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Depressive Symptoms and Risk of Uterine Leiomyomata

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Abstract

Objective—Uterine leiomyomata (UL) are a major source of gynecologic morbidity and the primary indication for hysterectomy. Depression can cause dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which may affect the synthesis of reproductive hormones involved in UL pathogenesis. We assessed the association between depressive symptoms and UL among 15,963 premenopausal women.

Study Design—Data were derived from the Black Women's Health Study, a prospective cohort study. In 1999 and 2005, the Center for Epidemiologic Studies Depression Scale (CES-D) was used to ascertain depressive symptoms. On biennial follow-up questionnaires from 1999 through 2011, women reported physician-diagnosed depression, antidepressant use, and UL diagnoses. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were estimated using multivariable Cox regression.

Results—There were 4,722 incident UL cases diagnosed by ultrasound (n=3,793) or surgery (n=929) during 131,262 person-years of follow-up. Relative to baseline CES-D scores <16, IRRs were 1.05 (95% CI, 0.98–1.13) for CES-D scores 16–24 and 1.16 (95% CI, 1.06–1.27) for CES-D scores ≥25 (*P*-trend=0.001). IRRs for current and past physician-diagnosed depression relative to no depression were 1.15 (95% CI: 0.98, 1.34) and 1.25 (95% CI: 1.13, 1.39), respectively. Results persisted after further control for antidepressant use. IRRs for current and past use of antidepressants (any indication) relative to never use were 1.11 (95% CI: 0.97, 1.28) and 1.32 (95% CI: 1.14, 1.52), respectively.

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AUTHORS' ROLES

Drs. Rosenberg and Palmer designed the parent study and directed its overall implementation, including quality assurance and control. Dr. Wise designed the validation study for uterine leiomyomata and the substudy on depressive symptoms, conducted the literature review, performed statistical analysis, and took the lead in drafting the manuscript for publication. Dr. Li performed data management and statistical analysis. All authors made contributions to the interpretation of results, drafting the article, and revising the article critically for intellectual content.

CONFLICT OF INTEREST

We have no competing interests to report.

Conclusions—In this cohort of black women, greater depressive symptoms were associated with UL, independent of antidepressant use, supporting the hypothesis that dysregulation of the HPA axis increases UL risk.

Keywords

Uterine neoplasms; Depressive symptoms; Prospective Studies; African Americans; Antidepressants

INTRODUCTION

Uterine leiomyomata (UL) are clinically recognized in 30% of reproductive-aged women^{1,2} and are a major contributor to gynecologic morbidity³ and medical costs.⁴ Black women are 2–3 times more likely to be diagnosed with UL than white women,² but established risk factors do not explain the racial disparity.⁵ Sex steroid hormones are thought to influence UL pathogenesis.^{6,7}

UL risk has been linked to greater exposure to psychosocial stress.⁸ A cross-sectional study found a higher prevalence of UL among women reporting more major life events and greater “stress intensity.”⁹ In the Black Women’s Health Study (BWHS), a prospective cohort study, perceived racism was positively associated with UL diagnoses.¹⁰ In agreement with a previous cohort study of white women,¹¹ the BWHS documented a positive association between child sexual abuse and UL diagnoses.¹²

Major depressive disorder is the second leading cause of years of life lost due to premature mortality in the United States,¹³ and the incidence in women is twice that of men.¹⁴ Depression is more common in black Americans than in other ethnic groups in some^{15–17} but not all^{18–20} studies, and black Americans with depression are less likely to take antidepressant medications.^{21,22} Studies limited only to those receiving medical treatment may miss an important segment of the black population suffering from depression.

A large body of clinical and basic research report an association between dysregulation of hypothalamic-pituitary-adrenal (HPA) axis hormone dynamics and mood disorders such as depression.^{23–25} HPA-axis abnormalities observed in depressed individuals include hypercortisolemia, as reflected by elevated levels of cortisol in plasma, cerebrospinal fluid, and 24-hour urine overall^{26–28} and in response to psychological stress.²⁹ Lower levels of DHEAS (androgen precursor produced by adrenal gland) have also been reported among depressed patients.³⁰ Alterations in the HPA axis can cause dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis,²⁵ which may influence the synthesis of sex steroid hormones.^{31–33} For instance, depressed women were found to have lower serum levels of estradiol but higher serum levels of progesterone compared with non-depressed women^{25,34,35} and progesterone may have a stimulatory effect on UL.^{7,36} Depressive symptoms can also deleteriously influence health-related behaviors, including sedentariness, alcohol consumption, and poor diet, all of which may increase UL risk.^{37–40}

In a large cohort of black women, we evaluated prospectively the association between depressive symptoms and UL risk, and the extent to which antidepressant use mediates this association.

