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ORIGINAL RESEARCH

Clinical Characteristics of Hyperandrogenism Include Hirsutism, Polycystic Ovary Syndrome, and Acne: Association with Psychiatric Disease in Women -A Nationwide Population-Based Cohort Study in Taiwan

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Objective: Previous studies have shown an increased in psychiatric disorders in women with disorders associated with hyperandrogenism, but few nationwide cohorts have studied this phenomenon. Therefore, this study is aimed to examine the association between the clinical manifestations of hyperandrogenism and subsequent psychiatric disorders.

Methods: Based on the National Health Insurance Research Database, 49,770 enrolled participants were matched for age and index date between January 1, 2000, and December 31, 2015. Hirsutism, polycystic ovary syndrome, and acne are characterized by hyperandrogenism. After adjusting for confounding factors, we used Cox proportional analysis to compare the risk of psychiatric disorders during the 16 years of follow-up.

Results: Of all the participants, 1319 (13.25%) had psychiatric disorders in the study group, whereas only 3900(9.80%) had psychiatric disorders in the control group. After adjusting for age, and monthly income, the Cox regression analysis showed that the study patients were more likely to develop psychiatric disorders (hazard ratio [HR]: 2.004, 95% confidence interval [CI] = 1.327–2.724, $P < 0.001$). The results demonstrated that women aged 20–29 years had a more significant risk.

Conclusion: Women with clinical characteristics of hyperandrogenism have a higher risk of developing psychiatric disorders, especially those aged 20–29 years.

Keywords: hyperandrogenism, psychiatric disorders, national health insurance research database, cohort study, women, Taiwan

Introduction

Previous literature has revealed that hirsutism, polycystic ovary syndrome (PCOS), and acne are linked by an association with hyperandrogenism.[1–3] Heidelbaugh (2016) argues that hirsutism is characterized as excessive terminal hair, typically occurring in male growth patterns in the androgen-dependent regions of the female body.[1] Moreover, PCOS has been defined using multifarious criteria, including hyperandrogenism, oligoovulation or anovulation, and polycystic ovaries.[2,4]

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Additionally, acne is a characteristic of PCOS.[2,3] Consequently, we used three clinical manifestations of hyperandrogenism, including hirsutism, PCOS, and acne, to represent the clinical characteristics of hyperandrogenism in this study.

In the previous research, hirsutism, PCOS, and acne have been linked to an increased risk for subsequent psychiatric disorders.[5–8] Brutocao (2018) suggested that PCOS is linked to an increased risk of depression, anxiety, and bipolar disorders after including 57 studies reporting on 172,040 patients.[5] A nationwide cohort study in the UK revealed acne is associated with an increased risk of depression.[6] In his epidemiological cohort study, Morgan asserted that the prevalence of eating disorders in women with hirsutism has increased.[7]

In addition to psychological disorders, the present study used other disorders to analyze depression, anxiety, sleep disorders, and eating disorders. Further, we added suicide to the study list of the considered variables.[9] Thus far, although numerous population-based studies have been published on the appearance characteristics of hyperandrogenism,[10] There has been was a lack of direct analysis of large databases to verify the clinical manifestations of hyperandrogenism and subsequent psychiatric disorders. We hypothesized that a nationwide population-based cohort study utilizing the National Health Insurance Research Database (NHIRD) could examine women with clinical manifestations of hyperandrogenism and the possible risk of psychiatric disorders. Nonetheless, the main limitation of this study is the lack of exact androgen level data. This study aimed to demonstrate the correlation between hirsutism, PCOS, acne, and subsequent psychiatric disorders.

Materials and Methods

Data Source

This study used data from the NHIRD to investigate the association between the three clinical manifestations of hyperandrogenism and psychiatric disorders over a 16-year period.[11] As a subset of the NHIRD, the Longitudinal Health Insurance Database of a two million randomized sampled population from 2000 to 2015 was used to study the association between clinical features of hyperandrogenism and the risk of psychiatric disorders.[12]

The National Health Insurance (NHI) program was launched in Taiwan in 1995. As of June 2009, it included contracts with 97% of medical providers with approximately 23 million beneficiaries or more than 99% of the population.[13,14] The NHIRD, which contains all claims data of beneficiaries, uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to record diagnoses.[15] The details of the program were documented in a previous study.[12]

In this study, we used data from the NHIRD to investigate the association between patients with hirsutism (ICD-9-CM: 704.1), PCOS (ICD-9-CM:256.4 and 628.0), acne (ICD-CM:706.1), and psychiatric disorders (ICD-9-CM:290–319) over a 16-year period, from the total hospitalization Longitudinal Health Insurance Database in Taiwan (2000–2015).[16]

Study Design and Sampled Participants

This study used a population-based, matched-cohort design. This study was observational. Patients newly diagnosed with any of the three clinical manifestations of hyperandrogenism, including hirsutism, PCOS, and acne, were selected from the Longitudinal Health Insurance Database from January 1, 2000, to December 31, 2015. Patients with these diseases before 2000 were excluded from the study. This method could be viewed as a way to ensure that these diseases were recent-onset, with references from other studies on the association between clinical characteristics of hyperandrogenism and psychiatric health, utilizing the NHIRD.[17]

