeast) were provided in the deidentified database. The ICD-9-CM and ICD-10-CM diagnosis and procedure codes in any position were used to detect the presence or absence of comorbid conditions on or any time before the cohort entry date (i.e., the baseline period). National Drug Code information was used to detect filled medication prescriptions, which served as a proxy for medication use during the baseline period (Web Table 2).

Statistical analysis

Baseline characteristics of women with and without endometriosis were assessed on the start of all available claims data before and including the date of cohort entry. A difference was calculated between the exposure and reference value. Confidence intervals around the difference were generated using the Wald method (28) and a 2-sample comparison of means using the *t* distribution for continuous variables. Outcomes were assessed in the follow-up period beginning 1 day after cohort entry to the occurrence of the event, database disenrollment, death, hysterectomy, or March 31, 2019, whichever occurred first. Cox proportional hazards regression was used to generate hazard ratios and 95% confidence intervals for each outcome.

Variables known or hypothesized to be associated with endometriosis and mental health conditions were selected as potential confounders (2, 29–32). Factors not associated with the exposure (i.e., had an absolute difference <5) or

on the causal pathway between endometriosis and mental health conditions (e.g., endometriosis-associated pain) were not included in the models. Estimates were adjusted for race/ethnicity, region of residence, uterine fibroids, chronic headaches or migraine headaches, chronic low back pain, fibromyalgia, asthma, type 2 diabetes mellitus, fatigue, hypertension, hypothyroidism, vitamin D deficiency, and use of opioid analgesics, antihypertensives, and corticosteroids. Additional adjustment for other variables in Table 1 did not further modify the hazard ratio (data not shown). Except for race/ethnicity (4 categories) and region of residence (4 categories), all other variables were defined as ever vs. never. We conducted stratified analyses by age group (<35 and ≥35 years) and used the Wald test to detect a potential interaction with endometriosis status.

We restricted the sample to women with endometriosis to assess the association between baseline factors and the rate of mood disorders. We developed 3 separate Cox proportional hazards regression models, with anxiety, depression, and self-directed harm as the dependent variable. The independent variables included in the models were mutually adjusted.

Sensitivity analysis

We performed several additional sensitivity analyses. First, we restricted the exposed population to women with an endometrioses diagnosis code that occurred within 30 days of a laparoscopic procedure (i.e., surgically confirmed endometriosis) because this would be the strictest method to define and confirm the disease. Notably, empiric treatment regimens often are prescribed before visualization of lesions (1, 33). Second, models with alternative definitions for depression and anxiety were used. In these analyses, depression was defined as 1) an ICD diagnosis code for depression or a prescription claim for a filled antidepressant medication, and 2) an ICD diagnosis code for depression and a prescription claim for a filled antidepressant medication. Similar criteria were applied to define anxiety using ICD diagnosis codes for anxiety and/or a prescription claim for a filled antianxiety medication. Finally, an adjusted model was generated that excluded uterine fibroids, chronic headaches or migraine headaches, chronic low back pain, fibromyalgia, asthma, type 2 diabetes, fatigue, and hypertension, because these may be downstream consequences of endometriosis. All analyses were performed using Aetion Evidence Platform, version 3.7 (New York, New York), which has been validated (34). All *P* values were 2 sided.

RESULTS

After applying inclusion and exclusion criteria, 72,677 women diagnosed with endometriosis were matched to 147,251 women never diagnosed with endometriosis (Web Figure 1). The median age was 34 years (interquartile range, 29, 40). The overall median follow-up time was 529 (interquartile range, 195, 1,164) days. Those with endometriosis were more likely to be White, non-Hispanic, and from the South. Women with endometriosis were more likely to have dysmenorrhea, dyspareunia, pelvic pain, infertility, and use nonopioid analgesics and opioids (Table 1). Other pain-related comorbidities were more frequently documented among women with endometriosis, including chronic headaches or migraine headaches and chronic low back pain. Immunological and chronic conditions such as allergies, asthma, fatigue, hypertension, hypothyroidism, and thyroid disease occurred more frequently in women with endometriosis (Web Table 3).

