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Highlights

Females with depression had a higher incidence of uterine leiomyoma (14.39% vs. 11.68%)

Depression linked to 17% higher uterine leiomyoma risk, up to 19.5% in recurrent cases

Findings highlight the need for leiomyoma screening in young females with depression

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Increased incidence of uterine leiomyoma in young females with depression: An observational study

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SUMMARY

Based on analyses of 22,487,947 person-years of follow-up data in a cohort of 2,523,565 young females, we found that the presence of depression was associated with a higher cumulative incidence of new-onset uterine leiomyoma than the absence of depression. This risk was even higher in patients with recurrent depression, and depression had a significant interaction with relatively old age and dyslipidemia. Screening for uterine leiomyoma is advisable in young females experiencing depression, as they appear to be at increased risk for developing this tumor type.

INTRODUCTION

Uterine leiomyoma is a solid, benign, hormone-dependent gynecological tumor.[1] The cumulative incidence of leiomyoma by age 50 is estimated to be between 50% and 80%.[2] Leiomyoma is usually asymptomatic, but 30% of patients suffer from vaginal bleeding, mass effects (e.g., pelvic pressure, back or abdominal pain), frequent urination, constipation, dysmenorrhea, sexual dysfunction, or infertility.[3] Leiomyoma can lead to adverse obstetric outcomes such as growth restriction, preterm birth, cesarean section, and antepartum hemorrhage.[3]

Medical treatment, iron supplementation, blood transfusion, interventional radiology, and surgery are options for treatment, which is based on symptoms, the possibility of future pregnancy, and the patient's desire to maintain her uterus.[2] One-third of hysterectomies worldwide are due to uterine leiomyoma. The annual cost of treating leiomyomas has been estimated to be $3.5–10.3 billion in the United States and $348 million in Germany (hospital costs).[4] Despite severe symptoms and the high cost of treatment, the risk factors for uterine leiomyoma have not been fully elucidated. Obesity, nulliparity, hypertension, late menopause, early menarche, family history of leiomyoma, and aging have been identified as risk factors for leiomyoma.[2]

Numerous investigations have documented elevated levels of emotional distress, depression, and anxiety among people diagnosed with leiomyoma, indicating that it might have a substantial influence on their overall quality of life.[5] It remains uncertain whether uterine leiomyoma induces depression. Given the adverse effects of uterine leiomyoma on patient health and the fact that the prevalence of depression in females is more than twice as high as in males, research to explore the association between these two conditions is needed. For this study, we used comprehensive data from a nationwide healthcare database to evaluate the risk associated with the inception of uterine leiomyoma.

RESULTS

Study baseline features

The data used in this study were sourced from the Korean National Health Insurance Service (K-NHIS) database and focused on young female adults in the Republic of Korea who underwent national health examinations between 2009 and 2012. Among the 6,891,400 individuals older than 20 years and younger than 40 years who received examinations, 2,755,790 were females. After excluding individuals diagnosed with hypothyroidism or uterine leiomyoma and those with missing data and incorporating a 1-year lag period, the finalized cohort contained 2,523,565 females (Figure 1).

In the comparison between females diagnosed with depression and those without, we observed that the former were older. Moreover, they exhibited a higher prevalence of diabetes, hypertension, dyslipidemia, and alcohol abuse (Table 1). While estimated glomerular filtration rates were notably lower in the depressed group compared with the non-depressed group, no clinically significant difference in chronic kidney disease (CKD) was apparent, likely attributable to age-related variations.