Additionally, the patients diagnosed with anxiety, depression, bipolar disorders, sleep disorders, posttraumatic stress disorders (PTSD) or acute stress disorders (ASD), dementia, eating disorders, substance-related disorders (SRD), psychotic disorders, autism, other mental disorders, suicide, before 2000, or before their first visit for any one of the three diseases mentioned above were also excluded.[18] Of the total patients enrolled, 9954 participants with any of the three clinical manifestations of hyperandrogenism and 39,816 controls were matched for age and index date. Each enrolled participant was required to have made at least three outpatient visits or one inpatient episode in the 1-year study period for any of the three diseases mentioned above, according to the ICD-9-CM codes. Participants fulfilling any of

clinical manifestation criteria were referred to the study group; participants without clinical features were referred to the control group (Figure 1).

Covariates

The covariates included age groups (≤ 19, 20–44, 45–64, and ≥ 65 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1–4), and monthly income (in New Taiwan Dollars [NT$]; < 18,000, 18,000–34,999,and ≥35,000). The urbanization level of a residence was defined according to the population and various indicators of the level of development.[19] Level 1 was defined as a population of > 1,250,000 and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as populations between 500,000 and 1,249,999 and as playing an important role in politics, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and <149,999, respectively.[20]

Comorbidities

Baseline comorbidities included diabetes mellitus (DM; ICD-9-CM: 250), hypertension (HTN; ICD-9CM: 401–405), renal disease (ICD-9-CM: 580–589),hyperlipidemia (ICD-9-CM: 272), thyrotoxicosis (ICD-9-CM: 242), pneumonia (ICD-9-CM: 480–486), chronic liver disease (CLD; ICD-9-CM: 571), injury (ICD-9-CM: 800–999), tumor (ICD-9-CM:

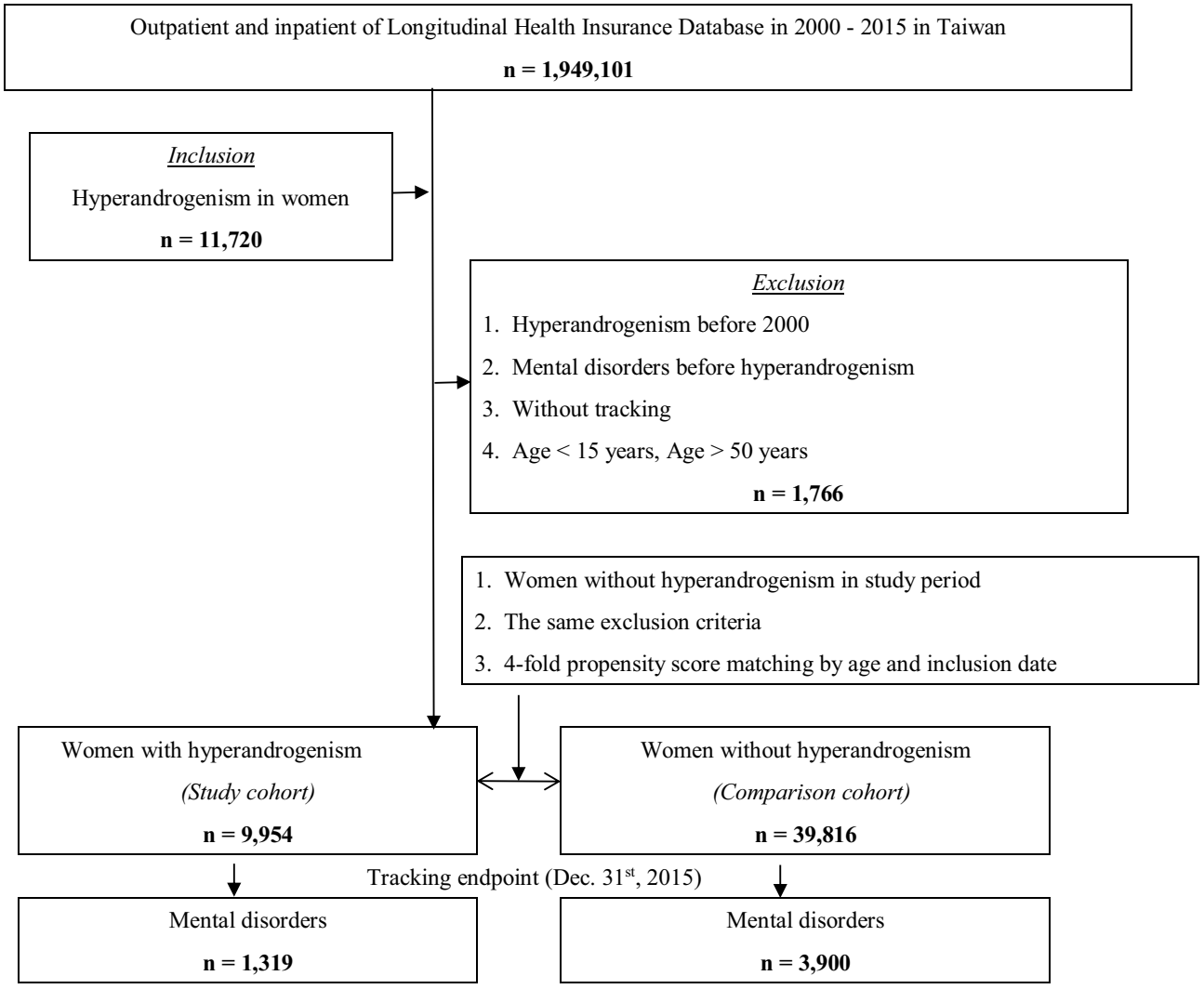

Figure 1 The flowchart of the study.