Overall, women with endometriosis had a higher rate of clinically recognized anxiety (57.1 vs. 39.8, respectively, per 1,000 person-years), depression (47.7 vs. 31.5, respectively, per 1,000 person-years), and self-directed violence (0.9 vs. 0.4, respectively, per 1,000 person-years) than those without endometriosis (Table 2). After multivariable adjustment (model 1), women with endometriosis were 1.38 (95% confidence interval (CI): 1.34, 1.42) times as likely to develop clinically recognized anxiety, 1.48 (95% CI, 1.44, 1.53) times as likely to have clinically recognized depression, and 2.03 (95% CI, 1.60, 2.58) times as likely to have clinically recognized self-directed violence (Table 2). In models stratified by age group, the hazard ratios for all outcomes were stronger in women younger than 35 years than women ≥35 years of age (Table 2), although statistically significant heterogeneity was only met for depression (*P* for heterogeneity <0.01 for depression, 0.41 for anxiety, and 0.60 for self-directed violence). When potential downstream consequences of endometriosis were removed from the model, the results were not appreciably altered (model 2) (Table 2).

The association between endometriosis and clinically recognized anxiety, depression, and self-directed violence was consistent across various sensitivity analyses. When depression and anxiety were defined using 1) diagnosis claims or medication use or 2) diagnosis claims and medication use, the hazard ratios did not meaningfully change (Web Tables 4–5). Furthermore, results were not appreciably different when analyses were restricted to women with laparoscopically confirmed endometriosis (Web Tables 6–7).

In the analysis restricted to women with endometriosis, characteristics associated with significantly greater rate of depression, anxiety, and self-directed harm were identified through multivariable models (Table 3). Endometriosis-associated pain (i.e., dysmenorrhea, dyspareunia, and pelvic pain) was associated with higher rates of anxiety, depression, and self-directed harm. Other risk factors associated with incident depression and incident anxiety included pain-related comorbidities, prior use of opioid analgesics, fatigue, and asthma. Prior use of gonadotropin-releasing hormone agonists and oral contraceptives was associated with elevated rates of depression, and interstitial cystitis, allergic rhinitis, and allergies were associated with elevated rates of anxiety. Factors associated with higher rates of self-directed harm included prior use of opioids, migraine headaches, and asthma.

Several factors were associated with significantly lower rates of depression and anxiety among women with endometriosis. Women who had a prior pregnancy, uterine fibroids, and hyperlipidemia had lower rates of depression and anxiety. Vitamin D deficiency was associated with lower risk of depression; use of oral contraceptives and history of infertility were associated with lower risk of anxiety.

Table 1. Baseline Characteristics of Women With and Without Endometriosis (*n* = 219,918), Optum Clinformatics DataMart, 2000–2019[a,b]

Characteristic	Endometriosis (*n* = 72,677)		No Endometriosis (*n* = 147,251)		Difference	95% CI
	No.	%	No.	%		
Demographics						
Age, years[c]	34.0 (7.4)		34.4 (7.4)		−0.4	−0.4, −0.3
Race/ethnicity[b]						
White, non-Hispanic	50,682	69.7	99,292	67.4	2.3	1.9, 2.7
Asian, non-Hispanic	4,304	5.9	11,769	8.0	−2.1	−2.3, −1.8
Black, non-Hispanic	8,315	11.4	16,923	11.5	−0.1	−0.3, 0.2
Hispanic	9,376	12.9	19,267	13.1	−0.2	−0.5, 0.1
Region of residence						
Northeast	6,350	8.7	19,160	13.0	−4.3	−4.5, −4.0
Midwest	18,789	25.9	36,752	25.0	0.9	0.5, 1.3
South	34,982	48.1	65,779	44.7	3.5	3.0, 3.9
West	12,556	17.3	25,560	17.4	−0.1	−0.4, −0.3
Gynecological/Reproductive Health Variables						
Any pain symptoms[d]	48,825	67.2	33,853	3.0	44.2	43.8, 44.6
Dysmenorrhea	23,579	32.4	6,775	4.6	27.8	27.5, 28.2
Dyspareunia	8,143	11.2	1,747	1.2	10.0	9.8, 10.3
Pelvic pain	36,391	50.1	28,652	19.5	30.6	30.2, 31.0
Infertility[e]	25,025	34.4	18,193	12.4	22.1	21.7, 22.5
Infertility diagnosis	14,050	19.3	4,653	3.2	16.2	15.9, 16.5
Infertility treatment, procedures	16,256	22.4	11,346	7.7	14.7	14.3, 15.0
Infertility treatment, medications	20,429	28.1	15,567	10.6	17.5	17.2, 17.9
Prior pregnancy	11,133	15.3	28,289	19.2	−3.9	−4.2, −3.6
Uterine fibroids	12,368	17.0	4,676	3.2	13.8	13.6, 14.1
Use of GnRH agonists	6,260	8.6	562	0.4	8.2	8.0, 8.4
Use of nonopioid analgesics	27,747	38.2	33,794	22.9	15.2	14.8, 15.6
Use of opioid analgesics	43,850	60.3	47,661	32.4	28.0	27.5, 28.4
Use of combined oral contraceptives	25,676	35.3	58,425	39.7	−4.3	−4.8, −3.9
General Pain-Related Comorbid Conditions						
Chronic headaches (including migraine)	12,910	17.8	21,050	14.3	3.5	3.1, 3.8
Chronic low back pain	15,436	21.2	25,788	17.5	3.7	3.4, 4.1
Fibromyalgia	4,237	5.8	6,997	4.8	1.1	0.9, 1.3
Interstitial cystitis	621	0.9	211	0.1	0.7	0.6, 0.8
Irritable bowel syndrome	3,057	4.2	2,940	2.0	2.2	2.0, 2.4