MATERIAL AND METHODS

Study population

The Black Women's Health Study is an ongoing prospective cohort study of 59,000 African-American women aged 21–69 at baseline.⁴¹ In 1995, subscribers of *Essence*—a magazine with a large black female readership—were invited to enroll in a long-term health study by completing comprehensive self-administered baseline questionnaires. Biennial follow-up questionnaires update exposure and medical information; cohort retention was 80% through 2011. Participants reside in more than 17 states across the United States. The institutional review board of Boston University Medical Center approved the study protocol.

Assessment of depressive symptoms, diagnosed depression, and antidepressant use

The 1999 and 2005 follow-up questionnaires included the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), which was designed to assess depressive symptoms in community samples and population-based studies.⁴² Respondents indicated the frequency of various feelings experienced during the previous week on a four-point scale ranging from “rarely or none of the time” to “most or all of the time.” The measure included items such as “I felt sad,” “I felt lonely,” “I felt depressed,” and “I enjoyed life.” Total scores ranged from 0 to 60, with higher scores indicating higher levels of depressive symptoms.

Women had the opportunity to report a clinical diagnosis of depression under an open-ended question about “other serious illness” in 1995, or under questions about “depression treated with medication” on biennial follow-up questionnaires from 1997 through 2009. Because black women are less likely to take medication for depression than other populations,^{21,22} we asked separately about “depression” and “depression treated with medication” in 2005 to capture clinically-depressed women we may have missed in previous years. Year of first diagnosis was elicited on all questionnaires.

Users of antidepressant medications were defined as participants who reported using “medication for depression” in 1997; “antidepressants (Prozac, Zoloft, Elavil, etc.)” in 1999, 2001, 2003, or 2005; or antidepressants under “Please list all other medications or supplements that you currently take at least 3 days a week” (all years), regardless of the indication for use. The Slone Drug Dictionary was used to code medications.⁴³

Assessment of UL

Incident cases were women who reported a first diagnosis of UL confirmed by ultrasound or surgery. Ultrasound has high sensitivity (99%) and specificity (91%) relative to histologic evidence.^{44,45} On follow-up questionnaires, women reported whether they had been diagnosed with “uterine fibroids” in the previous two-year interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by “pelvic exam” and/or by “ultrasound/hysterectomy” (1999 or 2001) or “ultrasound” and “surgery”

(2003 or later). To maximize the specificity of UL classification, cases identified by pelvic exam only (N=350) were treated as non-cases.⁴⁶

Assessment of covariates

On the 1995 and biennial follow-up questionnaires, we collected data on reproductive and contraceptive history, gynecologic surgeries, anthropometric factors, physical activity, smoking, alcohol consumption, geographic region of residence, socioeconomic correlates (education, marital status, occupation), medical conditions, and Pap smear frequency. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. We estimated total metabolic equivalents (METs) per week by summing the METs from moderate physical activity (hours/week $\times$ 3.5) and vigorous exercise (hours/week $\times$ 7.0).⁴⁷ In 2003, women reported their household income. In 2007, participants reported their recency of pelvic exam (never, <5, 5–9, 10 or more years ago) and pelvic ultrasound (never, <5, 5–9, 10 or more years ago). In 2005, participants completed the 10-item Carver coping scale,⁴⁸ with higher scores indicating higher coping skills.

