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Uterine fibroids and incidence of depression, anxiety and self-directed violence: a cohort study

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ABSTRACT

Background Depression and anxiety are prevalent among women with uterine fibroids (UF). The rate of mental health diagnoses in women with UF has not been studied.

Methods Women aged 18–50 years with diagnosed UF were identified in the Optum Clinformatics commercial insurance claims database (OptumInsight, Eden Prairie, Minnesota) from 1 May 2000 to 31 March 2020 (n=313 754) and were matched 1:2 on age and calendar time to women without (n=627 539). Cox proportional hazards models estimated HRs and 95% CIs between UF and diagnosed depression, anxiety and self-directed violence, adjusting for demographics and comorbidities. Among women with diagnosed UF, the association between hysterectomy and mental health outcomes was estimated.

Results After adjusting for confounders, women with diagnosed UF had a higher rate of depression (HR: 1.12; 95% CI 1.10 to 1.13), anxiety (HR: 1.12; 95% CI 1.10 to 1.13) and self-directed violence (HR: 1.46; 95% CI 1.29 to 1.64) than women without. Among women with pain symptoms and heavy menstrual bleeding, the HR comparing women with diagnosed UF to women without was 1.21 (95% CI 1.18 to 1.25) for depression, 1.18 (95% CI 1.15 to 1.21) for anxiety and 1.68 (95% CI 1.35 to 2.09) for self-directed violence. Among women with diagnosed UF, the HR comparing women who underwent a hysterectomy to women who did not was 1.22 (95% CI 1.17 to 1.27) for depression, 1.13 (95% CI 1.09 to 1.17) for anxiety and 1.86 (95% CI 1.39 to 2.49) for self-directed violence.

Conclusions Rates of depression, anxiety and self-directed violence were higher among women with diagnosed UF, particularly among those who experienced pain symptoms or who underwent hysterectomy.

INTRODUCTION

Uterine fibroids (UF) are the most common benign gynaecological tumours in women and the primary indication for hysterectomy in the USA.¹ The lifetime risk of ultrasound-detected UF is 80% in Black women and 70% in White women,² and 20%–50% of women with UF experience associated symptoms that may significantly impact their quality of life.³

The prevalence of depression and anxiety is high among women with UF⁴ and depressive symptoms and diagnosed depression have been associated with a greater risk of UF.⁵ The risk of depression and anxiety is higher among women with gynaecological conditions such as endometriosis⁶ and polycystic ovary syndrome,⁷ relative to women

without these conditions. However, studies evaluating the risk of incident mental health conditions in women with UF are limited.⁸ Important gaps remain in understanding the clinical presentation of other mental health conditions such as self-directed violence, and the extent to which this presentation is modified by age, race/ethnicity or symptoms of UF.

We compared the incidence of diagnosed depression, anxiety and self-directed violence among women with and without diagnosed UF. We further assessed the heterogeneity of these associations by demographics, including UF symptom-based phenotypes and hysterectomy procedures.

MATERIALS AND METHODS

Data source

We conducted a cohort study within the Optum Clinformatics DataMart database that includes healthcare utilisation data for a large nationwide commercial insurer, during 1 May 2000 to 31 March 2020. The database contains transactional data on reimbursement for outpatient prescription dispensing and inpatient and outpatient services, including diagnoses and procedures for ~86.3 million individuals. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act.

Exposure ascertainment

The base study population included women aged 18–50 years who were continuously enrolled in the health plan at least 183 days prior to and on the date of cohort entry. A 45-day gap in coverage was allowed. Women were excluded if they had evidence of a mental health condition (medical claim or a prescription claim for a filled antidepressant or antianxiety medication), prevalent cancer (to reduce potential for detection bias) or a hysterectomy (to reduce confounding by hysterectomy) during the baseline period. The baseline period included all available data prior to or on cohort entry date.

Women were included in the UF cohort if they met the following criteria: (1) ≥ 2 inpatient or outpatient claims ≥ 1 day apart with UF International Classification of Diseases Ninth Revision (ICD-9) and ICD-10 diagnosis codes in any position, or (2) one inpatient or outpatient claim with UF diagnosis code preceded by ultrasonography or pelvic MRI within 30 days prior ('image confirmed' UF) (online supplemental table 1). The cohort entry



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date was the date of the second claim or the date of the UF claim following imaging.

Women with UF were categorised into one of four symptom-based phenotypes based on the presence of symptoms during baseline. The four mutually exclusive groups were (1) heavy menstrual bleeding (HMB) only, (2) pain only, (3) HMB and pain, and (4) neither HMB nor pain. The pain phenotype included women with ICD diagnosis codes for dysmenorrhoea, dyspareunia or pelvic pain. The HMB phenotype included women with ICD diagnosis codes for HMB (menorrhagia or menometrorrhagia), anaemia or blood transfusion.