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone agonist.

[a] Patients were excluded if they had a prior diagnosis of depression, anxiety, or self-directed violence; prior filled prescription of an antianxiety or antidepressant medication; prior diagnosis of cancer; or prior hysterectomy.

[b] Data contain 4 mutually exclusive categories based on a combination of self-reported race/ethnicity and imputed race/ethnicity at the census-tract level.

[c] Values are expressed as mean (standard deviation).

[d] Includes dysmenorrhea, dyspareunia, and pelvic pain.

[e] Includes infertility diagnosis, procedures, medications, medical encounters, and use of GnRH antagonists.

Table 2. Association Between Endometriosis and Anxiety, Depression, and Self-Directed Violence, Overall and Stratified by Age Group (n = 219,918), Optum Clinformatics DataMart, 2000–2019[a]

Exposure Status	No.	No. of Events	Incidence Per 1,000 PY	Crude		Multivariable Model 1[b]		Multivariable Model 2[c]	
				HR	95% CI	HR	95% CI	HR	95% CI
Incident Anxiety									
Overall									
Endometriosis	72,677	8,377	57.1	1.42	1.38, 1.45	1.38	1.34, 1.42	1.25	1.21, 1.29
No endometriosis	147,251	14,840	39.8	1.00	Referent	1.00	Referent	1.00	Referent
Age 18–34 years									
Endometriosis	38,741	4,875	64.5	1.43	1.38, 1.48	1.36	1.31, 1.41	1.35	1.30, 1.40
No endometriosis	75,931	7,833	44.4	1.00	Referent	1.00	Referent	1.00	Referent
Age 35–50 years									
Endometriosis	33,936	3,502	49.3	1.37	1.31, 1.42	1.35	1.29, 1.41	1.34	1.28, 1.39
No endometriosis	71,320	7,007	35.6	1.00	Referent	1.00	Referent	1.00	Referent
Incident Depression									
Overall									
Endometriosis	72,677	7,105	47.7	1.48	1.44, 1.52	1.48	1.44, 1.53	1.31	1.27, 1.36
No endometriosis	147,251	11,933	31.5	1.00	Referent	1.00	Referent	1.00	Referent
Age 18–34 years									
Endometriosis	38,741	4,287	56.1	1.56	1.50, 1.63	1.52	1.46, 1.59	1.50	1.44, 1.56
No endometriosis	75,931	6,289	35.1	1.00	Referent	1.00	Referent	1.00	Referent
Age 35–50 years									
Endometriosis	33,936	2,818	38.9	1.35	1.29, 1.41	1.38	1.31, 1.45	1.34	1.28, 1.41
No endometriosis	71,320	5,644	28.3	1.00	Referent	1.00	Referent	1.00	Referent
Incident Self-Directed Violence									
Overall									
Endometriosis	72,677	151	0.91	2.32	1.86, 2.90	2.03	1.60, 2.58	1.70	1.30, 2.23
No endometriosis	147,251	162	0.39	1.00	Referent	1.00	Referent	1.00	Referent
Age 18–34 years									
Endometriosis	38,741	101	1.17	2.39	1.80, 3.16	1.98	1.47, 2.67	3.26	1.92, 5.53
No endometriosis	75,931	96	0.49	1.00	Referent	1.00	Referent	1.00	Referent
Age 35–50 years									
Endometriosis	33,936	50	0.63	2.09	1.45, 3.02	1.83	1.23, 2.72	2.01	1.02, 3.95
No endometriosis	71,320	66	0.30	1.00	Referent	1.00	Referent	1.00	Referent

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

[a] Patients began follow-up 1 day after cohort entry and were censored on occurrence of the outcome, hysterectomy, death, disenrollment, or end of data.