Validation studies

Uterine leiomyomata—We mailed supplemental questionnaires to a random sample of 248 cases and requested permission to review their medical records. We corroborated the self-report in 122 (96%) of 126 women from whom we received medical records. Most cases (87%) reported that their condition came to clinical attention because they sought treatment for symptoms or a tumor was palpable during a routine pelvic exam. Details about the validation study may be found elsewhere.⁴⁹

Depressive symptoms—The validity and reliability of the CES-D have been documented in several populations,^{15,42,50–53} including the BWHS.^{54,55} In the BWHS, factor analysis indicated that the four-factor structure of the CES-D was supported,^{54,55} and Cronbach alphas demonstrated high internal consistency of the CES-D responses.⁵⁵

Restriction criteria

Of the 22,284 BWHS premenopausal participants at baseline who had never been diagnosed with UL, we excluded women who were aged $\geq$ 50 years (N=1,576) or lost to follow-up after 1999 (N=890); cases that did not report a year of diagnosis (N=149) or method of confirmation (N=110), and women with incomplete data on the CES-D (N=3,043) or covariates (N=553), leaving 15,963 for analysis. Women with incomplete data on depressive symptoms tended to be older (mean age: 37.3 vs. 36.0), have a higher prevalence of clinical depression (ever: 7.0% vs. 6.2%), be current smokers (14.5% vs. 12.7%), have fewer years of education (mean: 14.6 vs. 14.9), and be parous (66% vs. 59%), but were similar with respect to menarcheal age (mean: 12.4 vs. 12.3 years) and BMI (28.9 vs. 28.6). The age-adjusted incidence of UL among those excluded (34.4 cases per 1,000 person-years) was similar to those included (36.0 cases per 1,000 person-years).

Data Analysis

Cox regression was used to estimate incidence rate ratios (RRs) and 95% confidence intervals (CI). We categorized depressive symptoms as “low” (CES-D <16), “moderate” (CES-D: 16–24) and “severe” (CES-D ≥ 25). The reference category for all analyses was “CES-D <16.” This categorization has been used in previous studies^{56,57} and was informed by previous observations that a mean CES-D score of 24.4 among patients in a private psychiatric facility was strongly associated with major depression.⁵⁸ Person-years at risk were calculated from the start of follow-up (March 1999) until first diagnosis of UL, menopause, death, loss to follow-up, or the end of follow-up (March 2011), whichever came first.

The Cox model conditioned on age (1-year intervals) and time period (2-year intervals). A second multivariable model further controlled for age at menarche (<10, 11, 12–13, 14 and 15 years), parity (0, 1, 2, ≥3 births), age at first birth (years), years since last birth (<5, 5–9, 10–14, ≥15), age at first oral contraceptive use (years), history of oral contraceptive use (ever, never), BMI (<20, 20–24, 25–29, ≥30 kg/m²), physical activity (<10, 10–19, 20–39, ≥40 METs/week), smoking (current, former, never), current alcohol intake (<1, 1–6, ≥7 drinks/week), participant’s education (<12, 13–15, 16, ≥17 years), marital status (married/living as married, divorced/separated/widowed, single), occupation (white collar, non-white collar, unemployed), annual household income (<\$25,000, \$25,001–50,000, \$50,001–100,000, >\$100,000, missing), and region of residence (South, Northeast, Midwest, West). In sensitivity analyses, we further stratified by and adjusted for history of depression treated with medication and antidepressant use. Antidepressant use was considered a possible mediator of the association between depressive symptoms and UL, as were other lifestyle factors such as smoking and alcohol consumption. Time-varying variables (e.g., antidepressant use, parity, years since last birth) were updated over time using the Anderson-Gill data structure.⁵⁹ Control for family history of UL, maternal age at participant’s birth, abuse, and perceived racism^{10,60} made little difference in the effect estimates and were omitted from multivariable models.

Primary analyses assessed CES-D scores reported at baseline (1999) in relation to UL risk. Secondary analyses assessed different specifications of the CES-D variable, including 1) updating the variable by using CES-D scores reported in 2005 (for 2005–2011 risk period), 2) assigning the 1999 CES-D to the 1999–2005 risk period and assigning the average of 1999 and 2005 CES-D measures to the 2005–2011 risk period (cumulative-average), and 3) examining the 2005 CES-D measure after restricting to the 2005–2011 risk period only.