The unexposed comparator group was sampled from women in the base population without a diagnosis of UF but who had a claim for a general medical or annual gynaecological examination on the same date as the cohort entry date for the matched exposed patient using risk set sampling. For each woman with diagnosed UF, up to two women from the referent cohort were matched on age (± 1 year) and cohort entry date. Women who had a myomectomy on or before cohort entry were excluded from the referent population to minimise exposure misclassification; women with a prior myomectomy were eligible to be in the exposure group if they met the criteria for UF. Women with prior uterine artery embolisation (UAE) procedures remained in the unexposed group, as these procedures can be used to reduce bleeding from causes other than UF.

Outcome ascertainment

Diagnosed depression and anxiety were identified using ICD-9 and ICD-10 diagnosis codes⁹ and self-directed violence was defined using ICD-9 and ICD-10 codes for a range of violent behaviours including suicidal behaviour, intentional self-inflicted injury or self-harm and suicide ideation.¹⁰ Postpartum depression was not included as a depression outcome. In sensitivity analysis, outcomes of depression and anxiety were defined using both diagnosis codes and prescription claims. For self-directed violence, codes for suicidal behaviour and intentional self-inflicted injury or self-harm were examined separately because they identify injuries resulting from intentional self-harm¹⁰ and are indicators of extreme psychological distress which may require more extensive evaluation or intervention,¹¹ whereas suicide ideation can be a risk factor for subsequent suicidal behaviours but does not focus on the actual suicide process.

Other covariates

ICD-9 and ICD-10 diagnosis codes and published validated algorithms used to define all variables in the baseline period are listed in online supplemental table 1. Race/ethnicity data were collected from a combination of public records (eg, driver's licence records, voter registration data) and consumer data (eg, surveys, purchase transactions), where available. Approximately 70% of these data were imputed using commercial software (E-Tech by Ethnic Technologies).¹² National Drug Code information was used to detect fills for prescription medications, which served as a proxy for medication use during the baseline period.

Statistical analysis

Follow-up time began 1 day after the cohort entry date (ie, UF diagnosis) until the occurrence of the event (depression, anxiety or self-harm), database disenrolment, death or end of data collection (31 March 2020), whichever occurred first. Women in the referent group with a diagnosis of UF during the follow-up period were censored on the date of diagnosis (7% of women). Cox proportional hazards regression models estimated HRs and

95% CIs for the association between UF and each outcome, matched on age and calendar time. Multivariable models were further adjusted for potential confounders identified by the literature and an assessment of a casual diagram. We included variables that were independent risk factors for mental health outcomes. We did not adjust for potential downstream effects of UF (ie, symptoms, infertility) as these factors may be intermediary variables in the causal pathway. We stratified associations according to age (<30, 30–39, ≥ 40), race and by decade (2000–2010 and 2011–2020) to account for changes in clinical practice over time.

Secondary analysis

In a secondary analysis restricted to women with diagnosed UF, we compared rates of diagnosed mental health conditions in women who underwent a hysterectomy after UF diagnosis (exposed group) to women who did not (referent group). The cohort entry date for the exposed group was date of hysterectomy. The referent group included women matched 1:2 on age (± 1 year) and cohort entry date who had not undergone a hysterectomy on or before the date of hysterectomy of the exposed patient (figure 1). We excluded women who had a diagnosis of depression, anxiety, self-directed violence, cancer or a prescription claim for a filled antidepressant or anti-anxiety before the cohort entry date. Multivariable Cox proportional hazards regression models, matched on age and calendar time, estimated HRs and 95% CIs for each outcome in women with UF who underwent a hysterectomy during follow-up and women who did not. These models were further adjusted for other UF treatments (myomectomy or UAE) prior to hysterectomy. Women in the referent category were censored on the date of a hysterectomy that occurred after the matching index date (9.7% of women).

All analyses were performed using Action Evidence Platform V.4.17. P values were two tailed, and significance was set at $p < 0.05$.

RESULTS

Of those eligible, 313 754 women with UF were matched to 627 539 women without UF (figure 1). Median follow-up time was 596 days (IQR: 231, 1293) for anxiety, 608 days (IQR: 236, 1319) for depression and 665 days (IQR: 258, 1445) for self-directed violence. The most common symptoms among women with UF were pelvic pain and HMB (table 1). Women with diagnosed UF who were excluded due to diagnosis of mental health conditions had a greater frequency of symptoms, comorbidities and medication use compared with women included in the study (online supplemental table 2). During follow-up, over half of the depression and anxiety claims came from a primary care or mental health provider and approximately 30% of self-directed violence events were captured by claims from emergency medicine or primary care providers (online supplemental table 3).