[b] Multivariable model 1 was adjusted for race/ethnicity, region of residence, uterine fibroids, chronic headaches (including migraine), chronic lower back pain, fibromyalgia, asthma, type 2 diabetes mellitus, fatigue, hypertension, hypothyroidism, vitamin D deficiency, and use of opioid analgesics, antihypertensives, and corticosteroids.

[c] Multivariable model 2 was adjusted for race/ethnicity, region of residence, hypothyroidism, vitamin D deficiency, and use of opioid analgesics, antihypertensives, and corticosteroids.

DISCUSSION

Rates of clinically recognized anxiety were 1.4 times higher, rates of depression were 1.5 times higher, and rates of self-directed violence were 2 times higher among women diagnosed with endometriosis compared with women never diagnosed with endometriosis, after adjusting for many potential confounders. The results were robust to several sensitivity analyses, including alternative definitions of the exposure, outcomes, and study population. Endometriosis-associated pain and prevalence of other chronic comorbidities were risk factors for incident depression, anxiety, and self-directed violence among women with endometriosis.

Table 3. Factors Associated With Anxiety, Depression, and Self-Directed Violence Among Women With Endometriosis (*n* = 219,918), Optum Clinformatics DataMart, 2000–2019

Factor	Anxiety		Depression		Self-Directed Violence	
	HR	95% CI	HR	95% CI	HR	95% CI
Demographic Characteristics						
Age group, years						
<25	1.76	1.67, 1.86	1.35	1.29, 1.41	4.23	2.87, 6.24
25–34	1.24	1.20, 1.28	1.14	1.11, 1.17	1.58	1.15, 2.18
≥35	1.00	Referent	1.00	Referent	1.00	Referent
Gynecological/Reproductive Health Variables						
Categories of pain and infertility						
No pain or infertility	1.00	Referent	1.00	Referent	1.00	Referent
Pain only	1.20	1.15, 1.25	1.19	1.15, 1.24	2.13	1.43, 3.17
Infertility only	0.74	0.69, 0.79	0.96	0.92, 1.01	0.55	0.27, 1.13
Pain and infertility	0.87	0.82, 0.91	1.11	1.07, 1.16	0.89	0.53, 1.50
Prior pregnancy	0.85	0.81, 0.89	0.89	0.86, 0.92	[a]	[a]
Uterine fibroids	0.68	0.65, 0.71	0.80	0.77, 0.83	[a]	[a]
Use of GnRH agonists	[a]	[a]	1.15	1.10, 1.20	[a]	[a]
Use of nonopioid analgesics	[a]	[a]	[a]	[a]	[a]	[a]
Use of opioid analgesics	1.20	1.16, 1.24	1.22	1.19, 1.26	2.06	1.48, 2.85
Use of combined oral contraceptives	0.88	0.84, 0.92	1.05	1.01, 1.09	[a]	[a]
General Pain-Related Comorbid Conditions						
Chronic headaches (including migraine)	1.28	1.23, 1.33	1.29	1.25, 1.33	1.81	1.32, 2.49
Chronic low back pain	1.18	1.13, 1.22	1.18	1.14, 1.22	[a]	[a]
Fibromyalgia	1.23	1.15, 1.31	1.23	1.17, 1.30	[a]	[a]
Interstitial cystitis	1.71	1.48, 1.98	[a]	[a]	[a]	[a]
Irritable bowel syndrome	1.38	1.29, 1.48	1.32	1.24, 1.40	[a]	[a]
Immunological Comorbid Conditions						
Allergic rhinitis	1.08	1.04, 1.13	[a]	[a]	[a]	[a]
Allergies	1.09	1.05, 1.13	[a]	[a]	[a]	[a]
Asthma	1.18	1.12, 1.25	1.20	1.15, 1.26	1.92	1.30, 2.86
Other Comorbid Conditions						
Fatigue	1.10	1.06, 1.15	1.15	1.11, 1.18	[a]	[a]
Hyperlipidemia	0.85	0.81, 0.89	0.93	0.90, 0.97	[a]	[a]
Vitamin D deficiency	[a]	[a]	0.91	0.84, 0.99	[a]	[a]

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone agonist; HR, hazard ratio.
[a] Variable not included in the adjusted model. Models were also adjusted for race/ethnicity and region. Reference category comprises those without the condition, unless otherwise specified.