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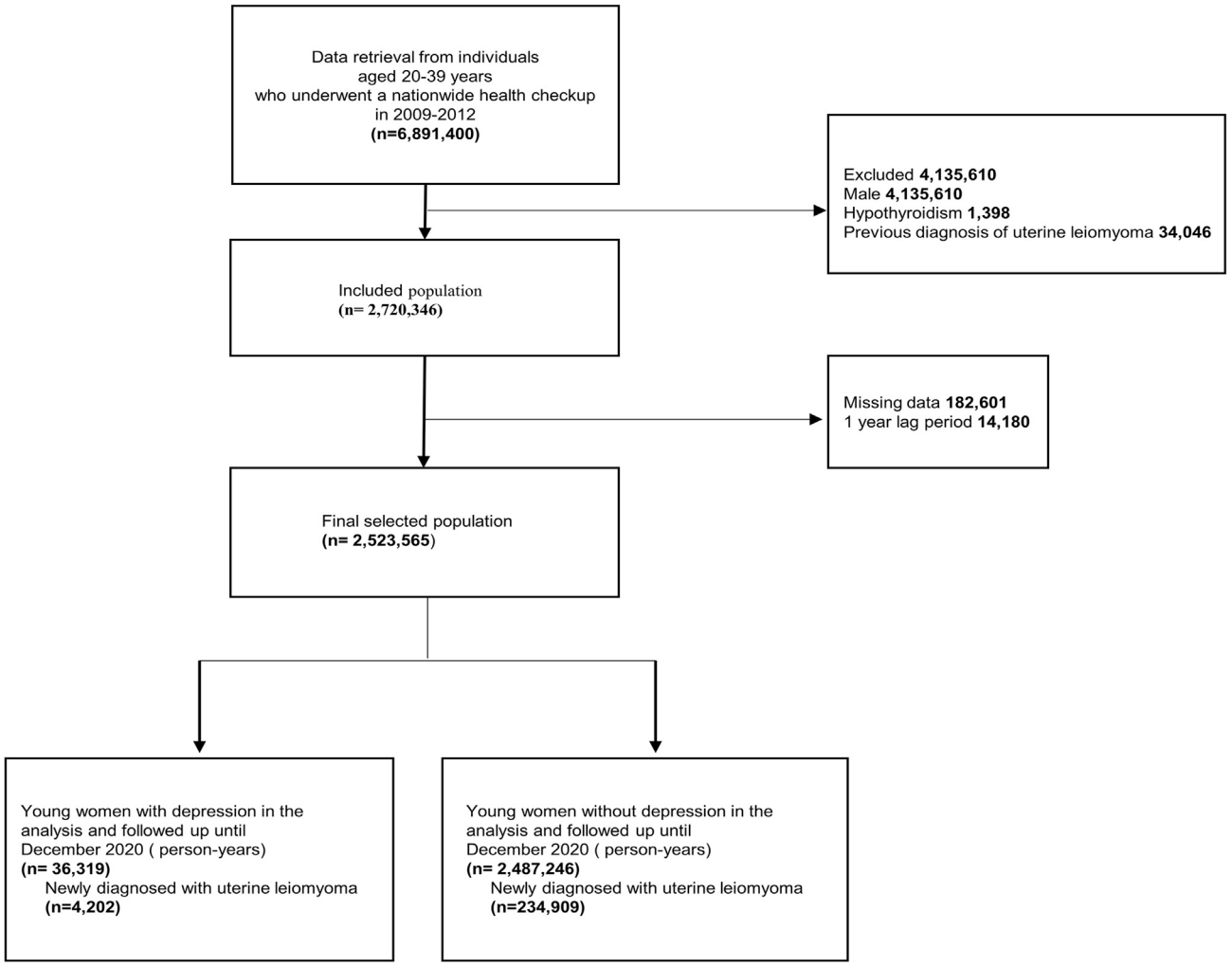

Figure 1. Related to study flowchart

Incidence of uterine leiomyoma

This study encompassed a follow-up period of 314,232 person-years for females with depression and 22,173,714 person-years for those without depression (Table 2). During follow-up, 234,909 (9.4%) of the 2,487,246 females without depression received an initial diagnosis of uterine leiomyoma, for an incidence of 13 cases per 1,000 person-years. The risk of newly developed uterine leiomyoma was notably higher in females with depression (hazard ratio [HR], 1.278; 95% confidence interval [CI], 1.24–1.318; $p < 0.001$) than in those without. Those with depression had an incidence rate of 13.37 per 1,000 person-years (4,202 incidents among a cohort of 36,319 individuals).

After multivariable adjustment for covariates, individuals with depression exhibited a 17.7% higher risk of developing uterine leiomyoma than those without depression (HR, 1.17; 95% CI, 1.14–1.21; $p < 0.001$). The Kaplan-Meier curve analysis revealed a markedly elevated cumulative occurrence of newly identified uterine leiomyoma in subjects experiencing depression compared with those without it (cumulative incidence, 14.39% vs. 11.68%; log rank $p < 0.0001$; Figure 2).

Repeated occurrences of depressive episodes

Among the 36,319 females diagnosed with depression, 11,493 were treated for repeated occurrences of depression. The incidence of new uterine leiomyoma in those who experienced more than two episodes of depression (incidence: 14.33 per 1,000 person-years) was notably higher than in both those with only one episode of depression (incidence: 12.93 per 1,000 person-years) and those without depression (incidence: 10.59 per 1,000 person-years) (Table 2). After multivariable adjustment, subjects with recurring depression exhibited a 19.9% higher risk (HR: 1.19; 95% CI: 1.13–1.26; $p < 0.001$) of developing new uterine leiomyoma than those without depression (Table 2; Figure 2). Furthermore, compared with subjects with a single episode of depression, those with recurrent episodes had a significantly heightened risk of new uterine leiomyoma (cumulative incidence: 15.27% vs. 14.00%; log rank $p < 0.0001$) (Table 2; Figure 2).