140–208), and obesity (ICD-9-CM: 278.0–278.1). These comorbidities were based on previous population-based literature.[21,22]

Major Outcome

All study participants were tracked from the index date until the onset of anxiety disorders (ICD-9-CM:300), depression (ICD-9-CM:296.2–296.3, 300.4, and 311), bipolar disorders (ICD-9-CM 296.0, and 296.4–296.8), sleep disorders (ICD-9-CM:307.4 and 780.5), PTSD or ASD (ICD-9-CM:308,309.81), dementia (ICD-9-CM: 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0), eating disorders (ICD-9-CM:307. 1, 307.5), SRD (ICD-9-CM:291–292, 303.3, 303.9, 304–305), psychotic disorders (ICD-9-CM: 295 and 297–298), autism (ICD-9-CM:299.0), other mental disorders (ICD-9-CM: 290–319 excluding listed above), suicide (ICD-9-CM: E950-E959), withdrew from the NHI program, or the end of 2015. Moreover, each psychiatric diagnosis was required to have made at least three outpatient visits within the 1-year study period for psychiatric disorders, according to the ICD-9-CM codes.[15,23]

Statistical Analyses

All statistical analyses were performed using SPSS Windows software version 22.0. $\chi 2$ and t-tests were used to evaluate the distributions of categorical and continuous variables, respectively.[24] The results are presented as hazard ratios (HR) with 95% confidence intervals (CI).[25,26] Differences in the risk of psychiatric disorders between the study and control groups were estimated using the Kaplan–Meier method with the Log rank test. Statistical significance was defined as a two-tailed p-value < 0.05.[27]

Results

Table 1 shows the age, comorbidities, urbanization, area of residence, and monthly insured premiums of the high-androgen females and controls. We identified 9954 patients with clinical manifestations of hyperandrogenism and 39,816 patients without hyperandrogenism. The difference between the two groups was not statistically significant in the

Table 1 Characteristics of Study in the Baseline

Hyperandrogenism	Total		with		without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Total	49,770		9954	20.00	39,816	80.00	
Age (years)	28.88 ± 13.69		28.81 ± 13.08		28.90 ± 13.85		0.557
Age group (yrs)							0.999
≦ 19	18,950	38.08	3790	38.08	15,160	38.08	
20–29	19,530	39.24	3906	39.24	15,624	39.24	
30–39	6050	12.16	1210	12.16	4840	12.16	
≧ 40	5240	10.53	1048	10.53	4192	10.53	
Insured premium (NT$)							< 0.001
< 18,000	36,499	73.34	7091	71.24	29,408	73.86	
18,000–34,999	7294	14.66	1622	16.29	5672	14.25	
≧ 35,000	5977	12.01	1241	12.47	4736	11.89	
DM							< 0.001
Without	44,484	89.38	8749	87.89	35,735	89.75	
With	5286	10.62	1205	12.11	4081	10.25	

(*Continued*)

Table 1 (Continued).

Hyperandrogenism	Total		with		without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
HTN							< 0.001
Without	43,000	86.40	8351	83.90	34,649	87.02	
With	6770	13.60	1603	16.10	5167	12.98	
Renal disease							0.437
Without	44,804	90.02	8940	89.81	35,864	90.07	
With	4966	9.98	1014	10.19	3952	9.93	
Hyperlipidemia							< 0.001
Without	47,277	94.99	9227	92.70	38,050	95.56	
With	2493	5.01	727	7.30	1766	4.44	
Thyrotoxicosis							0.055
Without	48,894	98.24	9756	98.01	39,138	98.30	
With	876	1.76	198	1.99	678	1.70	
Pneumonia							0.541
Without	44,782	89.98	8940	89.81	35,842	90.02	
With	4988	10.02	1014	10.19	3974	9.98	
CLD							0.293
Without	46,398	93.22	9256	92.99	37,142	93.28	
With	3372	6.78	698	7.01	2674	6.72	
Injury							0.949
Without	42,715	85.82	8541	85.80	34,174	85.83	
With	7055	14.18	1413	14.20	5642	14.17	
Tumor							0.462
Without	48,381	97.21	9687	97.32	38,694	97.18	
With	1389	2.79	267	2.68	1122	2.82	
Obesity							0.856
Without	49,144	98.74	9827	98.72	39,317	98.75	
With	626	1.26	127	1.28	499	1.25	
Season							0.999
Spring (Mar - May)	11,975	24.06	2395	24.06	9580	24.06	
Summer (Jun - Aug)	12,590	25.30	2518	25.30	10,072	25.30	
Autumn (Sep - Nov)	12,985	26.09	2597	26.09	10,388	26.09	
Winter (Dec - Feb)	12,220	24.55	2444	24.55	9776	24.55	
Location							< 0.001
Northern Taiwan	15,019	30.18	3255	32.70	11,764	29.55	
Central Taiwan	14,571	29.28	2971	29.85	11,600	29.13	
Southern Taiwan	14,014	28.16	2913	29.26	11,101	27.88	
Eastern Taiwan	5104	10.26	759	7.63	4345	10.91	
Outlying islands	1062	2.13	56	0.56	1006	2.53	