The positive association between endometriosis and mental health conditions is consistent with findings of 2 prior cohort studies. Within the Taiwan National Health Insurance Research Database, women with endometriosis had a greater risk of any depressive disorder (hazard ratio = 1.44, 95% CI, 1.25, 1.65), and anxiety disorder (hazard ratio = 1.44, 95% CI, 1.22, 1.70) compared with women without endometriosis (35). The strongest associations were among women younger than 40 years of age, similar to our findings (35). In a previous study that incorporated Optum claims data, the

association between endometriosis and depression and/or anxiety was somewhat weaker (hazard ratio = 1.2, 95% CI, 1.2, 1.3) than the association we found in the present study, although misclassification of endometriosis and mental health outcomes in this earlier study may have driven results toward the null (36).

Data on the association between endometriosis and self-directed violence are limited. Common chronic conditions, such as diabetes, epilepsy, and asthma, have been associated with a greater risk of both self-harm and suicide (37). Researchers conducting a population-based cohort study in Finland found that the mortality rate due to suicide and sequelae of intentional self-harm was not different in women with surgically verified endometriosis compared to those without endometriosis (38). In contrast, our findings suggest that rates of self-directed violence, which included nonfatal and fatal events, were nearly 2–3 times higher for women with endometriosis in the United States. It is also possible that the difference in the observed association is due to different patient characteristics and factors related to women's lifestyle and/or increased medical attention and care received.

Among women with endometriosis, we identified several potential risk factors for mental health conditions. Endometriosis-associated pain symptoms and other pain-related comorbidities were associated with greater risk of mental health conditions, Consistent with prior studies, our findings suggest that chronic endometriosis-associated pain (39, 40) and chronic pain comorbidities (16–18) may be a significant factor for the development of depression and anxiety among women with endometriosis. In a recent meta-analysis on endometriosis and depressive symptoms, women with endometriosis were found to be more likely to have depressive symptoms relative to women without endometriosis and, among women with endometriosis, those with pelvic pain reported higher levels of depression compared with those without pain. Depressive symptoms were not different between patients with endometriosis and pelvic pain compared with women with pelvic pain due to other conditions (19) The results of the present study expand on the findings on endometriosis and depressive symptoms by examining incident diagnosis of depression, as well as anxiety and self-directed harm.

Endometriosis may affect the development of depression and anxiety through several pathways. Chronic pain can lead to social isolation and can negatively affect emotional well-being (41, 42). Chronic pain may be related to depression through common neuroplasticity mechanism changes, including effects on monoamine neurotransmitters, brain-derived neurotrophic factor, and glutamate and its receptor subtypes (14). From animal studies, researchers found that endometriosis alters brain gene expression and electrophysiology that lead to an increase in pain sensitization, anxiety, and depression (43). Finally, the chronic inflammation of endometriosis may impair the brain–blood barrier and disturb certain areas of the brain, leading to mood or behavioral disturbances (14, 15, 44–49). Studies have shown treatment with proinflammatory agents, such as interferon-α, were associated with more symptoms of depression, (50) whereas the use of nonsteroidal anti-inflammatory drugs decreased depressive symptoms (51). In contrast, co-existing fibroids, prior pregnancy, and infertility were associated with lower risk of depression and anxiety. Although women undergoing infertility treatment may have increased anxiety, (52) the impact of infertility on depression and anxiety may be modified by treatment success (53–55).