We used stratification to examine whether associations were modified by other covariates such as coping skills, age, and smoking. P-values from interaction tests were obtained using the likelihood ratio test comparing models with and without cross-product terms between depressive symptoms and selected covariates. Departures from proportional hazards were evaluated in the same manner using cross-product terms between depressive symptoms and age (<35, ≥35 years). Analyses were performed using SAS version 9.2.⁶¹

RESULTS

Frequencies of CES-D scores <16, 16–24 and ≥25 were 70%, 19%, and 11%, respectively, with 6% reporting a history of physician-diagnosed depression and 4% reporting ever having used antidepressants (Table 1). Higher CES-D scores were associated with younger age at baseline, higher parity, earlier ages at first birth and first OC use, greater time since last birth, lower adult household income, higher BMI, greater tobacco and alcohol consumption, and lower coping scores. No appreciable differences were found for recent pelvic exam or ultrasound (within 5 years prior to 2007 questionnaire) across exposure categories. The correlation between CES-D scores reported in 1999 and 2005 among those with complete data for both measures was 0.54 ($p<0.0001$).

During 131,262 person-years of follow-up, there were 4,722 incident UL cases confirmed by ultrasound ($N=3,793$) or surgery ($N=929$). Higher CES-D scores were associated with higher UL risk (Table 2). Relative to baseline CES-D scores <16, multivariable-adjusted IRRs for CES-D scores 16–24 and ≥25 were 1.05 (95% CI, 0.98–1.13) and 1.16 (95% CI, 1.06–1.27), respectively (P -trend=0.001). Associations were similar when we used the cumulative average of the 1999 and 2005 CES-D scores (P -trend<0.001) and when we updated scores over time (P -trend<0.001). When we restricted the incident period to 2005–2011, the IRRs for 2005 CES-D 16–24 and ≥25 vs. <16 were 1.22 and 1.24, respectively (P -trend=0.003). The respective IRRs were 1.37 (95% CI: 1.10, 1.69) and 1.36 (95% CI: 1.06, 1.75) among women with low coping skills, and 1.09 (95% CI: 0.87, 1.36) and 1.10 (95% CI: 0.83, 1.47) among women with high coping skills, but the IRRs were not statistically different across coping strata (P -interaction=0.34). Women with CES-D scores ≥25 in 1999 and 2005 had 1.45 times the UL risk of women whose scores were <16 in both years (95% CI: 1.11, 1.88). Associations were somewhat stronger among women with greater gynecologic surveillance, as indicated by a recent pelvic exam and/or ultrasound: IRRs for CES-D scores 16–24 and ≥25 vs. <16 were 1.05 (95% CI: 0.97, 1.14) and 1.21 (95% CI: 1.10, 1.34), respectively. With regard to possible mediation by covariates, control for current smoking, alcohol consumption, BMI, and hormonal contraceptive use made little difference in the associations (data not shown).

IRRs for current and past physician-diagnosed depression relative to no depression were 1.15 (95% CI: 0.98, 1.34) and 1.25 (95% CI: 1.13, 1.39), respectively (Table 2). IRRs for the association between current and past use of antidepressants (for any indication) relative to never use were 1.11 (95% CI: 0.97, 1.28) and 1.32 (95% CI: 1.14, 1.52), respectively. Current users of antidepressants who scored ≥25 on the updated CES-D had 1.56 times the UL risk of never users of antidepressants with a CES-D <16 (95% CI: 1.26, 1.98). Further adjustment for current and past use of antidepressants slightly attenuated the association between depressive symptoms and UL: IRRs for baseline CES-D scores 16–24 and ≥25 vs. <16 were 1.04 (95% CI: 0.97, 1.12) and 1.14 (95% CI: 1.04, 1.25), respectively (P -trend=0.003) and IRRs for updated CES-D scores 16–24 and ≥25 vs. <16 were 1.10 (95% CI: 1.02, 1.19) and 1.16 (95% CI: 1.06, 1.28), respectively (P -trend=0.0002).

The association between depressive symptoms and UL was uniform across strata of age, BMI, smoking status, and hormonal contraceptive use (Table 3), and there was no evidence

that exogenous hormone use modified the association between antidepressants and UL (data not shown). Because the requirement for UL surgery may reflect more severe disease and longer duration of subclinical disease, we stratified the data by method of confirmation: surgery vs. ultrasound. The IRRs for updated CES-D scores of 16–24 and ≥25 vs. <16 were 1.16 (95% CI, 0.99–1.37) and 1.15 (95% CI, 0.94–1.42) respectively (P -trend=0.064) among the 929 surgical cases, and 1.10 (95% CI, 1.01–1.20) and 1.21 (95% CI, 1.09–1.33) respectively (P -trend<0.001) among the 3,793 ultrasound-confirmed cases. Results were similar using baseline CES-D scores (data not shown).

