

Risk of Mental Disorders in Polycystic Ovary Syndrome: Retrospective Cohort Study of a Korean Nationwide Population-Based Cohort

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Purpose: Polycystic Ovary Syndrome (PCOS) is one of the most common gynecological endocrine conditions, affecting both the physical and mental health, and the quality of life of women. PCOS was associated with diverse mental disorders but studies in Korean populations were limited. This study aims to investigate the risk of mental disorders in PCOS patients in Korea.

Patients and Methods: We evaluated the risk of five mental disorders in PCOS patients using health insurance billing data from the National Health Insurance Corporation. We selected 188,973 PCOS patients and 412,022 control individuals. Prevalence, cumulative incidence, and Hazard ratios (HR) were calculated for each mental disorder.

Results: We found PCOS patients to have increased prevalence of depressive disorders (Odds ratios (OR) 1.208[1.185–1.232]), bipolar disorders (OR 1.403[1.330–1.479]), and anxiety disorders (OR 1.089[1.064–1.114]); however, PCOS patients also had lower prevalence of schizophrenia (OR 0.686[0.638–0.737]) and sleep disorder (OR 0.911[0.888–0.935]). The PCOS patients exhibited a significantly greater HR in depressive disorder (adjusted HR 1.244[1.148–1.347]), bipolar disorder (adjusted HR 1.502[1.139–1.981]), anxiety disorder (adjusted HR 1.147[1.050–1.252]), and sleep disorder (adjusted HR 1.228[1.112–1.356]).

Conclusion: Our results suggest that PCOS patients have increased risk of depressive disorders, bipolar disorders, anxiety disorders, and sleep disorders. This study supports international PCOS guidelines that recommend screening for mental health disorders.

Keywords: depressive disorder, bipolar disorder, anxiety disorders, schizophrenia, sleep wake disorders

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common hormonal disturbances, affecting an estimated 8–13% of women of reproductive age.¹ PCOS is a multifaceted disease influenced by genetic, endocrine, environmental, and behavioral factors, resulting in a heterogeneous phenotype with reproductive, metabolic, and psychological effects on women's health and quality of life throughout life.² The Rotterdam Criteria, the most widely used diagnostic criteria for PCOS, requires at least two of three conditions be met to confirm the diagnosis: clinical or biochemical hyperandrogenism, evidence of oligo-anovulation, and/or polycystic appearing-ovarian morphology on ultrasound, with the exclusion of other relevant disorders.³

Mental disorders are a significant public health burden and are associated with, but not limited to, socioeconomic status, race/ethnicity, life events, genes, and stress.⁴ Mental and physical health conditions are common comorbidities⁵ and, affect each other both directly and indirectly.⁶ PCOS is related to mental disorders in several ways.⁷ Previous studies have demonstrated associations between PCOS and various mental disorders.^{8–13} Another study suggested that distinguishing PCOS and mental disorder could be challenging, given the significant overlap between the symptoms of PCOS and side effects of antipsychotic drugs (for example, menstrual irregularity, amenorrhea, weight gain).¹⁴ The 2023 International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome recommends that all healthcare professionals be aware of common psychological features that are important components of PCOS.¹⁵

Previous studies have shown the prevalence of PCOS,¹⁶ of type 2 diabetes mellitus with PCOS,¹⁷ and of impairment of glucose tolerance in PCOS patients¹⁷ differs among ethnicities. These findings suggest that the associations between PCOS and mental disorders might differ among ethnicities; however, there have been few studies assessing the risk of mental disorders in PCOS patients in the Korean population. A previous study investigating the prevalence of PCOS in Korean women of reproductive age indicated the need to examine the psychological problems associated with PCOS.¹⁸ We could find only one retrospective cohort study of Korean PCOS patients, which only covered major depressive disorder.¹⁹

We aimed to evaluate the risk of schizophrenia, depressive disorder, bipolar disorder, anxiety disorder, and sleep disorder in PCOS patients using billing data from Korea. We intended to clarify the relationship between PCOS and mental disorders within the Korean population and to contribute to PCOS-related research worldwide.

Materials and Methods

Study Design

This was a retrospective cohort study that utilized a nationwide population-based database. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Catholic Medical Center (IRB number: PC22ZISI0075). Patient consent was waived because individual patients cannot be identified within the database.

Data Source

We used the Korean health insurance claims data provided by the National Health Insurance Corporation (NHIC) from 2002 to 2020 (Database number: NHIS-2023-1-012). International Classification of Diseases, 10th revision (ICD-10) was used to identify PCOS, mental disorders, and comorbidities from the data.

Study Population

The process of selecting the study population is depicted in [Figure 1](#). Among 1,641,735 individuals, we identified individuals with a history of PCOS using ICD-10 code E.28.2 (n=328,347). We excluded individuals who were younger than 11 or older than 60 years of age at the initial PCOS diagnosis (N=365), initially diagnosed with PCOS before 2004 or after 2017 (N=109,069), or who had been diagnosed with Cushing's syndrome (E24), hyperprolactinemia (E22.1), or adrenogenital disorders (E25.0) (N = 13,214).