After adjusting for potential confounders, diagnosed UF was associated with higher rates of diagnosed depression, anxiety and self-directed violence (table 2). When the referent group was not censored on UF diagnosis, the results were not appreciably altered; women with diagnosed UF were more likely to have diagnosed depression (HR: 1.12; 95% CI 1.10 to 1.13), anxiety (HR: 1.11, 95% CI 1.10 to 1.13) and self-directed violence (HR: 1.36, 95% CI 1.21 to 1.52) than women without diagnosed UF. The magnitude of association was not appreciably altered when alternative definitions of the outcomes (online supplemental

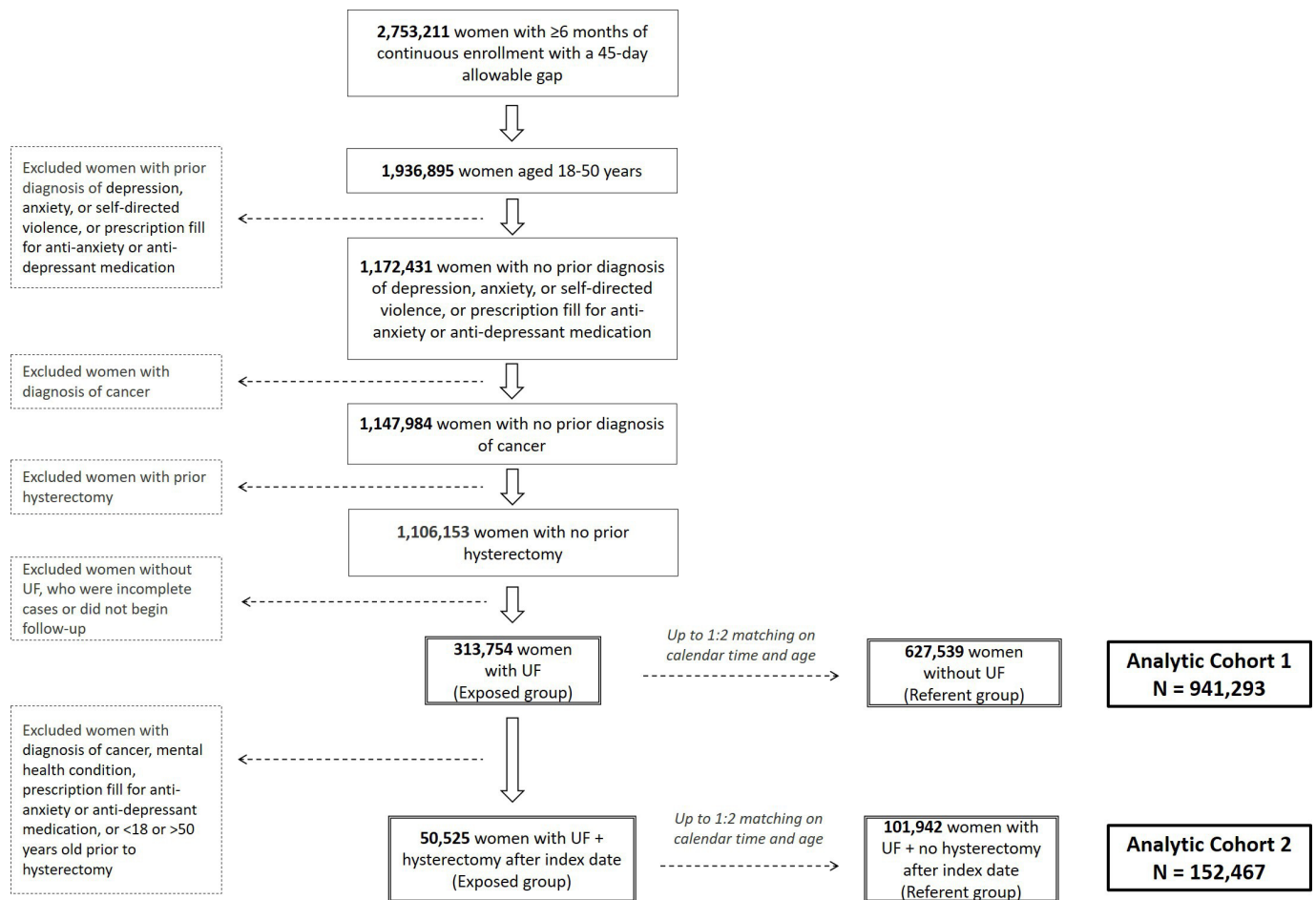


Figure 1 Cohort selection for women with uterine fibroids (UF) and a referent population of women without UF. Two study populations were used for the analysis. Analytical cohort 1 was used in the analyses to compare risk of mental health conditions in women with and without UF. Cohort entry date for analytical cohort 1 was the date of the second claim or the date of the UF claim following the ultrasonography/MRI, whichever came first, for the exposed group (UF diagnosis) and the date of a general medical or annual gynaecological examination for the referent group (no UF diagnosis). Analytical cohort 2 was used in the analyses to compare the risk of mental health conditions in women with UF who had a hysterectomy to women with UF who did not have a hysterectomy. Cohort entry date for analytical cohort 2 was the date of the hysterectomy after a diagnosis of UF for the exposed group and the date of a general medical or annual gynaecological examination after the diagnosis of UF for the referent group.

table 4) or exposure group (online supplemental table 5) were used.

The magnitude of association between diagnosed UF and diagnosed mental health outcomes was lowest in Black women and greatest in Asian women (table 2). The association between diagnosed UF and mental health outcomes was strongest among women with diagnosed UF and pain symptoms, with or without HMB (table 3). The magnitude of association between diagnosed UF and each mental health outcome was consistent across all age categories (online supplemental table 6) and the incidence rates and measures of association by decade of cohort entry were not meaningfully different (online supplemental table 7).