COMMENT

The present study documented a positive association between depressive symptoms and UL risk in black women. The association was similar after adjustment for antidepressant use and several health-related behaviors associated with depressive symptoms, such as smoking and alcohol consumption. Results based on updated or cumulatively-averaged CES-D measures also indicated a positive association. Results were similar across strata of age and other covariates. There was some indication of a larger association between depressive symptoms and UL risk among women with lower coping skills. Positive associations for depressive symptoms and UL incidence remained after controlling for antidepressant use.

It was difficult to disentangle the effects of depressive symptoms from antidepressant use because those using antidepressants may be more likely to have severe depression. We were also unable to assess whether poorly-controlled depression was associated with a higher risk of UL given our limited data on severity and treatment of depressive episodes over time. Nevertheless, we found that current users of antidepressants scoring ≥25 on the CES-D, a marker for more severe or poorly-controlled depression, had the highest risk of UL.

There are no previous studies with which to compare our results, but our data are consistent with studies showing associations between UL and other psychosocial stressors, including abuse,^{11,12} stress intensity,⁹ and perceived racism.¹⁰ Strengths of our study include the prospective design and validation of UL. While we were unable to validate depressive symptoms, the CES-D is a widely-used psychometric instrument that has demonstrated high reproducibility in our cohort and in other studies.^{42,54,55} Depressive symptoms were ascertained at two different points in time (1999 and 2005), permitting the evaluation of different classifications of exposure (baseline vs. updated). Results were robust to various exposure classifications. We controlled for several potential confounders in a time-varying manner.

UL rates in our cohort are similar to those from other national studies.^{3,49,62–64} Self-reported UL was confirmed in 96% of participants for whom we obtained medical records. However, because not all participants were screened, our case group likely overrepresents women with clinically-relevant UL because most cases reported symptoms. Distortion of results due to differential screening patterns across depressed groups is unlikely but, if present, would have attenuated findings given that depressed women are less likely to seek medical care.^{21,22} In support of this prediction, results were stronger when analyses were restricted to the ~80% of women with a recent pelvic exam or ultrasound. Nonetheless, detection bias

was possible if abnormal bleeding due to depressive effects on the HPA axis increased the probability of UL diagnosis,⁶⁵ if ultrasounds performed for bleeding were scrutinized to a greater degree than ultrasounds performed for other reasons (pelvic pain, family history of cancer), or if patients with bleeding were more likely to have had a sonohysterogram which can better differentiate UL than a standard ultrasound.

The CES-D has been widely used in community-based samples to screen for depression, but it is not a definitive clinical measure of depression. In one study, a cutoff of “16 or more” identified 65% of women with clinical depression.⁶⁶ Despite its low sensitivity, the CES-D is practical for large epidemiologic studies in which a more structured clinical interview is not feasible. Although depressed women may have been more likely to withdraw from the study, we found no appreciable differences in baseline characteristics according to loss-to-follow-up.

The BWHS is a volunteer cohort of women with higher education than the general population. However, prevalence estimates of established UL risk factors (e.g., early menarche)⁶⁷ and depressive symptoms (CES-D 16: 27%)^{17,69} are consistent with national data on black women. Our observed associations were also consistent across levels of age and education. Therefore, we expect our findings to extend to the general population of black women.

There is biologic plausibility for an adverse effect of depression on UL incidence. Depression has been linked to dysregulation of the HPA axis and the stress response,^{25,34,35} which may affect UL growth via alterations in sex steroid metabolism.^{6,7} However, in some studies, hormonal dysregulation has been found to precede depression onset,⁶⁸ which suggests that hormonal dysregulation could be a common cause of depressive symptoms and UL (i.e. unmeasured confounding). The present study was not able to directly test this hypothesis, but a study with hormone measurements possibly could. Likewise, because UL may not have been diagnosed until they were causing major symptoms, we cannot rule out reverse causation. For example, a spurious positive association would have arisen if symptoms of undiagnosed UL, such as menorrhagia-related anemia, caused depressive-type symptoms. Our observation of similar associations comparing baseline vs. updated CES-D scores, and ultrasound vs. surgical cases, suggests that reverse causation does not fully explain our associations. Regardless of whether the observed association is causal, depression might be a marker for a hormonal state that contributes to UL development.