Our exclusion criteria were to clarify the impact of PCOS on mental health and ensure data quality. Since such exclusions would inevitably result in data loss, we established criteria to ensure that minimal data could be excluded. We assumed that if the initial diagnosis age of PCOS was not between 11 and 60 years, it was likely to be a misdiagnosis or an outlier. Since the registered data were limited from 2002 to 2020, analysis of data beyond this range was not feasible. Hence, individuals initially diagnosed with PCOS from 2004 to 2017 were chosen for this study to ensure a minimum of two years of pre- and post-diagnosis medical history. For those initially diagnosed with PCOS in 2002 or 2003, verifying the accuracy of their initial diagnosis is challenging due to the inability to access past medical records. As the data only extended to 2020, our understanding of the post-diagnosis medical history was limited for those initially diagnosed after 2017. We excluded patients with hormonal diseases having symptoms similar to PCOS to study the impact of PCOS on mental health clearly.

The control group was randomly selected from individuals without PCOS and was matched 1:3 with PCOS patients using propensity matching according to age and index year. The index date for PCOS patients was their initial PCOS diagnosis, while that for the control group was the first medical record of the assigned index year. In conclusion, 188,973 PCOS patients and 412,022 control individuals were selected.

Baseline Characteristics

The follow-up duration for this study was the period between the index date and the day we stopped tracking, which is the date of death for individuals who died before 2021, or December 31, 2020 for individuals who did not die before 2021.

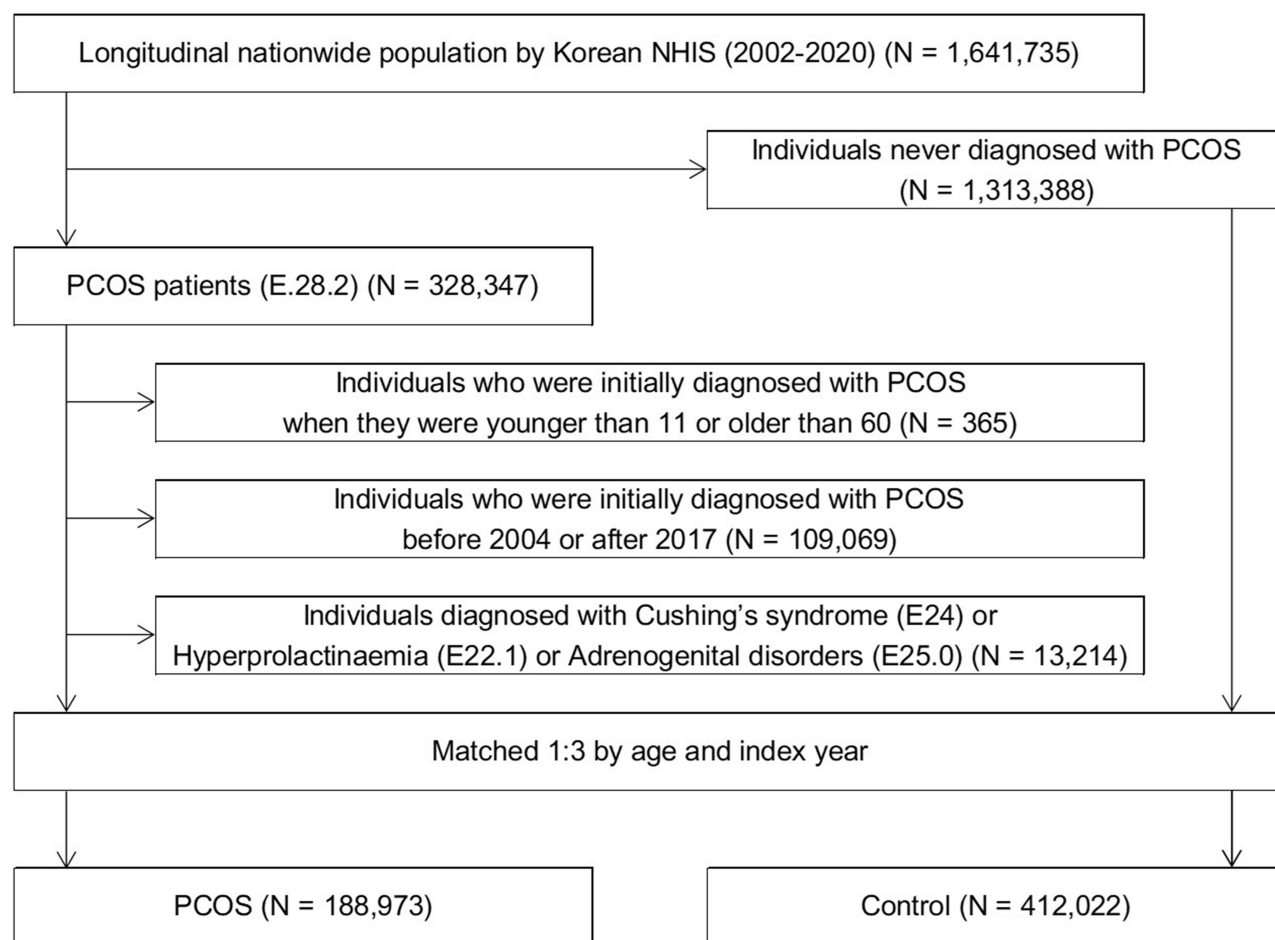


Figure 1 Flowchart of Included Participant.