There are several clinical implications for the knowledge gained in this study. First, consistent and active screening for mood disorders in this population of women would assist with diagnosis and also address potential underlying psychological disease processes that affect quality of life. Second, incorporating the conversation regarding psychological well-being into daily care for those with endometriosis provides a platform from which to influence the chronic pain cycle and worsening of psychological disease that often occurs due to pain perception (56). Third, treatment options can be offered for both emotion regulation difficulties and physical symptoms, including offering coping strategies from behavioral, cognitive, and emotional standpoints that may improve ultimate adherence to the continued management of these long-term medical conditions (57, 58). The significant presence of anxiety, depression, and self-directed harm in women with endometriosis as compared with women never diagnosed with endometriosis modifies our practice to identify and continue to destigmatize mental health issues in a population that is otherwise often considered healthy.

Strengths of this study include the use of a database with a large, contemporary cohort of commercially insured individuals with broad geographic coverage, the ability to adjust for many potential confounders, and the implementation of multiple sensitivity analyses that increase the confidence in the observed results. Furthermore, because of the prospective nature of this study, the temporal sequence between the endometriosis diagnosis and the mood disorders is more clearly indicated because women who had a received a mental health diagnosis before the first diagnosis of endometriosis were excluded. This is critical for establishing potential cause-and-effect directionality and for diminishing the risk of diagnostic bias.

Several limitations also should be noted, however. First, endometriosis and mood disorders are chronic conditions; therefore, we were unable to assess the timing of the onset of endometriosis or mental health conditions. Rather, we were able to assess the temporal relationship of receiving a clinically recognized diagnosis of mood disorders among women with previously clinically recognized endometriosis. This was further complicated by delays in diagnosis and limited observed follow-up time in this administrative database. Additional research on the long-term risk of mental health conditions in women with endometriosis and on the impact of diagnostic delays on mental health in databases with longer follow-up is needed. Second, we used data representing commercially insured, continuously enrolled adult women, so findings may not be generalizable to uninsured populations or young women. More effort is needed to examine the risk of mental health outcomes in women of different ethnic and cultural background and younger women with endometriosis (59). Furthermore, women with mild symptoms or who respond well to

treatment may have only 1 medical claim for endometriosis and would not meet the study definition for endometriosis; thus, results may not be generalizable to all women with endometriosis.

Other known limitations common to administrative claims data include lack of clinical documentation, misdiagnosis, and miscoding (60). For instance, misclassification of endometriosis is possible in claims data because a diagnosis code may not be used in women with suspected endometriosis or nonsurgically diagnosed endometriosis. Therefore, a proportion of our matched unexposed group included patients with asymptomatic or symptomatic but undiagnosed endometriosis, biasing the association toward the null. However, we expect this misclassification to be minimal because the likely community prevalence of severe or symptomatic endometriosis is <2% (61), and the characteristics of this small proportion of undiagnosed, exposed women will be diluted among the hundreds of true endometriosis-free unexposed women. In addition, the presence of a diagnosis code for endometriosis may have identified women whose symptoms progressed to have greater impact on quality of life, whose treatment included more advanced interventions, or whose disease advanced to a higher, revised American Society for Reproductive Medicine disease stage. Notably, data to quantify the revised American Society for Reproductive Medicine stage of disease were unavailable in these data because, unfortunately, they are not routinely or uniformly documented in claims or electronic medical records (62, 63). However, because the revised American Society for Reproductive Medicine disease stage is poorly correlated with severity of symptoms, their life impact, or response to treatment, it is unlikely to be an important confounder (64). In addition, <50% of women with endometriosis in this study had dysmenorrhea, a common symptom of endometriosis, so pain symptoms may not have been fully captured by ICD codes, because there is no standardization for documentation (65). Compared to administrative data for reimbursement, electronic health record databases capture a far richer source of clinical data and health behavior information, potentially providing useful insights into the clinical characteristics, symptom duration, and psychiatric symptoms of endometriosis patients (66).

Finally, as with other studies conducted using administrative claims data, filled prescriptions were used as a proxy for medication use. Although there is uncertainty whether a dispensed prescription is consumed by the patient, pharmacy dispensing claims data reliably predict medication exposure to prescription medications, especially for chronically used medications (67, 68).

Women diagnosed with endometriosis are at higher risk for clinically recognized depression, anxiety, and self-directed violence relative to women without endometriosis. Furthermore, among women with endometriosis, pain is an important risk factor for subsequent mood disorders. A multidisciplinary approach that identifies women with endometriosis who are at risk for development of depression and anxiety may improve patient-centered management and affect treatment strategies for preventing and managing mood disorders.

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