In conclusion, depressive symptoms were positively associated with UL diagnosis among black women, independent of antidepressant use. These results support the hypothesis that psychosocial stress increases UL risk. Prospective studies with biologic measurements of hormones, serial pelvic imaging of UL, and uniform screening of depression with clinically-based instruments would be worthwhile to clarify whether the depressive symptoms themselves, or alternative hormonal pathways or biases, explain the increase in UL risk.

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Abbreviations

BMI	body mass index
CES-D	Center for Epidemiologic Studies Depression Scale
CI	confidence interval
HPA	hypothalamic-pituitary-adrenal axis
MET	metabolic equivalent
IRR	incidence rate ratio
UL	uterine leiomyomata

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1 to 4 bullet points summarizing clinical or research implications of findings

- Depression can cause dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which may affect the synthesis of reproductive hormones involved in the pathogenesis of uterine leiomyomata (UL).
- In this prospective cohort study of African American women, greater depressive symptoms were associated with an increased risk of UL, independent of antidepressant use.
- Antidepressant users with the highest levels of depressive symptoms had the highest risk of UL.
- Prospective studies with biologic measurements of hormones, serial pelvic imaging of UL, and uniform screening of depression with clinically-based instruments are warranted to clarify whether the depressive symptoms themselves, or alternative hormonal pathways or biases, explain the increase in UL risk.

Characteristics of 15,963 women according to depressive symptoms, clinical depression, and antidepressant use, Black Women's Health Study, 1999.

Table 1

Characteristic ^a	CES-D score in 1999			Physician-diagnosed clinical depression (ever)		Use of Antidepressants (ever)	
	<16	16–24	25	No	Yes	No	Yes
Number of women	11,165	3,018	1,780	14,959	1,004	15,381	582
Age at baseline, y (mean)	36.3	35.4	35.1	35.9	37.4	35.9	37.9
Ever use of antidepressants (%)	2.0	5.2	11.7	1.2	38.6	0.0	100.0
Current use of antidepressants (%)	1.4	3.7	9.9	0.8	30.4	0.0	73.5
Age at menarche, y (mean)	12.3	12.3	12.3	12.4	12.2	12.3	12.2
Parous, yes (%)	58.4	59.3	59.9	58.9	57.3	58.9	55.9
Age at first birth, y (mean) ^b	24.1	23.3	22.5	23.9	22.3	23.9	22.2
Time since last birth, y (mean) ^b	9.9	10.5	10.8	10.1	11.0	10.1	11.4
Age at first OC use, y (mean) ^c	19.1	19.1	18.9	19.1	18.5	19.1	18.3
Education, y (mean)	15.1	14.7	14.5	14.9	14.8	14.9	14.8
Married or living with partner (%)	44.8	37.1	32.9	42.7	31.8	42.3	33.8
Income \$25,000 in 2003 (%)	6.9	11.4	16.4	8.4	13.0	8.6	11.9
Body mass index, kg/m ² (mean)	28.2	29.4	30.2	28.5	30.2	28.6	30.9
Metabolic equivalents of physical activity per week (mean)	22.5	19.6	18.9	21.8	18.4	21.7	17.3
Family history of UL (%)	35.8	34.6	35.7	35.4	37.2	35.6	35.7
Smoking, current (%)	10.7	16.1	19.9	12.2	19.9	12.5	19.6
Alcohol, current 7 drinks/wk (%)	2.9	4.8	7.0	3.5	5.2	3.6	5.1
Coping score in 2005 (mean)	29.3	28.3	27.5	28.9	28.8	28.9	28.4
Pelvic exam and/or ultrasound <5 y of 2007 questionnaire (%)	80.2	75.4	71.2	78.3	77.8	78.3	78.0

^a Characteristics are presented as means or percentages within depression categories and are age-standardized to distribution of cohort in 1999.

^b Restricted to parous women only.

^c Restricted to women with a history of OC use.