Table 1. Baseline demographic and clinical characteristics of the study cohort

Characteristic	No. of individuals (%) Without depression (*n* = 2,487,246)	With depression (*n* = 36,319)	*p* value
Age, mean, years (SD)	29.69 ± 5.22	30.88 ± 5.22	<0.0001
Age groups	NA	NA	<0.0001
<30 years	1,300,601 (52.29)	15,132 (41.66)	NA
≥30 years	1,186,645 (47.71)	21,187 (58.34)	NA
BMI, kg/m^2[a]	21.35 ± 3.25	21.51 ± 3.52	<0.0001
BMI category	NA	NA	<0.0001
<18.5	368,981 (14.83)	5,730 (15.78)	NA
<23	1,535,683 (61.74)	21,234 (58.47)	NA
<25	288,929 (11.62)	4,273 (11.77)	NA
<30	235,262 (9.46)	3,956 (10.89)	NA
≥30	58,391 (2.35)	1,126 (3.1)	NA
Smoking status	NA	NA	<0.0001
Non-smoker	2,252,198 (90.55)	30,671 (84.45)	NA
Former smoker	88,600 (3.56)	1,924 (5.3)	NA
Current smoker	146,448 (5.89)	3,724 (10.25)	NA
Drinking status	NA	NA	<0.0001
Non-drinker	1,353,951 (54.44)	20,499 (56.44)	NA
Mild drinker	1,073,855 (43.17)	14,608 (40.22)	NA
Heavy drinker	59,440 (2.39)	1,212 (3.34)	NA
Income, Lowest Q1[b]	728,576 (29.29)	12,005 (33.05)	<0.0001
Regular exercise	237,553 (9.55)	3,973 (10.94)	<0.0001
Diabetes mellitus	23,326 (0.94)	568 (1.56)	<0.0001
Hypertension	58,327 (2.35)	1,228 (3.38)	<0.0001
Dyslipidemia	92,064 (3.7)	1,847 (5.09)	<0.0001
CKD	68,772 (2.76)	1,059 (2.92)	0.0819
Proteinuria	47,467 (1.91)	762 (2.1)	0.0088
Waist circumference, cm, mean (SD)	70.63 ± 8.07	71.24 ± 8.59	<0.0001
SBP, mmHg	111.26 ± 11.53	111 ± 11.75	<0.0001
DBP, mmHg	69.86 ± 8.52	69.91 ± 8.7	0.1904
Fasting glucose, mg/dL	88.18 ± 13.21	88.86 ± 14.74	<0.0001
Total cholesterol, mg/dL	177.95 ± 30.85	179.96 ± 31.47	<0.0001
* Triglycerides, mg/dL	71.83 (71.79–71.87)	76.84 (76.46–77.23)	<0.0001
HDL -C, mg/dL	63.24 ± 23.59	63.1 ± 25.72	0.2326
LDL -C, mg/dL	99.18 ± 30.88	100.3 ± 32	<0.0001
eGFR, mL/min/1.73m^2	98.31 ± 41.23	97.73 ± 40.96	0.0081
* AST, IU/L	18.49 (18.49–18.5)	19.05 (18.99–19.11)	<0.0001
* ALT, IU/L	13.63 (13.62–13.64)	14.38 (14.31–14.45)	<0.0001
* r-GTP, IU/L	14.98 (14.97–14.99)	16.26 (16.17–16.35)	<0.0001

NA, not applicable.
SI conversion factor: to convert fasting glucose to mmol/L, this value was multiplied by 0.0555; to convert triglycerides levels to mmol/L, the obtained value was multiplied by 0.0113.
eGFR, estimated glomerular filtration rate.
[a]Calculated as weight in kilograms divided by height in meters squared.
[b]Q, quartile, Q1 represents the lowest income.

Table 2. Cox proportional hazards regression analysis of the association between depression and risk of new-onset uterine leiomyoma

Depression	No. of individuals	New-onset leiomyoma	Follow-up, person-years	Incidence rate	HR (95% CI)		
					Model 1	Model 2	Model 3
No	2,487,246	234,909	22173714.46	10.594	1(Ref.)	1(Ref.)	1(Ref.)
Yes	36,319	4,202	314232.45	13.3723	1.278 (1.240, 1.318)	1.176 (1.141, 1.213)	1.177 (1.141, 1.213)
Without recurrent episode	24,826	2,801	216503.8	12.9374	1.232 (1.187, 1.279)	1.166 (1.123, 1.210)	1.165 (1.122, 1.209)
With recurrent episode	11,493	1,401	97728.65	14.3356	1.381 (1.311, 1.456)	1.198 (1.137, 1.263)	1.199 (1.138, 1.264)

HR, hazard ratio.

Model 1: Non-adjusted.

Model 2: Adjusted for age.

Model 3: Model 2 plus adjustment for body mass index, income level, smoking status, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, waist circumference, SBP, fasting glucose, total cholesterol, triglycerides, LDL-C, AST, ALT, and r-GTP.

Subgroup analyses

A notable interplay among age, dyslipidemia, and depression was identified in the onset of uterine leiomyoma. Females aged 30 to 39 exhibited a 20% heightened risk of newly developed uterine leiomyoma associated with depression (adjusted HR, 1.20; 95% CI, 1.16–1.25) (Table 3). In contrast, females aged 20 to 29 with depression experienced only a 10% increased risk of new uterine leiomyoma (adjusted HR, 1.10; 95% CI, 1.04–1.17; p for interaction < 0.05). Moreover, the likelihood of new uterine leiomyoma rose by 36.3% in the group with both depression and dyslipidemia (adjusted HR, 1.30; 95% CI, 1.20–1.54), compared with 16.6% in the group with a normal lipid profile and depression (adjusted HR, 1.16; 95% CI, 1.13–1.20) (Table 3).