Abbreviations: NHIS, National Health Insurance Services; PCOS, polycystic ovary syndrome.

Baseline comorbidities evaluated in this study were dyslipidemia (ICD-10 code: E78), hypertension (I10–I15), and diabetes mellitus (E10–E14). To be counted as having comorbidity, at least one hospitalization or two outpatient visits due to such disease was required.

We used medical check-up records for the index year in the analyses. Individuals who were current or previous smokers on the date of medical check-up were classified as having a smoking history. Non-smokers were those who had never smoked at the time of medical check-up. Individuals who consumed alcohol three or more times per week were classified as consuming alcohol frequently. Individuals were categorized based on their body mass index (BMI): underweight ($\text{BMI} < 18.5\text{kg/m}^2$), healthy weight ($20\text{kg/m}^2 \leq \text{BMI} < 25\text{kg/m}^2$), healthy weight ($25\text{kg/m}^2 \leq \text{BMI} < 30\text{kg/m}^2$), or obese ($\text{BMI} \geq 30\text{kg/m}^2$).

Definition of Mental Disorder

Schizophrenia (ICD-10 codes: F20), depressive disorder (F32, F33, F34.1), bipolar disorder (F30, F31), anxiety disorder (F40, F41, F42, F43.0, F43.1), and sleep disorders (F51, G47) were noted in the subjects of this study. For an individual to be identified as having a mental disorder, their medical records had to include at least one hospitalization or two outpatient visits due to such disorders. Mental disorders diagnosed one year or more after the individual's index date were considered for incidence calculation.

Statistical Analysis

The characteristics of PCOS patients and controls were described using appropriate summary statistics. For continuous variables, the mean, standard deviation (SD), median, and quartiles were used. For categorical variables, frequencies and percentages were used.

Differences between PCOS patients and controls were assessed using appropriate statistics. For continuous variables, Student's *t*-test was used. For categorical variables, Chi-square tests were performed, and odds ratios (OR) with 95% confidence intervals (CIs) were calculated. The cumulative incidence of each mental disorder was calculated using the Kaplan-Meier method and compared between the case and control groups. For each mental disorder, unadjusted hazard ratio (HR) and HR adjusted for factors including age, diabetes, hypertension, dyslipidemia, BMI, smoking history, and alcohol intake frequency were calculated using univariate and multivariate Cox proportional hazards regression. Additionally, we calculated and compared HRs between subgroups of the study population: obese and non-obese individuals; individuals aged less than 35 and aged 35 or older. For sensitivity analysis, we calculated HRs in absence of individuals having smoking history or taking alcohol frequently. All data analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC). A *p*-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Comparisons of the baseline characteristics of the PCOS patients and controls are presented in Table 1. The mean age was 26.36 (SD 6.11) years for PCOS patients and 35.02 (SD 6.89) years for the controls, while the median age was 26 (interquartile range 22 to 30) years for PCOS patients and 35 (interquartile range 30 to 39) years for the controls. Among

Table 1 Baseline Characteristics of PCOS Patients and Controls

	PCOS (N=188,973)	Control (N=412,022)	P value
Age (years), mean (SD)	26.36 (6.11)	35.02 (6.89)	<0.05
Age (years), median (q1–q3)	26 (22–30)	35 (30–39)	
Age group, n (%)			<0.05
10–19	23,343 (12.35)	2,632 (0.64)	
20–29	114,601 (60.64)	83,370 (20.23)	
30–39	46,285 (24.49)	226,071 (54.87)	
40–49	4,685 (2.48)	86,849 (21.08)	
50–60	59 (0.03)	13,100 (3.18)	
Follow-up duration (years), mean (SD)	8.57 (3.91)	8.69 (3.81)	<0.05
Comorbidities, n (%)			
Dyslipidemia	68,923 (36.47)	152,276 (36.96)	<0.05
Hypertension	14,709 (7.78)	45,970 (11.16)	<0.05
Diabetes mellitus	29,318 (15.51)	58,314 (14.15)	<0.05
Medical check-up record on their index year, n(%)	33,652 (17.81)	98,167 (23.83)	
Smoking history, n (%)	3,365 (10.07)	7,300 (7.49)	<0.05
Frequent alcohol intake, n (%)	2,184 (6.52)	5,775 (5.91)	<0.05
Physical measurement			
Waist circumference (cm), mean (SD)	71.94 (8.77)	72.88 (8.11)	<0.05
Body mass index (kg/m ²), mean (SD)	22.13 (4.08)	22.15 (3.48)	0.30
Body mass index group, n (%)			<0.05
Underweight	4,399 (13.08)	9,527 (9.71)	
Healthy weight	22,908 (68.10)	71,585 (72.96)	
Overweight	4,350 (12.93)	13,597 (13.86)	
Obese	1,981 (5.89)	3,401 (3.47)	

(Continued)

Table 1 (Continued).