(*Continued*)

Table 1 (Continued).

Hyperandrogenism	Total		with		without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Urbanization level							< 0.001
1 (The highest)	14,480	29.09	3038	30.52	11,442	28.74	
2	15,592	31.33	3362	33.78	12,230	30.72	
3	9486	19.06	1607	16.14	7879	19.79	
4 (The lowest)	10,212	20.52	1947	19.56	8265	20.76	
Level of care							< 0.001
Hospital center	17,387	34.93	5678	57.04	11,709	29.41	
Regional hospital	17,251	34.66	2264	22.74	14,987	37.64	
Local hospital	15,132	30.40	2012	20.21	13,120	32.95	

Note: *P*: Chi-square/Fisher exact test on category variables and *t*-test on continue variables.

distribution of age, renal disease, thyrotoxicosis, pneumonia, chronic liver disease (CLD), injury, tumor, obesity, or season of medical visits. Most patients were under 30 years of age (77.32% in the hyperandrogenism participant group and the non-hyperandrogenism control cohort). The hyperandrogenism cohort had more DM, HTN, and hyperlipidemia cases than the non-hyperandrogenism control cohort. Patients with clinical features of hyperandrogenism tended to pay a higher insurance premium, lived in the northern and central regions of Taiwan, had urbanization levels 1 and 2, and received medical care from hospital centers.

Of the total 49,770 participants, 1319 were from 9954 (13.25%) in the hyperandrogenism cohort, compared to 3900 from the 39,816 (9.80%) non-hyperandrogenism cohort. Kaplan-Meier survival analysis revealed that the difference in the development of psychiatric disorders was statistically significant (log-rank, p<0.001). (Figure 2)

Table 2 shows the results of the COX regression analysis: the incidence of psychiatric disorders was higher in the hyperandrogenism group than that in the non-hyperandrogenism control cohort (13.25% vs 9.80%). The Cox regression revealed that the crude HR was 2.267 (95% CI = [1.385,2.916], p < 0.001), and the adjusted HR was 2.004 (95% CI = [1.327, 2.724], p < 0.001) in the risk of psychiatric disorders after adjusting for age, comorbidities, geographical area of residence, urbanization level of the residence, and monthly income. For the subgroup of participants aged 20–29 years, the risk of psychiatric disorders was 1.878 times that of the age group ≤19 years. The results show that those with DM,

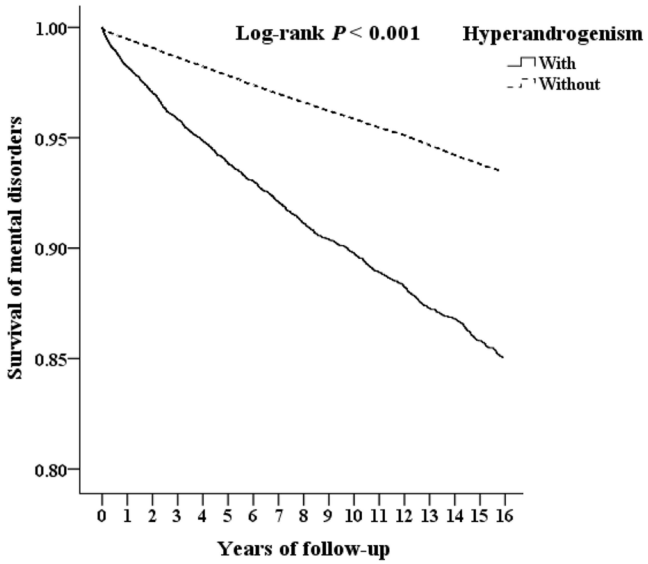

Figure 2 Kaplan-Meier for survival of mental disorders among aged 15–49 women stratified by hyperandrogenism with Log rank test.