Table 2
Depressive symptoms and risk of uterine leiomyomata, Black Women's Health Study in 1999–2011

Characteristic	Cases	Person-years	Age-adjusted model ^a		Multivariable model ^b	
			IRR	95% CI	IRR	95% CI
CES-D score in 1999						
<16	3,254	92,554	1.00	Ref.	1.00	Ref.
16–24	898	24,600	1.04	0.96, 1.12	1.05	0.98, 1.13
25	570	14,108	1.15	1.05, 1.25	1.16	1.06, 1.27
<i>P</i> -value, test for trend ^c			<i>P</i> =0.004		<i>P</i> =0.001	
CES-D score in 2005 ^d						
<16	792	26,289	1.00	Ref.	1.00	Ref.
16–24	213	5,588	1.20	1.04, 1.39	1.22	1.05, 1.41
25	139	3,501	1.24	1.04, 1.48	1.24	1.04, 1.49
<i>P</i> -value, test for trend ^c			<i>P</i> =0.001		<i>P</i> =0.003	
Updated CES-D score ^e						
<16	3,237	93,300	1.00	Ref.	1.00	Ref.
16–24	909	23,753	1.09	1.02, 1.18	1.11	1.03, 1.20
25	576	14,209	1.17	1.07, 1.28	1.19	1.09, 1.30
<i>P</i> -value, test for trend ^c			<i>P</i> <0.001		<i>P</i> <0.001	
Cumulative average CES-D score ^e						
<16	3,257	93,474	1.00	Ref.	1.00	Ref.
16–24	930	24,603	1.08	1.00, 1.16	1.10	1.02, 1.18
25	535	13,185	1.16	1.05, 1.27	1.18	1.07, 1.30
<i>P</i> -value, test for trend ^c			<i>P</i> <0.001		<i>P</i> <0.001	
CES-D in 1999 vs. 2005 ^d						
<16 in 1999 and 2005	652	21,486	1.00	Ref.	1.00	Ref.
<16 in 1999, 16–24 in 2005	115	2,798	1.29	1.06, 1.56	1.31	1.08, 1.60
<16 in 1999, 25 in 2005	42	1,259	1.03	0.76, 1.40	1.03	0.76, 1.41
16–24 in 1999, <16 in 2005	105	3,721	0.89	0.73, 1.09	0.90	0.74, 1.10
16–24 in 1999, 16–24 in 2005	61	1,746	1.09	0.84, 1.41	1.09	0.84, 1.42

Characteristic	Cases	Person-years	Age-adjusted model ^a		Multivariable model ^b	
			IRR	95% CI	IRR	95% CI
16–24 in 1999, 25 in 2005	36	969	1.18	0.85, 1.41	1.20	0.86, 1.67
25 in 1999, <16 in 2005	35	1,082	1.01	0.72, 1.42	1.00	0.71, 1.40
25 in 1999, 16–24 in 2005	37	1,045	1.10	0.79, 1.52	1.10	0.79, 1.53
25 in 1999 and 2005	61	1,274	1.46	1.13, 1.89	1.45	1.11, 1.88
Physician-diagnosed depression						
Never	4,154	117,794	1.00	Ref.	1.00	Ref.
Past	405	9,440	1.27	1.14, 1.40	1.25	1.13, 1.39
Current	163	4,029	1.12	0.96, 1.31	1.15	0.98, 1.34
Antidepressant use (for any indication)						
Never	4,309	121,419	1.00	Ref.	1.00	Ref.
Past	201	4,564	1.34	1.16, 1.54	1.32	1.14, 1.52
Current	212	5,279	1.13	0.98, 1.30	1.11	0.97, 1.28
Updated CES-D score and antidepressant use						
<16, never use	3,046	88,674	1.00	Ref.	1.00	Ref.
16–24, never use	812	21,166	1.11	1.02, 1.19	1.12	1.0, 1.21
25, never use	451	11,577	1.13	1.03, 1.25	1.16	1.05, 1.28
<16, past use	100	2,157	1.47	1.20, 1.79	1.45	1.19, 1.77
16–24, past use	54	1,190	1.43	1.09, 1.88	1.44	1.10, 1.89
25, past use	47	1,218	1.17	0.87, 1.56	1.17	0.87, 1.56
<16, current use	91	2,470	1.09	0.89, 1.35	1.07	0.87, 1.32
16–24, current use	43	1,395	0.88	0.65, 1.19	0.88	0.65, 1.19
25, current use	78	1,415	1.57	1.26, 1.97	1.56	1.26, 1.98

IRR, incidence rate ratio; CI, confidence interval.