During the follow-up, 63 523 (20.2%) women with UF had a hysterectomy. Of those, 50 525 women were matched to 101 942 who did not have a hysterectomy (figure 1). Median follow-up time after hysterectomy was 620 days (IQR: 238, 1351) for depression, 611 days (IQR: 235, 1327) for anxiety and 673 days (IQR: 258, 1475) for self-directed violence. Hysterectomy was associated with a 22% higher rate of depression, 13% higher rate of anxiety and 86% higher rate of self-directed violence, after adjusting for covariates and prior procedures to treat UF (table 4). When the referent group was not censored

on hysterectomy, the magnitude of the association was attenuated but remained significant. The HR comparing women who underwent a hysterectomy on the index date to women who did not was 1.09 (95% CI 1.05 to 1.12) for depression, 1.06 (95% CI 1.03 to 1.09) for anxiety and 1.43 (95% CI 1.12 to 1.82) for self-directed violence.

DISCUSSION

Among women without prior diagnoses of anxiety, depression or self-harm, those with newly diagnosed UF are more likely to be diagnosed or treated for anxiety, depression and self-harm compared with women without diagnosed UF. These associations were highest among women experiencing pain-related UF symptoms. The magnitude of association varied by race and was lowest among non-Hispanic Black women. Women with diagnosed UF had a greater risk of self-directed harm, although the absolute rate was low (6 per 10 000 person-years).

Clinical context to prior studies

A cohort study conducted in an administrative database in Taiwan reported increased rates of depression in women

Table 1 Baseline characteristics in women with diagnosed uterine fibroids (UF) and women without diagnosed UF

Variable	Diagnosed UF	No diagnosed UF*	Difference (95% CI) between groups
n	313 754	627 539	
Demographics			
Age, mean (SD)	40.3 (6.5)	40.7 (6.5)	-0.4 (-0.4 to -0.3)
Race, n (%)			
White	168 479 (53.7)	429 656 (68.5)	-14.8% (-15.0% to -14.6%)
Asian	23 776 (7.6)	50 586 (8.1)	-0.5% (-0.6% to -0.4%)
Black	74 601 (23.8)	66 365 (10.6)	13.2% (13.0% to 13.4%)
Hispanic	46 898 (14.9)	80 932 (12.9)	2.1% (1.9% to 2.2%)
Region of residence, n (%)			
Northeast	41 689 (13.3)	76 374 (12.2)	1.1% (1.0% to 1.3%)
Midwest	60 629 (19.3)	153 106 (24.4)	-5.1% (-5.2% to -4.9%)
South	159 774 (50.9)	282 796 (45.1)	5.9% (5.6% to 6.1%)
West	51 662 (16.5)	115 263 (18.4)	-1.9% (-2.1% to -1.7%)
Encounter with a mental health provider	12 073 (3.8%)	26 678 (4.3%)	-0.4% (-0.5% to -0.3%)
Symptoms, n (%)			
Heavy menstrual bleeding	134 103 (42.7)	77 223 (12.3)	30.4% (30.2% to 30.6%)
Anaemia or blood transfusion	18 459 (5.9)	9661 (1.5)	4.3% (4.3% to 4.4%)
Dysmenorrhoea	36 067 (11.5)	22 187 (3.5)	8.0% (7.8% to 8.1%)
Dyspareunia	6768 (2.2)	6367 (1.0)	1.1% (1.1% to 1.2%)
Pelvic pain	107 601 (34.3)	118 774 (18.9)	15.4% (15.2% to 15.6%)
Medical conditions, n (%)			
Pregnancy	44 055 (14.0)	93 769 (14.9)	-0.9% (-1.1% to -0.8%)
Live birth	21 174 (6.7)	70 697 (11.3)	-4.5% (-4.6% to -4.4%)
Infertility	70 172 (22.4)	90 879 (14.5)	7.9% (7.7% to 8.1%)
Allergic rhinitis	49 945 (15.9)	112 218 (17.9)	-2.0% (-2.1% to -1.8%)
Asthma	22 044 (7.0)	41 509 (6.6)	0.4% (0.3% to 0.5%)
Irritable bowel syndrome	6520 (2.1)	12 850 (2.0)	0.0% (0.0% to 0.1%)
Psoriasis	2582 (0.8)	7093 (1.1)	-0.3% (-0.3% to -0.3%)
Eczema	26 217 (8.4)	63 725 (10.2)	-1.8% (-1.9% to -1.7%)
Chronic low back pain	57 187 (18.2)	118 266 (18.8)	-0.6% (-0.8% to -0.5%)
Fatigue	63 534 (20.2)	122 462 (19.5)	0.7% (0.6% to 0.9%)
Vitamin D deficiency	12 289 (3.9)	25 007 (4.0)	0.1% (-0.2% to 0.0%)
Chronic headaches/migraines	45 976 (14.7)	89 816 (14.3)	0.3% (0.2% to 0.5%)
Thyroid disease	38 741 (12.3)	77 470 (12.3)	0.0% (-0.1% to 0.1%)
Hypothyroidism	31 080 (9.9)	66 442 (10.6)	-0.7% (-0.8% to -0.6%)
Type 2 diabetes mellitus	17 018 (5.4)	26 010 (4.1)	1.3% (1.2% to 1.4%)
Hyperlipidaemia	57 158 (18.2)	115 477 (18.4)	-0.2% (-0.3% to 0.0%)
Hypertension	51 029 (16.3)	77 184 (12.3)	4.0% (3.8% to 4.1%)
Fibromyalgia	15 213 (4.8)	33 244 (5.3)	-0.4% (-0.5% to -0.4%)
Medication use, n (%)			
Combined hormonal contraceptives	68 719 (21.9)	169 948 (27.1)	-5.2% (-5.4% to -5.0%)
Oral progestin	9262 (3.0)	29 120 (4.6)	-1.7% (-1.8% to -1.6%)
Depot medroxyprogesterone acetate	18 356 (5.9)	24 834 (4.0)	1.9% (1.8% to 2.0%)
Intrauterine device	21 921 (7.0)	59 541 (9.5)	-2.5% (-2.6% to -2.4%)
Non-opioid analgesics	85 557 (27.3)	149 745 (23.9)	3.4% (3.2% to 3.6%)
Opioid analgesic	107 983 (34.4)	203 783 (32.5)	1.9% (1.7% to 2.1%)
Antihypertensives	41 595 (13.3)	68 295 (10.9)	2.4% (2.2% to 2.5%)
Statins	11 546 (3.7)	24 597 (3.9)	-0.2% (-0.3% to -0.2%)
Corticosteroids	89 124 (28.4)	199 403 (31.8)	-3.4% (-3.6% to -3.2%)
Tranexamic acid	1821 (0.6)	809 (0.1)	0.5% (0.4% to 0.5%)
Prior procedures, n (%)			
Uterine artery embolisation	36 (0.0)	5 (0.0)	0.0% (0.0% to 0.0%)
Myomectomy	6612 (2.1)	0 (0.0)	2.1% (2.1% to 2.2%)