	PCOS (N=188,973)	Control (N=412,022)	P value
Laboratory test results, mean (SD)			
Systolic blood pressure (mmHg)	111.60 (11.72)	113.20 (12.66)	<0.05
Diastolic blood pressure (mmHg)	70.16 (8.76)	71.24 (9.20)	<0.05
Fasting blood sugar (mg/dL)	88.93 (13.85)	91.06 (15.42)	<0.05
Serum glutamic oxaloacetic transaminase (IU/L)	21.25 (12.62)	20.41 (10.47)	<0.05
Serum glutamic pyruvate transaminase (IU/L)	19.07 (19.23)	16.91 (13.81)	<0.05
Gamma-glutamyl transferase (U/L)	20.24 (19.89)	19.11 (19.85)	<0.05
Total cholesterol (mg/dL)	184.80 (33.03)	186.10 (33.60)	<0.05
Triglycerides (mg/dL)	95.80 (66.09)	91.75 (60.09)	<0.05
High-density lipoprotein (mg/dL)	65.06 (20.07)	62.92 (18.53)	<0.05
Low-density lipoprotein, calculated (mg/dL)	102.00 (30.04)	107.60 (30.81)	<0.05

Abbreviations: PCOS, polycystic ovary syndrome; SD, standard deviation.

the PCOS patients, those aged 20–29 years comprised the largest age group ($n = 114,601$, 60.64%), while that of the controls was 30–39 years ($n = 226,071$, 54.87%). The mean follow-up duration was 8.57 years (SD 3.91) for PCOS patients and 8.69 years (SD 3.81) for the controls.

In both PCOS patients and controls, the most common comorbid conditions were dyslipidemia ($n = 68,923$ and $n = 152,276$, respectively), followed by diabetes mellitus ($n = 29,318$ and $n = 58,314$) and hypertension ($n = 14,709$ and $n = 45,970$).

The number of individuals with medical check-up records in the index year was 33,652 (17.81%) for PCOS patients and 98,167 (23.83%) for the controls. The number of individuals with a smoking history was 3,365 (10.07%) for PCOS patients and 7,300 (7.49%) for the controls. The number of individuals who consumed alcohol more than three times a week was 2,184 (6.52%) for PCOS patients and 5,775 (5.91%) for the control group. The mean BMI was 22.13 kg/m² (SD 4.08) for PCOS patients and 22.15 kg/m² (SD 3.48) for controls. In both PCOS patients and controls, most individuals were of healthy weight ($n = 22,908$ and $n = 71,585$, respectively). The differences between all laboratory test results of PCOS patients and controls were significant. The numbers and proportion of individuals in subgroups are shown in [Supplementary Tables 1](#) and [2](#), and those of individuals with or without a history of smoking or frequent alcohol consumption are presented in [Supplementary Table 3](#).

Prevalence of Mental Disorders in PCOS

The prevalence of mental disorders in the PCOS patients and controls is presented in [Table 2](#) and [Figure 2](#). The PCOS patients had significantly greater prevalence of depressive disorder (OR: 1.208, 95% CI = 1.185–1.232), bipolar disorder (OR: 1.403, 95% CI = 1.330–1.479), and anxiety disorder (OR: 1.089, 95% CI = 1.064–1.114) than controls; however, PCOS patients had a significantly lower prevalence of schizophrenia (OR: 0.686, 95% CI = 0.638–0.737) and sleep disorders (OR: 0.911, 95% CI = 0.888–0.935).

Cumulative Incidence of Mental Disorders in PCOS

The incidence of depressive disorders, bipolar disorders, anxiety disorders, and sleep disorders in PCOS patients was significantly greater than in controls ([Figure 3](#), Log-rank test P -value < 0.05), while the incidence of schizophrenia did not differ significantly between PCOS patients and controls (Log-rank test P -value: 0.69).

Hazard Ratios for the Incidence of Mental Disorders in PCOS

The results of Cox proportional-hazards regression analyses are presented in [Table 3](#) and [Figure 4](#). The PCOS patients exhibited significantly greater HRs for depressive disorder (unadjusted HR: 1.443, 95% CI: 1.405–1.483; adjusted HR: 1.244, 95% CI: 1.148–1.347), bipolar disorder (unadjusted HR: 1.779, 95% CI: 1.651–1.916; adjusted HR: 1.502, 95% CI: 1.139–1.981), anxiety disorder (unadjusted HR: 1.228, 95% CI: 1.191–1.266; adjusted HR: 1.147, 95% CI: 1.050–1.252),

Table 2 Prevalence of Mental Disorders Among PCOS Patients and Controls

	PCOS (N =188,973)	Control (N =412,022)	Odds Ratio (95% CI)	P value
Schizophrenia	976 (0.52)	3,097 (0.75)	0.686 (0.638–0.737)	<0.05
Depressive disorder	17,550 (9.29)	32,183 (7.81)	1.208 (1.185–1.232)	<0.05
Bipolar disorder	2,275 (1.20)	3,549 (0.86)	1.403 (1.330–1.479)	<0.05
Anxiety disorder	11,861 (6.28)	23,878 (5.80)	1.089 (1.064–1.114)	<0.05
Sleep disorder	8,530 (4.51)	20,319 (4.93)	0.911 (0.888–0.935)	<0.05

Abbreviations: PCOS, polycystic ovary syndrome; CI, confidence interval.

and sleep disorder (unadjusted HR: 1.062, 95% CI: 1.026–1.099; adjusted HR: 1.228, 95% CI: 1.112–1.356). However, for schizophrenia, HRs were not significant (unadjusted HR: 0.974, 95% CI: 0.858–1.107; adjusted HR: 0.717, 95% CI: 0.427–1.204).