Time to uterine leiomyoma onset

The mean time to the onset of uterine leiomyoma in patients without depression was 5.56 $\pm$ 2.74 years, whereas in patients with depression, it was 5.42 $\pm$ 2.69 years (Table 4). The onset of uterine leiomyoma was thus significantly earlier, approximately 0.24 years, in patients with depression (Table 4).

DISCUSSION

For this study, we explored the correlation between a prior diagnosis of depression and an elevated likelihood of developing new uterine leiomyoma. We analyzed nationwide medical data sourced from a substantial cohort of 2,755,790 females for an extensive follow-up period totaling 22,487,947 person-years. A diagnosis of depression in young females exhibited a significant association with an increased risk of newly developed uterine leiomyoma (adjusted HR, 1.17; 95% CI, 1.14–1.21), and the presence of recurrent depression correlated with a heightened risk of uterine leiomyoma (adjusted HR, 1.20; 95% CI, 1.13–1.26). The subgroup analyses revealed noteworthy interactions among depression, advanced age, and dyslipidemia in those who developed uterine leiomyoma. The onset of uterine leiomyoma was significantly earlier in females with depression than in those without it.

Depression and uterine leiomyoma

To date, national population-based cohort investigations have predominantly discerned an elevated prevalence of depression in patients with uterine leiomyoma.[6,7] A retrospective cohort study in Taiwan conducted in 2017 revealed that the overall incidence of depression was 54% higher in subjects with uterine leiomyoma than in those without it (7.48 vs. 4.88/1,000 person-years, p < 0.001), yielding an HR of 1.46 (95% CI, 1.36–1.57).[7] Similar findings were recently reported in the United States, indicating a higher incidence of new-onset depression in females with uterine leiomyoma than those without it (HR, 1.12; 95% CI, 1.10–1.13).[6]

Conversely, a prospective study assessed self-reported uterine leiomyoma status based on the level of depressive symptoms.[8] In the Black Women's Health Study, subjects with higher depressive symptom scores were more likely than others to self-report uterine leiomyoma (HR, 1.25; 95% CI, 1.13–1.39). Moreover, the group using antidepressants, presumed to be associated with more severe depression, exhibited a higher incidence of uterine leiomyoma than the group not taking medication. In this context, our study underscores the clear association between depression and uterine leiomyoma, which we found by investigating the incidence of new-onset uterine leiomyoma during a 10-year period in females diagnosed with depression.

The mechanism underlying the connection between uterine leiomyoma and depression has not yet been fully elucidated, but an exploration of psycho-neuro-endo-immunology might provide valuable insights. Clinical manifestations of uterine leiomyoma, such as vaginal bleeding, dysmenorrhea, or chronic pelvic pain, might contribute to the development of stress and subsequent depression.[5] Individuals with uterine leiomyoma might harbor concerns about tumor growth, fertility, and other factors, potentially contributing to heightened stress levels. Shared neuroplasticity mechanisms between chronic pain and depression could involve a reduction in the activity of monoamine