*Matched referent includes women with no UF or prior myomectomy.

Table 2 Association between UF and diagnosis of mental health outcomes, overall and stratified by race/ethnicity

	Depression		Anxiety		Self-directed violence	
	Diagnosed UF	No diagnosed UF	Diagnosed UF	No diagnosed UF	Diagnosed UF	No diagnosed UF
Overall						
n	313 754	627 539	313 754	627 539	313 754	627 539
Events, n	26 171	46 103	34 003	60 683	509	616
Days between index date and outcome diagnosis, median (IQR)	609 (240, 1330)	607 (234, 1313)	596 (234, 1302)	596 (229, 1289)	670 (264, 1471)	662 (256, 1432)
Rate per 1000 person-years	30.9	27.8	41.0	37.3	0.6	0.3
Age-matched HR (95% CI)	1.12 (1.10 to 1.13)	1.0 (Ref)	1.10 (1.09 to 1.12)	1.0 (Ref)	1.60 (1.42 to 1.80)	1.0 (Ref)
Adjusted HR (95% CI)*	1.12 (1.10 to 1.13)	1.0 (Ref)	1.12 (1.10 to 1.13)	1.0 (Ref)	1.46 (1.29 to 1.64)	1.0 (Ref)
Non-Hispanic White						
n	168 479	429 656	168 479	429 656	168 479	429 656
Events, n	15 888	34 612	20 240	44 905	263	430
Rate per 1000 person-years	34.1	29.6	44.4	39.1	0.5	0.3
Age-matched HR (95% CI)	1.16 (1.14 to 1.18)	1.0 (Ref)	1.14 (1.12 to 1.15)	1.0 (Ref)	1.51 (1.29 to 1.76)	1.0 (Ref)
Adjusted HR (95% CI)*	1.13 (1.10 to 1.15)	1.0 (Ref)	1.12 (1.10 to 1.14)	1.0 (Ref)	1.41 (1.21 to 1.65)	1.0 (Ref)
Non-Hispanic Black						
n	74 601	66 365	74 601	66 365	74 601	66 365
Events, n	5465	4383	6937	5479	141	81
Rate per 1000 person-years	27.5	26.8	35.5	33.9	0.7	0.5
Age-matched HR (95% CI)	1.04 (1.00 to 1.08)	1.0 (Ref)	1.05 (1.02 to 1.09)	1.0 (Ref)	1.43 (1.09 to 1.88)	1.0 (Ref)
Adjusted HR (95% CI)*	1.03 (0.99 to 1.07)	1.0 (Ref)	1.05 (1.02 to 1.09)	1.0 (Ref)	1.38 (1.05 to 1.82)	1.0 (Ref)
Hispanic						
n	46 898	80 932	46 898	80 932	46 898	80 932
Events, n	3821	5390	5230	7653	78	79
Rate per 1000 person-years	32.4	27.8	45.5	40.5	0.6	0.4
Age-matched HR (95% CI)	1.17 (1.13 to 1.22)	1.0 (Ref)	1.13 (1.09 to 1.17)	1.0 (Ref)	1.60 (1.17 to 2.19)	1.0 (Ref)
Adjusted HR (95% CI)*	1.15 (1.10 to 1.20)	1.0 (Ref)	1.11 (1.08 to 1.15)	1.0 (Ref)	1.57 (1.14 to 2.15)	1.0 (Ref)
Asian						
n	23 776	50 586	23 776	50 586	23 776	50 586
Events, n	997	1718	1596	2646	27	26
Rate per 1000 person-years	15.6	13.2	25.5	20.6	0.4	0.2
Age-matched HR (95% CI)	1.19 (1.10 to 1.29)	1.0 (Ref)	1.24 (1.17 to 1.32)	1.0 (Ref)	2.09 (1.22 to 3.57)	1.0 (Ref)
Adjusted HR (95% CI)*	1.17 (1.08 to 1.27)	1.0 (Ref)	1.23 (1.16 to 1.31)	1.0 (Ref)	1.98 (1.15 to 3.41)	1.0 (Ref)