In the subgroup analysis based on obesity, presented in [Supplementary Table 4](#), non-obese PCOS patients exhibited higher HRs for the four mental disorders, excluding schizophrenia, which were similar to the HRs in the total study population. In contrast, all adjusted HRs for obese PCOS patients were insignificant. In the subgroup analysis based on age, presented in [Supplementary Table 5](#), PCOS patients aged less than 35 showed higher HRs for the four mental disorders, excluding schizophrenia. However, PCOS patients aged 35 or older exhibited higher HRs only for depressive disorder and sleep disorder. Sensitivity analysis, presented in [Supplementary Table 6](#), yielded results consistent with the main findings, showing that PCOS patients had significantly higher adjusted HRs for depressive disorder, bipolar disorder, anxiety disorder, and sleep disorder.

Discussion

In a regression model adjusted for age, diabetes mellitus, hypertension, dyslipidemia, BMI, smoking history, and alcohol intake frequency, PCOS patients had a 1.244–fold greater incidence of depressive disorder, 1.502–fold greater incidence of bipolar disorder, 1.147–fold greater incidence of anxiety disorder, and 1.228–fold greater incidence of sleep disorder than the general population. The prevalence of depressive disorder, bipolar disorder, and anxiety disorder was greater in

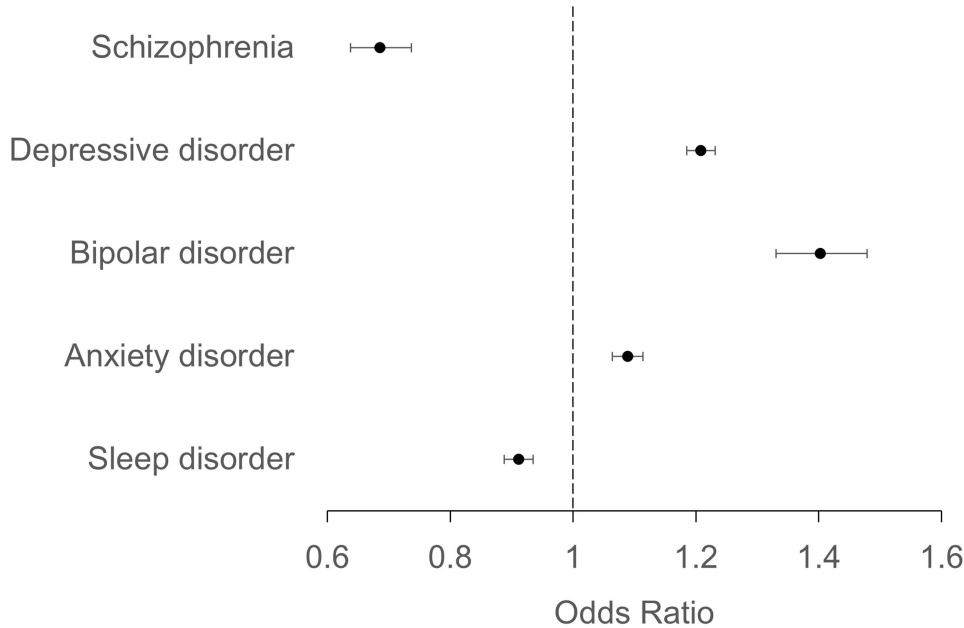


Figure 2 Hazard Ratios for Incidence of Mental Disorders in PCOS Patients.