Table 2 Factors of Mental Disorders by Using Cox Regression

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Hyperandrogenism								
Without	Reference				Reference			
With	2.267	1.385	2.916	< 0.001	2.004	1.327	2.724	< 0.001
Age group (yrs)								
≦ 19	Reference				Reference			
20–29	1.878	1.344	2.128	< 0.001	1.718	1.333	2.064	< 0.001
30–39	1.578	1.074	1.807	< 0.001	1.431	1.041	1.786	0.009
≧ 40	0.900	0.510	1.306	0.389	0.839	0.492	1.244	0.422
Insured premium (NT$)								
< 18,000	Reference				Reference			
18,000–34,999	1.072	0.848	1.306	0.298	1.042	0.795	1.219	0.382
≧ 35,000	1.206	0.892	1.314	0.222	1.112	0.819	1.295	0.271
DM								
Without	Reference				Reference			
With	1.908	1.205	2.281	< 0.001	1.814	1.121	2.204	< 0.001
HTN								
Without	Reference				Reference			
With	1.986	1.229	2.392	< 0.001	1.916	1.197	2.253	< 0.001
Renal disease								
Without	Reference				Reference			
With	1.763	1.241	2.166	< 0.001	1.713	1.219	2.049	< 0.001
Hyperlipidemia								
Without	Reference				Reference			
With	1.310	0.868	1.808	0.295	1.254	0.857	1.746	0.384
Thyrotoxicosis								
Without	Reference				Reference			
With	1.132	0.658	1.617	0.411	1.093	0.521	1.512	0.427
Pneumonia								
Without	Reference				Reference			
With	1.306	0.761	1.700	0.535	1.209	0.603	1.603	0.562
CLD								
Without	Reference				Reference			
With	1.512	1.122	1.909	< 0.001	1.492	1.100	1.835	< 0.001

(*Continued*)

Table 2 (Continued).

Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Injury								
Without	Reference				Reference			
With	1.349	1.072	1.666	< 0.001	1.333	1.042	1.623	0.007
Tumor								
Without	Reference				Reference			
With	1.463	1.109	1.714	< 0.001	1.410	1.066	1.684	0.000
Obesity								
Without	Reference				Reference			
With	1.117	0.898	1.492	0.275	1.080	0.819	1.431	0.299
Season								
Spring	Reference				Reference			
Summer	1.394	0.847	1.855	0.244	1.312	0.730	1.787	0.313
Autumn	1.411	0.949	1.936	0.101	1.392	0.838	1.814	0.265
Winter	1.502	1.012	2.011	0.039	1.435	0.919	1.911	0.097
Location					**Multicollinearity with urbanization level**			
Northern Taiwan	Reference				**Multicollinearity with urbanization level**			
Central Taiwan	0.993	0.426	1.627	0.498	**Multicollinearity with urbanization level**			
Southern Taiwan	0.887	0.378	1.562	0.513	**Multicollinearity with urbanization level**			
Eastern Taiwan	0.809	0.335	1.396	0.597	**Multicollinearity with urbanization level**			
Outlying islands	0.803	0.288	1.212	0.656	**Multicollinearity with urbanization level**			
Urbanization level								
1 (The highest)	1.684	1.265	2.403	< 0.001	1.583	1.142	2.281	< 0.001
2	1.570	1.233	2.227	< 0.001	1.451	1.110	2.028	< 0.001
3	1.214	1.048	1.899	0.001	1.128	0.993	1.855	0.056
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	3.007	1.958	4.038	< 0.001	2.720	1.498	3.399	< 0.001
Regional hospital	2.284	1.863	3.913	< 0.001	1.878	1.314	2.910	< 0.001
Local hospital	Reference				Reference			

Abbreviations: HR, hazard ratio; CI, confidence interval; Adjusted HR, Adjusted variables listed in the table.

HTN, renal disease, CLD, injury, and tumors are more likely to suffer from subsequent psychiatric disorders. Additionally, the mean years from clinical features of hyperandrogenism diagnosis to psychiatric disorders were 5.82 ± 5.69 years in the participant group, shorter than 6.06 ± 5.92 years for the control group from tracking the course of psychiatric disorders. (Table 3)

Table 3 Years to Mental Disorders

Hyperandrogenism	Min	Median	Max	Mean ± SD
With	0.02	4.21	15.29	5.82 ± 5.69
Without	0.02	4.83	15.33	6.06 ± 5.92
Overall	0.02	4.32	15.33	6.01 ± 5.88

Table 4 Factors of Mental Disorders Stratified by Variables Listed in the Table by Using Cox Regression

Hyperandrogenism Stratified	With vs Without *(Reference)*			
	Adjusted HR	95% CI	95% CI	*P*
Overall	2.004	1.327	2.724	< 0.001
Age group (yrs)				
≦ 19	1.987	1.316	2.701	< 0.001
20–29	2.032	1.346	2.764	< 0.001
30–39	2.009	1.330	2.730	< 0.001
≧ 40	1.959	1.297	2.662	< 0.001
Insured premium (NT$)				
< 18,000	1.956	1.295	2.658	< 0.001
18,000–34,999	2.059	1.364	2.799	< 0.001
≧ 35,000	2.169	1.437	2.950	< 0.001
DM				
Without	1.923	1.273	2.614	< 0.001
With	2.681	1.776	3.644	< 0.001
HTN				
Without	1.896	1.256	2.578	< 0.001
With	2.816	1.864	3.828	< 0.001
Renal disease				
Without	1.935	1.282	2.632	< 0.001
With	2.510	1.662	3.412	< 0.001
Hyperlipidemia				
Without	1.997	1.322	2.714	< 0.001
With	2.117	1.402	2.877	< 0.001
Thyrotoxicosis				
Without	1.998	1.323	2.716	< 0.001
With	2.257	1.495	3.069	< 0.001
Pneumonia				
Without	1.995	1.321	2.712	< 0.001
With	2.088	1.382	2.838	< 0.001
CLD				
Without	1.999	1.324	2.717	< 0.001
With	2.052	1.359	2.790	< 0.001

(*Continued*)

Table 4 (Continued).