*HR adjusted for race, region of residence, allergic rhinitis, asthma, irritable bowel syndrome (IBS), eczema, chronic low back pain, fatigue, vitamin D deficiency, chronic headaches/migraines, thyroid disease, hypothyroidism, type 2 diabetes mellitus, hyperlipidaemia, hypertension, fibromyalgia, live birth and use of antihypertensives, corticosteroids, non-opioid analgesics, opioid analgesics, combined hormonal contraceptives, statins, oral progestin, depot medroxyprogesterone acetate or progestogen-releasing intrauterine system. Race-stratified models adjusted for all the covariates listed above except race.
UF, uterine fibroid.

with an ICD diagnosis code for UF (HR: 1.46, 95% CI 1.36 to 1.57) compared with women without.⁸ Our results suggest that UF is also associated with diagnosis of anxiety and self-directed violence. UF and mental health disorders are chronic conditions with significant delay in clinical diagnosis after the initial presentation of symptoms. Therefore, temporality in relation to disease onset is hard to establish from administrative claims data. In the Black Women's Health Study, women with diagnosed depression had a relative risk for incident self-reported UF of 1.25 (95% CI 1.13 to 1.39) compared with women without depression.⁵ Thus, the relation of UF and mental health disorders may be bidirectional, and an underlying common cause of UF and depression, such as an abnormal hormonal milieu, may increase a woman's susceptibility to both diseases.

Pain-related symptoms and mental health

The association between diagnosed UF and diagnosed mental health outcomes was stronger among women with pain-related symptoms, implying that poorly managed pain is an important pathway underlying the association between UF and subsequent mental health outcomes. Chronic pain and depression may share common neuroplasticity mechanisms, including effects on monoamine neurotransmitters, brain-derived neurotrophic factor and glutamate and its receptor subtypes.¹³ Further, the prevalence of anxiety and depression is high in patients with chronic pain conditions, including chronic pelvic pain,¹⁴ low back pain¹⁵ and migraines.¹⁶

Hysterectomy and depression

Among women with diagnosed UF, hysterectomy was associated with greater rates of diagnosed mental health outcomes. Prior

Table 3 Association between UF and diagnosis of mental health outcomes, stratified by symptom-based UF phenotypes

	No diagnosed UF	Diagnosed UF phenotype			
		No bleeding or pain	Heavy bleeding only*	Pain only†	Bleeding and pain
n	627 539	110 259	100 001	86 650	95 889
Depression					
Events, n	46 103	8 352	8 158	7 230	8 331
Rate per 1000 person-years	27.8	26.6	28.6	32.3	33.1
Age-matched HR (95% CI)	1.0 (Ref)	0.95 (0.93 to 0.98)	1.08 (1.05 to 1.11)	1.18 (1.15 to 1.21)	1.26 (1.23 to 1.30)
Adjusted HR (95% CI)‡	1.0 (Ref)	1.00 (0.97 to 1.02)	1.09 (1.06 to 1.12)	1.16 (1.12 to 1.19)	1.21 (1.18 to 1.25)
Anxiety					
Events, n	60 683	11 011	10 257	9 868	11 106
Rate per 1000 person-years	37.3	35.9	36.6	45.3	45.2
Age-matched HR (95% CI)	1.0 (Ref)	0.97 (0.95 to 0.99)	1.03 (1.01 to 1.06)	1.18 (1.15 to 1.21)	1.21 (1.19 to 1.24)
Adjusted HR (95% CI)‡	1.0 (Ref)	1.03 (1.00 to 1.05)	1.06 (1.04 to 1.09)	1.17 (1.14 to 1.20)	1.18 (1.15 to 1.21)
Self-directed violence					
Events, n	616	122	141	157	179
Rate per 1000 person-years	0.3	0.4	0.5	0.6	0.7
Age-matched HR (95% CI)	1.0 (Ref)	1.04 (0.84 to 1.30)	1.29 (1.04 to 1.59)	1.86 (1.50 to 2.31)	1.87 (1.52 to 2.29)
Adjusted HR (95% CI)‡	1.0 (Ref)	0.98 (0.78 to 1.23)	1.16 (0.93 to 1.44)	1.66 (1.33 to 2.08)	1.68 (1.35 to 2.09)

*Heavy bleeding defined as heavy menstrual bleeding (menorrhagia or menometrorrhagia), anaemia or blood transfusion.