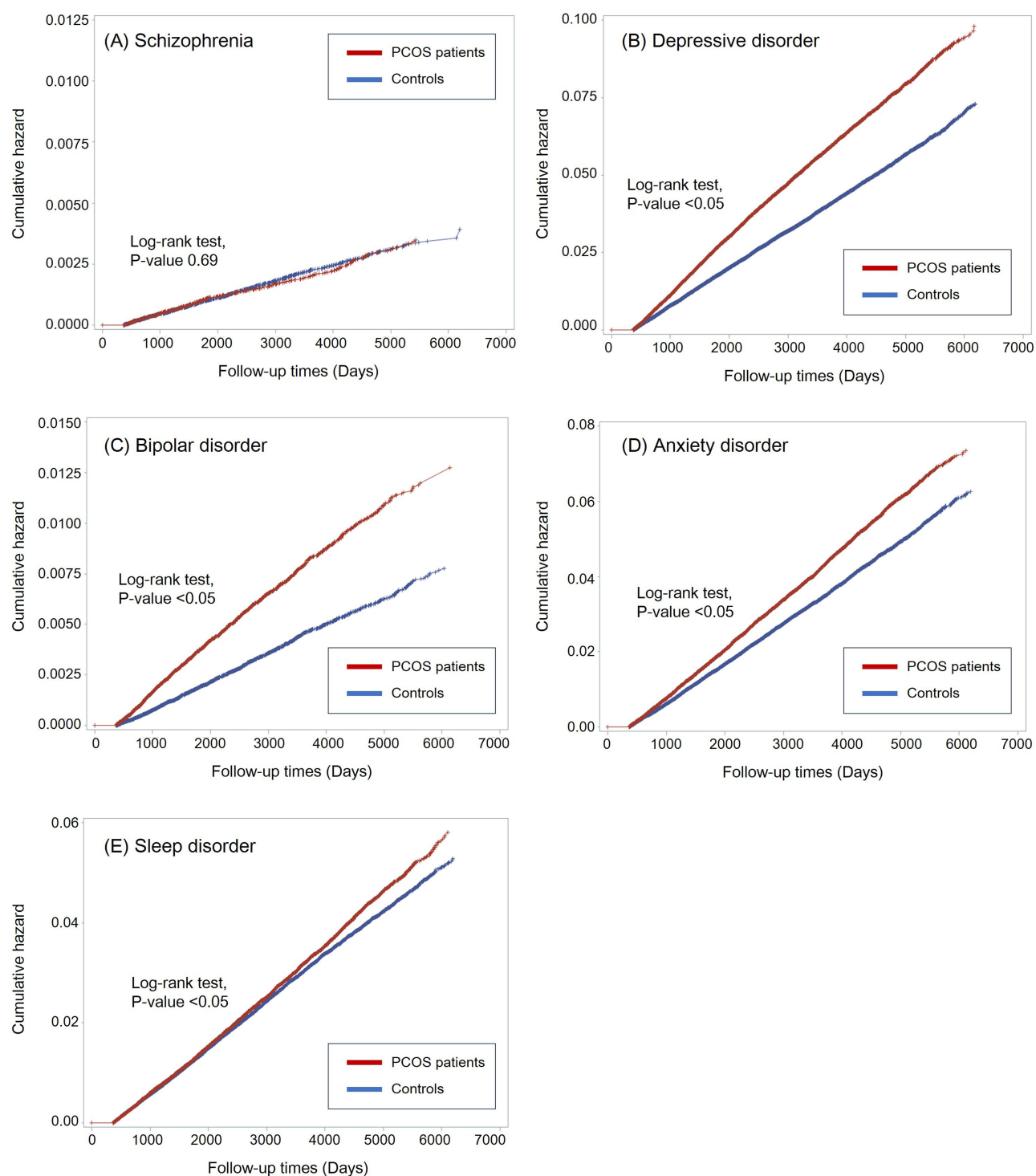


Figure 3 Cumulative Incidence of Mental Disorders in PCOS Patients and Controls: (A) Schizophrenia, (B) Depressive disorder, (C) Bipolar disorder, (D) Anxiety disorder, (E) Sleep disorder.

PCOS patients than in the general population, while the prevalence of schizophrenia and sleep disorders was lower in PCOS patients than in the general population.

We adjusted several factors before calculating HR to clarify the association between PCOS and mental disorders. We considered three chronic medical conditions related to the common metabolic features of PCOS² for calculation, as chronic medical conditions have been associated with mental disorders.⁴ DM was associated with various mental

Table 3 Hazard Ratios for Incidence of Mental Disorders in PCOS Patients

	Total Numbers	Number of Events (%)	Unadjusted		Adjusted*	
			Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Schizophrenia (F20)						
Control	409,701	776 (0.19)	I (Reference)		I (Reference)	
PCOS	188,339	342 (0.18)	0.974 (0.858–1.107)	0.69	0.717 (0.427–1.204)	0.21
Depressive disorder (F32, F33, F34.1)						
Control	393,143	13,304 (3.39)	I (Reference)		I (Reference)	
PCOS	180,017	8,594 (4.78)	1.443 (1.405–1.483)	<0.05	1.244 (1.148–1.347)	<0.05
Bipolar disorder (F30, F31)						
Control	410,028	1,555 (0.38)	I (Reference)		I (Reference)	
PCOS	187,945	1,247 (0.66)	1.779 (1.651–1.916)	<0.05	1.502 (1.139–1.981)	<0.05
Anxiety disorder (F40, F41, F42, F43.0, F43.1)						
Control	399,800	11,656 (2.92)	I (Reference)		I (Reference)	
PCOS	183,561	6,449 (3.51)	1.228 (1.191–1.266)	<0.05	1.147 (1.050–1.252)	<0.05
Sleep disorder (F51, G47)						
Control	401,923	10,220 (2.54)	I (Reference)		I (Reference)	
PCOS	185,351	4,908 (2.65)	1.062 (1.026–1.099)	<0.05	1.228 (1.112–1.356)	<0.05

Notes: *Adjusted for age, diabetes mellitus, hypertension, dyslipidemia, body mass index, smoking history, and alcohol intake frequency.