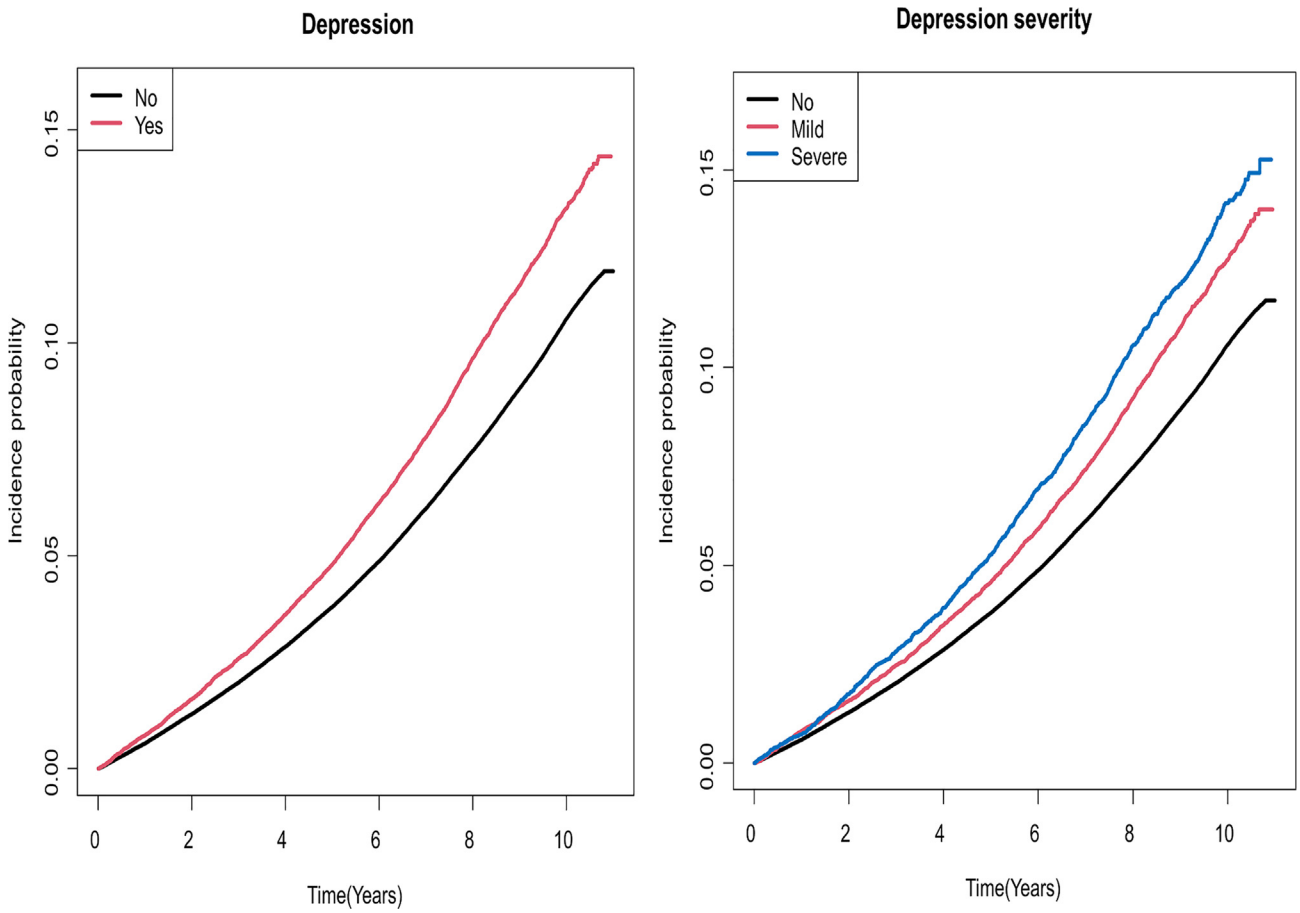

Figure 2. Related to risk of new-onset uterine leiomyoma according to presence/absence of depression

Left, risk of new-onset uterine leiomyoma was substantially higher in females with a diagnosis of depression. Right, women with recurrent episodes of depression had the highest risk of new-onset uterine leiomyoma.

neurotransmitters (e.g., serotonin, dopamine, etc.) and thereby influence brain-derived neurotrophic factor, glutamate, and their receptor subtypes.[9]

The link between depression and the onset of uterine leiomyoma was explored in studies focusing on the cannabinoid system, a neuromodulatory system crucial for orchestrating the appropriate behavioral responses essential for long-term survival and physical health. Dysfunction in that system can contribute to adverse emotional states such as anxiety and depression. Individuals with depression often demonstrate a decrease in cannabinoid receptor 1 (CB1R) signaling in brain regions associated with emotional processing, including the hippocampus, nucleus accumbens, prefrontal cortex, dorsal raphe nucleus, hypothalamus, and amygdala.[10] Surprisingly, analyses of tissues obtained from intrauterine leiomyoma, myometrium near the leiomyoma, and normal myometrium from patients with uterine leiomyoma revealed a reduction in the expression of CB1R in leiomyoma tissue.[11] The activation of cannabinoid receptors could have the potential to alleviate anxiety and be considered a prospective treatment option for leiomyoma in the future.

As a potential psycho-neurological dimension of the association between depression and uterine leiomyoma, sex steroid hormones, whose serological levels are known to vary between females with and without depression, might play a role in the development of leiomyoma.[12,13] In females with depression, a decrease in dopamine concentration, particularly that synthesized in the substantia nigra of the brain, leads to the inhibition of prolactin secretion.[14] That alteration inhibits the production of gonadotropin-releasing hormone in the parvocellular neurons of the hypothalamus, suppressing gonadotropin secretion in the pars distalis of pituitary gland and impairing sex hormone synthesis in the ovaries. Moreover, stress and fear, which are stimuli for prolactin secretion, further accentuate the suppression of the hypothalamic-pituitary-ovarian (HPO) axis and alter sex hormone levels. Previous studies have highlighted the association between psychological stressors, such as depression, and the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to hormone imbalances such as hypercortisolemia in plasma, cerebrospinal fluid, and urine.[15,16] Additionally, patients with depression often exhibit lower than normal levels of dehydroepiandrosterone sulfate.[17] Disruptions in the HPA axis can lead to disturbances in the HPO axis, potentially affecting the synthesis of sex steroid hormones. In this context, females experiencing depression tend to have lower serum levels of estradiol but higher levels of progesterone than non-depressed females, and progesterone might have a stimulatory influence on uterine leiomyoma.