†Pain defined as dysmenorrhoea, dyspareunia or pelvic pain.

‡HR adjusted for race, region of residence, allergic rhinitis, asthma, irritable bowel syndrome (IBS), eczema, chronic low back pain, fatigue, vitamin D deficiency, chronic headaches/migraines, thyroid disease, hypothyroidism, type 2 diabetes mellitus, hyperlipidaemia, hypertension, fibromyalgia, live birth and use of antihypertensives, corticosteroids, non-opioid analgesics, opioid analgesics, combined hormonal contraceptives, statins, oral progestin, depot medroxyprogesterone acetate or progestogen-releasing intrauterine system.

UF, uterine fibroid.

studies reported improvement in quality of life and psychological conditions after a hysterectomy,^{17–19} although these studies were limited by short follow-up, small sample size or outcomes reported around the time of surgery. Recent cohort studies found a 20%–78% higher risk of depression^{20–22} and a 22% higher risk of anxiety²⁰ after a hysterectomy for any benign condition, and the risk was greatest in women experiencing perioperative pain.²³ When stratified by indication, hysterectomy for UF was associated with an HR of 1.12 (95% CI 0.92 to 1.35) for depression and 1.14 (95% CI 0.93 to 1.40) for anxiety.²⁰ Although the CIs were wide, due to a low number of cases (n=223 for depression and 199 for anxiety), the point estimates were consistent with results from the current study. Conversely, in a Taiwan administrative database, hysterectomy for UF was associated with a 36% lower risk of diagnosed depression (HR: 0.64; 95% CI 0.51 to 0.81)⁸; however, the overall rate of diagnosed depression (7.5 per 1000 person-years) was half the rate of depression in Asian women in the present study. Discrepancies may be due to reporting bias, differences in healthcare practice or underlying representation of the administrative databases. While we adjusted for myomectomy and UAE procedures prior to hysterectomy, we are not able to control completely for UF severity that may influence the decision to undergo hysterectomy.

Hysterectomy may lead to depression through numerous pathways, including oestrogen deficiency caused by oophorectomy²⁴ if ovaries are removed, or loss of endocrine activity of the endometrium,²⁵ or detrimental effects of the ovaries via ovarian-independent mechanisms, in the context of ovarian conservation.²⁶ The procedure codes for hysterectomy and/or oophorectomy limited the ability to separate hysterectomy with ovarian conservation and ovarian removal in the analysis. Additionally, the loss of fertility in women before the end of child-bearing may influence future mental health.²⁷ However, data on pregnancy intentions and desired family size were unavailable.

Racial disparities in UF and mental illness

Black women are diagnosed with UF at earlier ages, experience greater symptom severity and are more likely to have hysterectomy for UF.²⁸ Further, these surgeries are more likely to be performed abdominally rather than laparoscopically.²⁹ Despite greater disease burden, rates of diagnosed depression and anxiety were not elevated in Black women. Individuals from minority groups are less likely to meet criteria for depression and anxiety disorders or receive psychotropic medications compared with White women.³⁰ In addition, the stigma of mental health conditions may lead to self-silencing of symptoms and underdiagnosis of mental illness.³¹ The lower rates of diagnosed depression in Black women with UF mirror the ‘Black-White depression paradox’, in which Black women have greater exposure to psychological, social and economic stressors relative to White women, yet the prevalence of diagnosed depression is lower.³² Additional research is needed to understand whether these observed differences are due to differences in disease burden, clinical or cultural presentation of symptoms and/or access to healthcare.

Postulated biological mechanisms

There are several plausible biological pathways that may link UF and depression. First, hormonal dysregulation may be a common cause of both depression and UF.³³ Sex steroid hormones may influence the pathogenesis of UF³⁴ and the serum levels of sex hormones are different in women with depression relative to women without.³⁵ Psychological stressors, such as depression, are associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and these HPA abnormalities may influence the hypothalamic-pituitary-ovarian axis and alter sex steroid hormone production.³⁶ Other psychosocial stressors, such as childhood abuse and perceived racism, have been associated

Table 4 Association between hysterectomy after UF diagnosis and diagnosis of mental health outcomes, restricted to women with diagnosed UF