Hyperandrogenism Stratified	With vs Without *(Reference)*			
	Adjusted HR	**95% CI**	**95% CI**	***P***
Injury				
Without	1.985	1.314	2.698	< 0.001
With	2.110	1.397	2.868	< 0.001
Tumor				
Without	2.000	1.324	2.719	< 0.001
With	2.137	1.416	2.905	< 0.001
Obesity				
Without	2.001	1.325	2.711	< 0.001
With	2.126	1.403	2.889	< 0.001
Season				
Spring	1.853	1.227	2.518	< 0.001
Summer	2.008	1.330	2.729	< 0.001
Autumn	2.047	1.355	2.783	< 0.001
Winter	2.115	1.401	2.875	< 0.001
Urbanization level				
1 (The highest)	2.045	1.354	2.781	< 0.001
2	2.032	1.346	2.763	< 0.001
3	1.984	1.313	2.697	< 0.001
4 (The lowest)	1.907	1.263	2.592	< 0.001
Level of care				
Hospital center	2.201	1.457	2.992	< 0.001
Regional hospital	1.967	1.302	2.673	< 0.001
Local hospital	1.897	1.256	2.579	< 0.001

Abbreviations: PYs, Person-years; Adjusted HR, Adjusted Hazard ratio: Adjusted for the variables listed in Table 2; CI, confidence interval.

We analyzed the data by stratifying factors, such as age, urbanization level, geographic areas of residence, seasons of medical visits, monthly insured premiums, and levels of care from medical service providers. We found that different urbanization levels, residence areas, seasons of medical visits, insured premiums, and levels of care were associated with an increased risk of psychiatric disorders. Patients with clinical characteristics of hyperandrogenism between the ages of 20 and 29 years had an increased risk of developing psychiatric disorders Tables 4 and 5 shows the adjusted HR of anxiety with adjusted HR: 2.196, $p < 0.001$, depression with adjusted HR: 2.389, $p < 0.001$, bipolar disorders adjusted HR: 2.047, $p < 0.001$; SRD adjusted HR: 1.933, $p < 0.001$; psychotic disorders adjusted HR: 1.768 $p < 0.001$, and other mental disorders adjusted HR: 1.997, $p < 0.001$ in patients with three clinical manifestations of hyperandrogenism when compared to the patients without clinical characteristics of hyperandrogenism. Surprisingly, we found that eating disorders were significant. Nonetheless, there was no statistical significance when the first year was excluded, and there was statistically a significant difference when the first five years were excluded.

Overall, the differences between people with and without psychiatric disorders, including hirsutism, PCOS, and acne were statistically significant. Nevertheless, the difference in the hirsutism and acne subgroups was not statistically significant; the p-values for hirsutism and acne were 0.342 and 0.053 respectively. The adjusted HR values of all subgroups, including hirsutism and acne, were greater than 1. For PCOS, the adjusted HR values were 3.165. (Table 6)

Table 5 Factors of Mental Disorders Subgroups by Using Cox Regression

Sensitivity Test	Hyperandrogenism Mental Disorders Subgroups	With vs Without *(Reference)*			
		Adjusted HR	95% CI	95% CI	*P*
Overall	Overall	2.004	1.327	2.724	< 0.001
	Anxiety	2.196	1.454	2.984	< 0.001
	Depression	2.389	1.583	3.248	< 0.001
	Bipolar	2.047	1.354	2.784	< 0.001
	Sleep disorders	1.958	1.297	2.661	< 0.001
	PTSD/ASD	1.346	0.891	1.829	0.123
	Dementia	1.305	0.864	1.773	0.184
	Eating disorders	1.872	1.239	2.545	< 0.001
	SRD	1.933	1.280	2.629	< 0.001
	Psychotic disorders	1.768	1.171	2.403	< 0.001
	Autism	1.555	1.001	2.113	0.050
	Other mental disorders	1.997	1.323	2.715	< 0.001
	Suicide	1.296	0.858	1.761	0.225
In the first year excluded	Overall	2.020	1.337	2.746	< 0.001
	Anxiety	1.843	1.221	2.505	< 0.001
	Depression	2.046	1.355	2.781	< 0.001
	Bipolar	2.752	1.823	3.740	< 0.001
	Sleep disorders	2.826	1.872	3.842	< 0.001
	PTSD/ASD	1.401	0.927	1.903	0.104
	Dementia	1.336	0.885	1.816	0.135
	Eating disorders	1.482	0.982	2.015	0.062
	SRD	2.250	1.490	3.058	< 0.001
	Psychotic disorders	2.318	1.535	3.151	< 0.001
	Autism	1.440	0.954	1.957	0.080
	Other mental disorders	3.307	2.190	4.494	< 0.001
	Suicide	1.107	0.733	1.505	0.299
In the first 5 years excluded	Overall	1.980	1.310	2.691	< 0.001
	Anxiety	1.741	1.153	2.366	< 0.001
	Depression	2.219	1.469	3.016	< 0.001
	Bipolar	2.178	1.442	2.960	< 0.001
	Sleep disorders	2.311	1.530	3.141	< 0.001
	PTSD/ASD	1.019	0.675	1.384	0.362

(*Continued*)

Table 5 (Continued).