Abbreviations: PCOS, polycystic ovary syndrome; CI, confidence interval.

disorder, such as mood disorders,^{20,21} anxiety disorders,^{20,21} eating disorders,²¹ and severe mental illness.²² For dyslipidemia, people with severe mental illness had increased risk for hypertriglyceridemia and low high density lipoprotein cholesterol.²³ However, reported association between mental health and blood pressure was mixed.²⁴ We also considered lifestyle factors: alcohol consumption and smoking. PCOS international guideline recommends assessing alcohol consumption and smoking in regards of fertility¹⁵ and modifying alcohol consumption and smoking is important in long-term treatment of PCOS.²⁵ Though the association between alcohol consumption and PCOS was controversial in

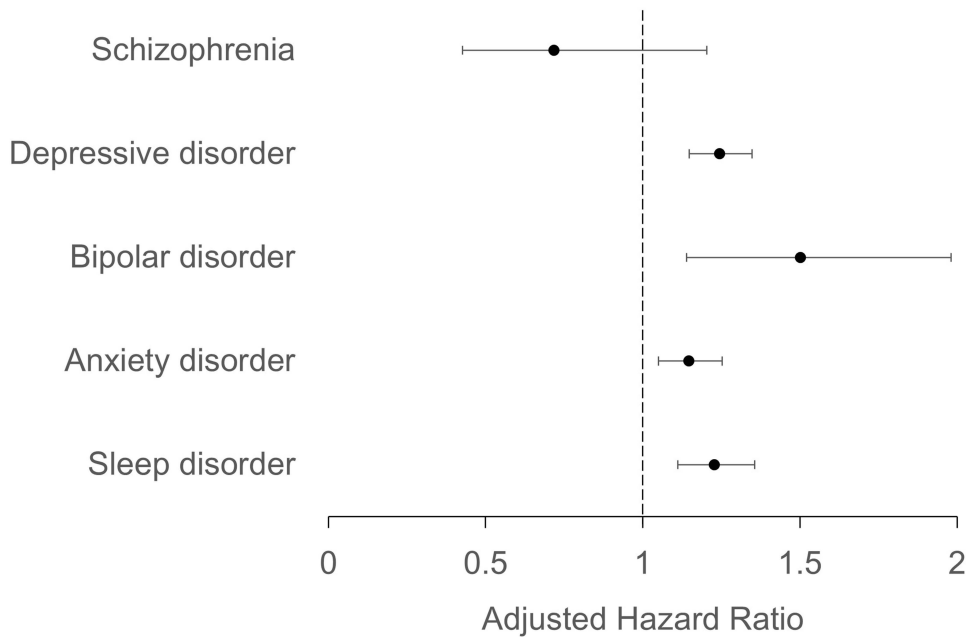


Figure 4 Hazard Ratios for Incidence of Mental Disorders in PCOS Patients.

Notes: Adjusted for age, diabetes mellitus, hypertension, dyslipidemia, body mass index, smoking history, and alcohol intake frequency.

previous studies,²⁶ association between alcohol consumption and decreased mental health^{27,28} is well known. Smoking is a risk factor for PCOS²⁶ and various psychiatric conditions.²⁹ It is worth noting that PCOS exhibited a higher risk for several mental disorders, even after adjusting for these factors in the main analysis and excluding individuals with a history of frequent alcohol consumption or smoking in the sensitivity analysis.

There have been few previous studies of schizophrenia in PCOS patients, and the reported HRs vary. A previous study reported a greater prevalence in PCOS patients than in controls,¹² which is not consistent with our results. In one study, the crude HR and adjusted HR of schizophrenia were greater in PCOS patients than in the general population,³⁰ while several studies have reported nonsignificant crude HR for schizophrenia.^{9,13} In our study, the crude HR and adjusted HR were not significant. The small number of patients with schizophrenia may have influenced our results. An inverse relationship between testosterone level and severity of negative schizophrenia symptoms has been reported.³¹ Therefore, PCOS, which is characterized by hyperandrogenemia, and schizophrenia may be associated with each other; however, additional research is required to address this hypothesis.

The prevalence^{8,10,12,32,33} and HR^{9,34} of depressive disorder and odds of depressive symptoms³⁵ have been reported to be greater in PCOS patients than in the general population. Our results were consistent with these earlier studies. PCOS has biochemical characteristics highly related to the occurrence of depression: the decrease in inhibitory neurotransmitters (serotonin, dopamine, gamma-aminobutyric acid, acetylcholine, etc.) that leads to hyperactivity of the hypothalamic-pituitary-adrenal axis,³⁶ and high inflammatory markers.³⁷ Also, neurotransmitters such as dopamine might affect the gut-brain axis and regulate appetite and satiety.³⁸ Obesity is a common clinical characteristic in PCOS and depressive disorders.^{37,39} A previous study showed that depressed PCOS patients had higher BMIs than non-depressed PCOS patients,³³ and another study reported PCOS patients with lower BMI to have slightly lower depression score.⁴⁰ Also, weight loss induced by dietary interventions improved PCOS-related chronic inflammation.⁴¹ These findings suggested that obesity, PCOS, and depressive disorder should be considered altogether during treatment.

Several studies have reported that the prevalence of bipolar disorder is greater in PCOS patients than in the general population.^{10,12,34} Our results were similar to those of prior studies. However, the reported HRs for bipolar disorder among PCOS patients are not consistent. Two previous studies reported greater HRs for bipolar disorder in PCOS patients than controls^{34,42} as in our study, while another study found no significant association between the two diseases.⁹ Patients with PCOS or bipolar disorder share common endophenotypes with regard to insulin resistance, hyperlipidemia, and other metabolic abnormalities.⁴³ Several studies have suggested that valproic acid, a drug commonly prescribed for bipolar disorder, might be associated with PCOS,^{44,45} and valproate-treated females more frequently exhibited menstrual abnormalities, features of hyperandrogenism, and other adverse metabolic parameters than lithium-treated females.⁴⁶ The similarities between the two diseases described above might, in part, explain the greater prevalence and HR of bipolar disorder in PCOS patients.