	Hysterectomy	No hysterectomy
n	50525	101942
Depression		
Events, n	4368	6588
Days between index date and outcome diagnosis, median (IQR)	638 (247, 1394)	612 (235, 1330)
Rate per 1000 person-years	31.1	24.3
Age-matched HR (95% CI)	1.29 (1.24 to 1.34)	1.0 (Ref)
Adjusted HR (95% CI)*	1.22 (1.17 to 1.27)	1.0 (Ref)
Anxiety		
Events, n	5259	8970
Days between index date and outcome diagnosis, median (IQR)	631 (245, 1378)	601 (231, 1302)
Rate per 1000 person-years	38.0	33.7
Age-matched HR (95% CI)	1.13 (1.09 to 1.17)	1.0 (Ref)
Adjusted HR (95% CI)*	1.13 (1.09 to 1.17)	1.0 (Ref)
Self-directed violence		
Events, n	99	97
Days between index date and outcome diagnosis, median (IQR)	704 (271, 1546)	657 (253, 1435)
Rate per 1000 person-years	0.7	0.3
Age-matched HR (95% CI)	1.94 (1.47 to 2.57)	1.0 (Ref)
Adjusted HR (95% CI)*	1.86 (1.39 to 2.49)	1.0 (Ref)

*HR adjusted for race, region of residence, allergic rhinitis, asthma, irritable bowel syndrome (IBS), eczema, chronic low back pain, fatigue, vitamin D deficiency, chronic headaches/migraines, thyroid disease, hypothyroidism, type 2 diabetes mellitus, hyperlipidaemia, hypertension, fibromyalgia, live birth and use of antihypertensives, corticosteroids, non-opioid analgesics, opioid analgesics, combined hormonal contraceptives, statins, oral progestin, depot medroxyprogesterone acetate, progestogen-releasing intrauterine system, prior myomectomy and prior uterine artery embolisation (UAE).

UF, uterine fibroid.

with UF.^{37 38} Pain symptoms may also be chronic stressors that lead to depression and anxiety in women with symptomatic UF.

Strengths and limitations

Strengths of this study included the use of a large database with a contemporary cohort of commercially insured individuals with broad geographic coverage. All patients were enrolled in an insurance plan and had access to healthcare and mental healthcare services, and the women in the unexposed group were required to have at least one healthcare encounter to minimise bias in health-seeking behaviours between patients with and without diagnosed UF. Finally, the prospective design of this study and exclusion of prevalent mental health diagnoses allow for the establishment of the temporal sequence between the diagnosis of UF and mental health outcomes.

There are limitations of the study that warrant discussion. First, misclassification of the exposure is likely, given that a significant proportion of women with UF are asymptomatic² and may not have claims with UF diagnosis codes. Due to this misclassification the associations may be overestimated and may be most generalisable to women with symptomatic UF. The optimal interpretation of these results is that women seeking care for UF are at greater risk of receiving a diagnosis of mood disorders.

The diagnosis of mental health conditions was likely underestimated, as only women who sought medical attention for these

conditions would be identified through claims. Although all women were enrolled in a commercial insurance plan, the access to mental healthcare and healthcare in general may not be equal for everyone. We are unable to assess subsyndromal symptoms of depression and anxiety in this secondary database; only diagnosed disease was captured. Additionally, UF and mood disorders are chronic conditions, and due to the limited longitudinal observability in individuals in the claims data, we were unable to assess the timing of the onset of either condition. Women who had undiagnosed UF at the time of a mental health diagnosis did not contribute to the analysis. As these women may have greater disease burden, their exclusion from the analysis may have underestimated the impact of symptomatic UF on risk of mood disorders. Importantly, this study assessed the temporal relationship of receiving a clinical diagnosis of mood disorders in women after a diagnosis of UF.

Race, which was imputed in the majority of the population,¹² is misclassified in these data. The imputation method was validated previously and demonstrated 97% specificity, and 71% positive predictive value, but only 48% sensitivity, for estimating the race of Black individuals.³⁹ This misclassification would increase the heterogeneity within racial subgroups and underestimate any differences in the association between UF and diagnosed mental health conditions between these subgroups. Finally, the generalisability of these results to an uninsured population may be limited.

CONCLUSIONS

Women with diagnosed UF may be at a higher risk for diagnosed depression, anxiety and self-directed violence relative to women without, particularly among women who experience pain symptoms. Obstetricians and gynaecologists can play an important role in early detection, prevention and treatment of mood disorders by screening for symptoms at routine examinations.⁴⁰ The potential for precipitating or exacerbating mental health disorders may be considered while counselling patients on UF treatment options, especially hysterectomy. A multidisciplinary approach that identifies women with UF at higher risk of depression and anxiety may improve management of mood disorders and improve strategies for prevention.

What is already known on this subject

- ▶ The prevalence of depression and anxiety is high among women with uterine fibroids (UF). The rate of diagnosed mental health outcomes among women with a diagnosed UF has not been well studied.

What this study adds

- ▶ Women with diagnosed UF, particularly those who experienced pain-related symptoms from UF or who underwent hysterectomy, are at higher risk for diagnosis of mental health outcomes than women without diagnosed UF. Obstetricians and gynaecologists can play an important role in early detection, prevention and treatment of mood disorders by screening for symptoms at routine examinations.

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Contributors SEC generated the idea for the study, formulated an analytical plan, interpreted the results and drafted the manuscript. CH contributed to the design of the study, analysed the data, interpreted the results and revised the manuscript. NPI, CO, WK and LAW contributed to the design of the study and interpretation of

the results, and revised the manuscript. All authors approved the final version of the manuscript.

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