Table 3. Subgroup analysis

	Hazard ratio (95% CI)[a]	*P* for interaction
Age		
<30 years	1.101 (1.037, 1.169)	0.0104
≥30 years	1.205 (1.163, 1.249)	
Obesity		
No	1.174 (1.135, 1.213)	0.7087
Yes	1.193 (1.103, 1.289)	
Smoking		
Non	1.165 (1.126, 1.204)	0.1388
Ex, Current	1.240 (1.149, 1.338)	
Drinking		
Non	1.179 (1.132, 1.228)	0.8695
Mild, Heavy	1.173 (1.120, 1.229)	
Regular exercise		
No	1.173 (1.135, 1.211)	0.6043
Yes	1.203 (1.100, 1.315)	
Diabetes mellitus		
No	1.177 (1.142, 1.214)	0.7228
Yes	1.127 (0.886, 1.434)	
Hypertension		
No	1.178 (1.141, 1.215)	0.7071
Yes	1.144 (0.987, 1.326)	
Dyslipidemia		
No	1.166 (1.130, 1.203)	0.0164
Yes	1.363 (1.204, 1.543)	
CKD		
No	1.178 (1.142, 1.215)	0.6
Yes	1.124 (0.943, 1.338)	

[a]Hazard ratios were adjusted for age, body mass index, income level, smoking status, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia and chronic kidney disease, waist circumference, SBP, fasting glucose, total cholesterol, triglycerides, LDL-C, AST, ALT, and r-GTP.

Immune mechanisms are also implicated in the pathogenesis of major depressive disorder (MDD) and are recognized as potential risk factors for uterine leiomyoma in people with childbearing potential.[18,19] Previous studies have demonstrated that individuals with depression exhibit an elevation in white blood cells and neutrophils but a decrease in T lymphocytes or B lymphocytes, resulting in an increased $CD4^+$ to $CD8^+$ T cell ratio compared with non-depressed individuals.[20] Depression might influence or be influenced by altered $CD4^+$ cell differentiation, with individuals experiencing MDD showing fewer Treg cells and an increase in TH1 cells and TH17 cells, compared with those without depression.[21] Moreover, leiomyoma patients, when compared with healthy controls, exhibit a notable increase in central memory CD4/CD8 T cells, Tregs, and Tfh cells, along with a decrease in natural killer (NK) and γδ T cells.[19] The current lack of research makes it premature to conclude that the immunological similarities between the two diseases could imply a causal relationship. Further studies are needed to elucidate the correlation between the simultaneous or sequential increase in prevalence.

It is conceivable that a shared health environment could play a role in both depression and leiomyoma development. Individuals experiencing depression often exhibit unfavorable health markers, socioeconomic characteristics, and unhealthy behaviors, such as a sedentary lifestyle, alcohol consumption, and poor diet, which could potentially contribute to risk factors associated with leiomyoma formation. Therefore, the association between leiomyoma and depression is likely to be bidirectional rather than following a linear sequential relationship.[6]

Age and dyslipidemia

Age is recognized as a predisposing factor for both depression and uterine leiomyoma.[2,22] Physical aging, coupled with hormonal fluctuations and imbalances, increased disease burden, and psychological stress stemming from heightened socioeconomic pressure, likely contributes to the observed associations among advanced age, depression, and uterine leiomyoma.[23] Fluctuations in estrogen levels in females have

Table 4. Time to uterine leiomyoma onset

	Depression, no	Depression, yes	*p* value
Mean ± SD	5.56 ± 2.74	5.42 ± 2.69	0.001
Median (Q1–Q3)	5.86 (3.40–7.79)	5.69 (3.33–7.58)	0.0108

been proposed as a mechanism contributing to the higher incidence of depression in females than males.[24,25] Notably, estrogen levels were found to be significantly lower in individuals with recurrent depression than in those with first-time depression.[26] The potential association between impaired estrogen homeostasis in depression and an elevated risk of developing uterine leiomyoma is an avenue for future research.

Dyslipidemia has been associated with both depression and uterine leiomyoma, with evidence derived from studies examining the effects of statins. Specifically, individuals with pre-existing hyperlipidemia who were not receiving statin treatment had a higher risk of new-onset depression than those without dyslipidemia.[25] Estrogen (estradiol), a steroid-derived hormone, and its receptors, particularly estrogen receptor-α, play crucial roles in the development and growth of uterine leiomyoma.[27] Simvastatin has been observed to modulate estrogen signaling in uterine leiomyoma by affecting the modification, movement, and breakdown of receptors.[28] These insights, drawn from studies of immunodeficient mice xenografted with human leiomyoma tissue explants, suggest that simvastatin might inhibit the growth of estrogen-hyper-responsive leiomyomas.

Gynecological disease and depression

Patients with endometriosis or adenomyosis, common estrogen-dependent gynecological disorders during reproductive age, exhibit higher prevalence rates of depression than control groups. Depression in endometriosis patients ranges from 9.8% to 98.5%, and depression affects up to 57.1% of adenomyosis patients.[29,30] Depression in these patients is associated with symptoms such as pain and infertility.