^a Adjusted for age and questionnaire cycle.

^b Adjusted for age, questionnaire cycle, age at menarche, parity, age at first birth, years since last birth, age at first oral contraceptive use, history of oral contraceptive use, BMI, physical activity, smoking, current alcohol intake, participant's education, marital status, occupation, annual household income, region of residence.

^c *P*-value from Wald test of ordinal variable.

^d Restricted to period 2005–2011.

^e 1999 CES-D score carried forward for 470 cases and 14,266 person-years who did not complete 2005 CES-D score.

Table 3

Depressive symptoms and risk of uterine leiomyomata by selected factors, Black Women's Health Study in 1999–2011

Characteristic	Multivariable model ^a			
	Cases	Person-years	IRR	95% CI
Age <35				
Updated CES-D score				0.405
<16	782	23,960	1.00	Ref.
16–24	271	7,353	1.17	1.02, 1.35
25	162	4,669	1.11	0.94, 1.32
<i>P</i> -value, test for trend ^b			<i>P</i> =0.065	
Age 35				
Updated CES-D score				
<16	2,455	69,340	1.00	Ref.
16–24	638	16,400	1.09	1.00, 1.9
25	414	9,540	1.22	1.10, 1.36
<i>P</i> -value, test for trend ^b			<i>P</i> <0.001	
BMI <25				
Updated CES-D score				0.762
<16	1,077	30,881	1.00	Ref.
16–24	229	6,325	1.03	0.89, 1.19
25	149	3,621	1.18	0.99, 1.41
<i>P</i> -value, test for trend ^b			<i>P</i> =0.092	
BMI 25–29				
Updated CES-D score				
<16	1,035	28,713	1.00	Ref.
16–24	286	7,153	1.10	0.96, 1.26
25	166	3,969	1.18	1.00, 1.40
<i>P</i> -value, test for trend ^b			<i>P</i> =0.027	
BMI 30				
Updated CES-D score				
<16	1,125	33,706	1.00	Ref.

Characteristic	Cases	Person-years	Multivariable model ^a		
			IRR	95% CI	P-value, interaction
16-24	394	10,275	1.16	1.03, 1.30	
25	263	6,620	1.20	1.05, 1.38	
<i>P</i> -value, test for trend ^b			<i>P</i> =0.002		
Current smoking					0.601
Updated CES-D score					
<16	262	9,098	1.00	Ref.	
16-24	116	3,294	1.19	0.95, 1.49	
25	85	2,640	1.12	0.87, 1.44	
<i>P</i> -value, test for trend ^b			<i>P</i> =0.239		
Non-smoking					
Updated CES-D score					
<16	2,975	84,203	1.00	Ref.	
16-24	793	20,459	1.10	1.01, 1.19	
25	491	11,570	1.20	1.09, 1.32	
<i>P</i> -value, test for trend ^b			<i>P</i> <0.001		
Current hormonal contraceptive use					0.719
Updated CES-D score					
<16	2,470	71,090	1.00	Ref.	
16-24	714	18,326	1.12	1.03, 1.22	
25	460	11,196	1.20	1.08, 1.32	
<i>P</i> -value, test for trend ^b			<i>P</i> <0.001		
Never or former hormonal contraceptive use					
Updated CES-D score					
<16	767	22,211	1.00	Ref.	
16-24	195	5,427	1.08	0.92, 1.26	
25	116	3,014	1.16	0.94, 1.41	
<i>P</i> -value, test for trend ^b			<i>P</i> =0.123		

IRR, incidence rate ratio; CI, confidence interval.

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Adjusted for age, questionnaire cycle, age at menarche, parity, age at first birth, years since last birth, age at first oral contraceptive use, history of oral contraceptive use, BMI, physical activity, smoking, current alcohol intake, participant's education, marital status, occupation, annual household income, region of residence.

^b P-value from Wald test of ordinal variable.