Sensitivity Test	Hyperandrogenism Mental Disorders Subgroups	With vs Without *(Reference)*			
		Adjusted HR	95% CI	95% CI	*P*
	Dementia	1.399	0.925	1.900	0.108
	Eating disorders	1.548	1.026	2.105	0.025
	SRD	2.010	1.331	2.732	< 0.001
	Psychotic disorders	2.635	1.745	3.581	< 0.001
	Autism	1.072	0.709	1.457	0.372
	Other mental disorders	2.229	1.476	3.030	< 0.001
	Suicide	1.426	0.944	1.938	0.065

Abbreviations: PYs, Person-years; Adjusted HR, Adjusted Hazard ratio: Adjusted for the variables listed in Table 2; CI, confidence interval.

Table 6 Factors of Mental Disorders Among Different Hyperandrogenism Subgroups by Using Cox Regression

Hyperandrogenism subgroups	Adjusted HR	95% CI	95% CI	*P*
Without hyperandrogenism	Reference			
With hyperandrogenism	2.004	1.327	2.724	<0.001
Hirsutism	1.248	0.804	1.684	0.342
PCOS	3.165	2.203	4.303	<0.001
Acne	1.625	0.998	2.211	0.053

Abbreviations: PYs, Person-years; Adjusted HR, Adjusted Hazard ratio: Adjusted for the variables listed in Table 2; CI, confidence interval.

Discussions

This study examined the association between three clinical manifestations of hyperandrogenism and the risk of psychiatric disorders. After adjusting for covariates, the adjusted HR was 2.004 for the participants (95% CI = 1.327–2.724, $p < 0.001$) compared to the control group. Kaplan–Meier analysis demonstrated that the study participants had a significantly higher 16-year psychiatric disorders-free survival rate than controls.

Using the two million NHIRD with the advantage of a larger dataset, our study confirmed the association between three clinical manifestations of hyperandrogenism and the increased risk of depressive disorder, bipolar disorder, anxiety disorders, and sleep disorders. Our study excluded patients and controls with psychiatric disorders before the follow-up period. Patients with clinical characteristics of hyperandrogenism were associated with a higher risk of overall psychiatric disorders than the control group, especially anxiety, depression, bipolar disorders, SRD, and other mental disorders. In this group, hyperandrogenism was associated with an increased risk of overall psychiatric disorders, especially depression and anxiety. Therefore, regular psychiatric follow-up may be vital for patients with hyperandrogenism.[10,28]

Our study did not find an association between the clinical characteristics of hyperandrogenism and suicide, which may be due to several reasons. Suicidal ideation occurs more frequently in women than in men; nevertheless, men are more likely to commit suicide than woman.[29,30] Utilizing the NHIRD, we could not count patients with suicidal ideation, which may have affected the results of this study. A previous article suggested that androgens in men are a risk factor for

completed suicide.[30,31] However, our study included only women, which may be a critical reason for the lack of statistical significance due to sex differences. The underlying association between androgens and suicide requires clarification in future research. Most previous population-based studies on psychiatric morbidity were related to patients with hirsutism, PCOS, or acne.[10] Therefore, to the best of our knowledge, this is the first population-based study on the incidence of psychiatric disorders with clinical manifestations of hyperandrogenism.

A crucial question is whether the increased risk of psychiatric disorders after exposure to high androgen levels is associated with high androgen levels. Previous animal studies have shown that supraphysiological doses of androgens contribute to neurodegeneration, decreased brain-derived neurotrophic factors, increased inflammation, and increased neuronal density, which may correspond to changes in mood, cognition, and aggression.[32] Neural alterations likely play a role in the common mental health problems in patients with high androgen levels.[33] The total cerebral cortex volume of people with high androgen levels was more compact than that of controls.[34] A trophy of the cerebral cortex is a risk factor. Specifically, the brain neurons of patients with high androgen levels may have become atrophied.[35] Although the mechanism between the atrophied brain and high androgen levels is yet to be clarified, there is a dose-response relationship.[32] Further, patients with high androgen levels are more likely to develop cerebrovascular problems.[36] Epidemiological studies have confirmed high comorbidity between cerebrovascular problems and psychiatric disorders, particularly depression. Comorbidity is bidirectional, and the mechanisms responsible are complex and multifaceted.[37] One study indicated that high androgen levels demonstrated more attention-deficit hyperactivity disorder (ADHD) symptoms; however, we do not emphasize this section in this study.[38]