Studies have demonstrated electrophysiological changes in pain processing in mice with endometriosis, identifying numerous genes associated with pain, mobility, anxiety, and depression. Thus, pain sensitization, depression, and anxiety related to endometriosis might alter the electrophysiology of the brain.[31] Underlying genetic predispositions might contribute to the development of mental health disorders, including anxiety, in endometriosis patients. Koller et al. showed consistent genetic correlations between depression and endometriosis in a genome-wide association study and demonstrated significant associations with depression (OR, 1.09; 95% CI, 1.08–1.11) using linkage disequilibrium score regression and Mendelian randomization analyses.[32]

Research has shown that adenomyosis patients exhibit reduced expression of CB1 compared with those with uterine fibroids, suggesting that disruptions in the endocannabinoid system might contribute significantly to the increased prevalence of anxiety in adenomyosis patients.[33] Xu et al. proposed that norepinephrine, a neurotransmitter derived from sympathetic nerves, could promote the development of adenomyosis by activating receptors. Activation of presynaptic peripheral CB1 receptors inhibits the release of norepinephrine from sympathetic nerve terminals.[10]

The relationship between these disorders and changes in the pain-related nervous system remains unclear, as does the potential influence of genetic differences on the increased pain and depression prevalent with these conditions. Reports indicate that depression is not significantly alleviated even when pain is managed, and findings are mixed about the reduction of depression following surgical intervention for these conditions. Large-scale population studies are needed to further investigate the association between gynecological disorders and depression. It is also imperative to provide guidelines for assessing and addressing depression in patients diagnosed with these disorders.

Strengths and limitations of this study

One strength of this study is that our cohort comprised a large population from one country. A variety of blood tests, medical records, and health status indicators were collected regularly, and the same questionnaire was used. These elements distinguish our study from other claims-based studies. In the K-NHIS system, most patients treated for depression receive treatment prescriptions from licensed psychiatrists because antidepressant prescriptions require an ICD-10 code related to depression, and the prescription period is limited to two months for non-psychiatrists. This policy ensures the reliability of depression diagnoses and prevents the misdiagnosis of depression.

Our study also has certain limitations. First, we did not assess whether the symptoms observed were specifically attributed to uterine leiomyoma, consider the mass size, or account for treatment received. Second, reliance on insurance claims with ICD-10 codes for uterine leiomyoma might have led to an underestimation of leiomyoma incidence, particularly if abdominal and pelvic imaging tests were not conducted. Third, we could not differentiate between persistent and recurrent depression. Fourth, because the K-NHIS database primarily contains data from Northeast Asians, the generalizability of our findings to other racial and ethnic groups might be limited.

Conclusion

A significant association was identified between depression and the occurrence of newly developed uterine leiomyoma in young females from a nationwide Korean health examination cohort. Notably, an exposure-response relationship was observed, indicating that recurring depression was linked to a heightened risk of developing new leiomyoma compared with a single episode of depression. These findings underscore the importance of medical attention and monitoring for new-onset uterine leiomyoma in young females presenting with suspected or

diagnosed depression. Additionally, the potential effects of depression treatment on reducing the risk of leiomyoma development or mitigating the growth and progression of existing leiomyoma warrant further investigation.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Mee-Ran Kim (drmrkim@gmail.com).

Materials availability

This study did not generate new unique materials.

Data and code availability

- The data mentioned in this paper is publicly available from the K-NHIS.
- All the codes are available online at Github and are fully publicly available as of the date of publication. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.
- The data are available from the Korean National Health Insurance Sharing Service (NHISS; https://nhiss.nhis.or.kr/) database which is open to researchers on request with approval by the IRB.

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The funders of this study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

A.L. and K.H. served as co-first authors and contributed to the study design and data interpretation. A.L. contributed to writing of the first draft of the manuscript. K.H. contributed to statistical analysis. J.S., S.K., D.K., J.N., M.K., and Y.-J.C. was involved in critical revision of the manuscript for important intellectual content and administrative support. A.L. and J.Y. was involved in obtained funding. M.-R.K. and J.Y. supervised the entire project. All authors reviewed or revised the manuscript and approved the final manuscript for submission.

DECLARATION OF INTERESTS

All authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- METHOD DETAILS
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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
the Korean National Health Insurance Service (K-NHIS)	–	https://www.nhis.or.kr/english/index.do

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This work was limited to human subjects. The total number of 2,523,565 participants (patients and controls) was divided into females with depression and those without. Throughout the text, when sex is mentioned, the term sex assigned at birth is meant. Age ranged from 20 to 40 years. All participants originated from the South Korea. Other racial or ethnic information was not registered. More details are presented in Table 1. Approval to use the K-NHIS database was granted by the government's official review committee, and the institutional review board of St. Vincent's Hospital, Catholic University of Korea granted approval for this study (Approval No. SSU-202007-HR-236-01). In consideration of its retrospective design, the study was exempted from the requirement for informed consent.