Elevated anxiety scores⁴⁰ and greater prevalence^{8,10,12,34} and HR^{9,34} of anxiety disorder in PCOS patients were reported in previous studies. Two systemic reviews reported increased prevalence of anxiety symptoms in PCOS patients,^{47,48} consistent with our results. The factors contributing to the development of anxiety disorder in PCOS patients are under investigation. Hormonal features, such as hypothalamic-pituitary-adrenal-axis⁴⁹ or hyperandrogenism,⁴⁸ may associated with anxiety in PCOS patients. The BMI might also be associated with anxiety,^{40,48} which may have a significant impact on PCOS patients, considering that one of the most common symptoms of PCOS is obesity.

Several studies have shown that PCOS patients are at high risk of obstructive sleep apnea⁵⁰ and sleep disturbance,^{51,52} which is not consistent with our findings, as the PCOS patients in our study population had a lower prevalence of sleep disorders. This difference may have resulted from our study and the previous studies having had different research scopes. The sleep disorders we studied were not limited to sleep apnea or sleep disturbance. A study using a more similar definition of sleep disorder to ours showed higher HR of sleep disorder in PCOS patients compared with controls⁹ and aligned with our results. Common symptoms experienced by PCOS patients, like obesity and insulin resistance,⁵⁰ could be contributing to sleep disorder or sleep disturbance. In addition, several studies suggested that treatment of obstructive sleep apnea could improve cardiometabolic functions.^{53,54} It seems likely that there is an association between sleep disorders and PCOS, but the degree of association may vary depending on the type of sleep disorder. Further research on this subject is needed.

The overlapping symptoms of PCOS and mental disorders suggest that the two conditions may be inter-related, and that treatment of one condition might help improve the other. However, a careful approach is needed, as some treatments for one condition may aggravate the other condition: for example, some antipsychotic drugs can have negative consequences on the symptoms of PCOS.¹⁴ Therefore, we encourage medical staff to more seriously consider the possibility that PCOS patients might have comorbid mental disorders and carefully to select the treatment options.

Our subgroup analysis revealed disparities in the risk of mental disorders among PCOS patients. These findings suggest that the need for mental disorder screening in PCOS patients may differ according to age and obesity status. Clinical and biochemical manifestations of PCOS change with age,⁵⁵ and obesity was related to PCOS⁵⁵ and mental health⁵⁶ both. How to approach these complex relationships requires further research.

We checked the liver enzyme level of study populations as an indirect index of liver function because PCOS is associated with non-alcoholic fatty liver disease.⁵⁷ While our results showed a statistically significant difference in liver enzyme levels between PCOS patients and controls, the clinical relevance of this finding was unclear. In previous studies, most PCOS patients with elevated liver enzymes had a high BMI.^{58,59} This suggests that PCOS diagnosis alone was not enough to identify the association between liver function and PCOS.

This study had several limitations. The National Health Insurance Services (NHIS) database used in this study was subject to a few restrictions, as it consisted of billing records. We could not identify any treatments not covered by medical insurance. Misdiagnosis or misclassification of PCOS and mental disorders may have occurred. We did not consider other potential confounders, such as socioeconomic status or the effects of drugs related to PCOS or mental disorders, because they could not be identified in our database. A small percentage of individuals had a medical check-up record for the index year, possibly due to the biennial national health examination schedule. The initial population data we received already exhibited age differences between individuals with and without PCOS, even though we requested the age-matched individuals' data from the NHIS database. We used the matching technique to overcome the imbalance, though we couldn't eliminate it. The patients were not matched with controls for BMI, which could significantly affect mental health. Therefore, we adjusted age and BMI when calculating HR. We didn't distinguish the patients based on the usage of psychiatric medications, like sodium valproate, as we aimed to describe the overall association between PCOS and mental disorders in the Korean population. Further study could explore the potential effect of drugs that patients had taken. Nevertheless, this study is meaningful as it shows insight into the relationships between PCOS and mental disorders in the Korean population.

Conclusion

We evaluated the risk of mental disorders in PCOS patients using a Korean nationwide population-based cohort. Our results suggest that PCOS patients have increased risks of depressive disorder, bipolar disorder, anxiety disorder, and sleep disorder. There are a few limitations in our study in that our database consisted of data claimed for a limited period. This study supports the current international PCOS guidelines, which recommend screening for mental health disorders.¹⁵ Therefore, our study advocates for more active screening of mental disorders in Korean PCOS patients, taking into account the changing needs based on individual factors such as age and obesity.

Data Availability Statement

Data sharing is not applicable to this article due to the principles and restrictions of NHIC.

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Disclosure

Professor Jeong Namkung reports grants from Catholic Medical Center, outside the submitted work. The authors report no other conflicts of interest in this work.

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