METHOD DETAILS

Patient recruitment and sample collection

The data for this study were sourced from the K-NHIS. The Korean government mandates health insurance for the entire populace, around 51 million individuals, so the K-NHIS database stands as a comprehensive representation of the entire South Korean population. The database includes results from routine health examinations conducted uniformly at specific time points, incorporating health indicators, laboratory test outcomes, and surveys on social habits. Additionally, it contains comprehensive details such as members' medical expenses, hospitalization and outpatient treatment records, prescription-dispensing data, insurance claims, and income level information. Diagnostic coding within this database adheres to the International Statistical Classification, 10th Revision (ICD-10) codes.

Approval to use the K-NHIS database was granted by the government's official review committee, and the institutional review board of St. Vincent's Hospital, Catholic University of Korea granted approval for this study (Approval No. SSU-202007-HR-236-01). In consideration of its retrospective design, the study was exempted from the requirement for informed consent.

Study population

Our study cohort comprised individuals who, between 2009 and 2012, underwent a health examination offered nationwide in the Republic of Korea. Screening encompassed the period from January 1, 2002, to the examination day to establish a baseline medical history for each participant. We excluded individuals who met the following conditions: (1) male sex assigned at birth, (2) age less than 20 years or more than 40 years, (3) a history of hypothyroidism, or (4) a prior diagnosis of uterine leiomyoma. Patient follow-up extended from January 1, 2009, to December 31, 2020.

Principal endpoint and definitions

The principal endpoint in this study was the incidence of newly emerging uterine leiomyoma during the follow-up period. Uterine myoma was discovered and diagnosed through imaging tests such as pelvic sonograms, computed tomography scans, magnetic resonance imaging, and positron emission tomography-computed tomography, which were conducted by physicians, including gynecologists, and interpreted by radiologists. New uterine leiomyoma were detected in this study as (1) the presence of two or more outpatient claims featuring ICD-10 codes for uterine leiomyoma or (2) one or more inpatient claims incorporating ICD-10 codes for uterine leiomyoma.

During health examinations, depression is diagnosed through a semi-structured interview conducted by a physician using scales such as the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, the Mini International Neuropsychiatric Interview, or the Schedule for Affective Disorders and Schizophrenia, and an ICD-10 code is assigned. In this study, a diagnosis of depression was established when there was an insurance claim with an ICD-10 code for depression within the 12 months preceding the health examination conducted between 2009 and 2012. Recurrent depression, indicative of a more severe form of the disease, was defined by the presence of additional claims with ICD-10 codes for depression within 12 months after the national health examination. The specific ICD-10 codes used in this study are outlined in Table S1.

Diabetes was identified as a fasting blood glucose level $\geq$126 mg/dL; hypertension was defined as systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg; dyslipidemia was defined as a total cholesterol level $\geq$240 mg/dL; and CKD was diagnosed as an estimated glomerular filtration rate of <60 mL/min/1 · 73 m^2. Each condition was identified by a claim featuring an ICD-10 code from a physician and the prescription of medication. Individuals classified as "current smokers" were those who had consumed a minimum of 100

cigarettes during their lifetime and reported smoking within one month before their health examination. Heavy drinkers were characterized as individuals who regularly consumed 30g or more of alcohol per week. Regular physical activity was identified as the completion of high-intensity exercise (such as running, climbing, or intense cycling) more than 3 days a week or moderate-intensity exercise (such as brisk walking, tennis, or moderate bicycle activities) more than five days a week.

QUANTIFICATION AND STATISTICAL ANALYSIS

To compare continuous variables we used Student's t-test and present means ± standard deviations, whereas we assessed categorical variables with the χ^2 test, as appropriate. A Cox proportional hazards regression analysis was used to compute unadjusted and adjusted HRs with 95% CIs. In the multivariable analysis, three models were applied: model 1 remained unadjusted, model 2 accounted for age alone, and model 3 incorporated adjustments for age, body mass index (BMI), income level, smoking status, alcohol consumption status, regular physical activity, diabetes, hypertension, dyslipidemia, and CKD. Covariate selection in the multivariable models was based on risk factors for uterine leiomyoma established in previous studies or significant differences reported between subjects in this cohort with and without depression.[34] The Kaplan-Meier curve analysis assessed the cumulative incidence of new uterine leiomyoma, comparing individuals with and without depression using the log rank test. The baseline time for both the Cox proportional hazards regression and Kaplan-Meier curve analysis was defined as the days between the 2009 and 2012 nationwide health examinations for all study participants. Censoring occurred for individuals who (1) passed away, (2) were no longer followed up by the K-NHIS due to immigration or administrative reasons, or (3) experienced new-onset uterine leiomyoma (primary study outcome). All statistical tests were two-tailed, and significance was set at $P \leq \cdot 05$. SAS software (version 9 · 2; SAS Institute Inc.) was used to conduct the statistical analyses.