Table 6 demonstrates that the p-value of hirsutism is 0.342, which is far from the significance standard, although there is an association between hirsutism and psychiatric disorders in previous studies.[39] The number of patients with hirsutism is far less than that of patients with PCOS, which may be an important influencing factor of the p-value. Despite their clinical importance, the prevalence of different pathological conditions associated with androgen excess is not apparent.[10] The most recognizable clinical feature of androgen excess may be hirsutism. However, not all patients with hirsutism have overt evidence of androgen excess, with some women suffering from what we understand to be idiopathic hirsutism.[40] Nevertheless, the mechanisms underlying idiopathic hirsutism are not completely known.[1,41] Alternatively, not all patients with an androgen excess disorder have hirsutism, as in Asian patients with PCOS.[42] East Asian females have fewer hirsute compared to Caucasians.[42,43] Thus, owing to ethnic differences, it is important to discuss different standards.

Women aged 20–29 years had the highest risk for psychiatric disorders, followed by those aged 30–39 years. In previous studies, compared to females aged >40 years, females aged 20–40 years produced more androgens and testosterone, a type of androgen.[44] Women aged 20–29 years secreted more significant amounts of androgens than those between the ages of 30 and 39 years in most previous studies.[45] Furthermore, psychiatric disorders were associated with age.[46] Although females' physical function worsens with age; they simultaneously feel less stressed.[47] Another reason is that women aged 20–40 years may face the task of reproduction and may come down with psychiatric disorders during this experience.[48,49] The mechanisms associated with androgen and psychiatric disorders have not been completely confirmed; consequently, age may be an influencing factor leading to this result.

Hirsutism, PCOS, and acne are risk factors that influence patients' mental health.[50–55] A Poor prognosis included psychiatric disorders and suicide in this study. Women with hirsutism have an increased risk of depression linked to their circulating active testosterone levels.[50] Similarly, in Derogatis' research, the findings indicate that depression in hirsute women is more likely to be affected by a malfunctioning neuroendocrine system than by psychosocial factors.[51] The underlying mechanisms of psychopathology are needed to clarify the underlying mechanisms of psychopathology. Daisung et al's meta-analysis observed a 26% increase risk of suicide deaths and a 17% increase risk of suicide attempts after concluding 32 papers.[52] Yin argues that women with PCOS tend to experience a low quality of life and suffer from depression and anxiety after conducting a meta-analysis of 46 studies.[53] Cesta suggests that PCOS in women might be a risk factor for psychiatric disorders and attempted suicide.[54] However, concerning completed suicide, the estimate attenuates, and the significance disappears when adjusting for comorbid psychiatric disorders.[54] Conversely, the results of this study demonstrate that the three clinical manifestations of hyperandrogenism could be a risk factor for completed

suicide. Due to the limitations of the NHIRD, suicide in this study only included completed suicide. Hull maintained that acne may have considerable psychological influence, including anxiety, depression, and suicide.[55]

Concerning the laboratory testing for hirsutism, screening for serum testosterone and 17-hydroxyprogesterone levels is sufficient in most cases.[56] In 2003, new guidelines for the diagnosis of PCOS were suggested by the European Society for Human Reproduction and Embryology and the American Society of Reproductive Medicine to replace the guidelines for the diagnosis of PCOS launched by the National Institutes of Health.[57] PCOS should be diagnosed when at least two of the following three characteristics are present: oligoovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries.[4] Furthermore, new guidelines concerning the diagnosis of PCOS were launched at the 2018 European Society for Human Reproduction and Embryology meeting in Barcelona.[58] However, this cohort study were conducted between 2000 and 2015; hence, the latest principle is not applicable. Acne can be diagnosed by a simple visual inspection.[59] Nevertheless, a dermatologist may recommend a blood test to determine if the progesterone and androgen levels are low.[59]

Hyperandrogenism is a defining feature of PCOS.[60] As such, patients with PCOS have a higher risk of psychiatric disorders and vice versa.[61] PCOS is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism, and polycystic ovaries.[2] Moreover, the negative influence on body image may contribute to subsequent psychiatric disorders.[62,63] Research in the United States maintains that women with PCOS are more likely to have low body image stress scores and the lower BIS scores, which may be associated with anxiety and depression.[62] A cross-sectional study suggests that PCOS is correlated with lower satisfaction with body images, which may lead to sexual dysfunction, anxiety, and depression.[63]

Hirsutism, PCOS, and acne were not separated. Thus, clarifying the mechanisms underlying the interaction between these diseases and hyperandrogenism is necessary.

First, one of the primary strengths of this study is the set of ICD-9 codes, and several studies have demonstrated the accuracy and validity of several diagnoses in the NHIRD, including cancer and central nervous system diseases, such as stroke or comorbidity.[64,65] Some studies have also demonstrated concordance between Taiwan's National Health Survey and the NHIRD for various diagnoses.[64,66] Second, the relatively long-term observation period allowed for more credibility compared with similar studies to propose mechanisms and plausible hypotheses. Third, we attempted to explain the lack of statistical significance when people experience hirsutism. Fourth, and most importantly, we attempted to explain the mutual biological and psychological mechanisms between the three clinical manifestations of hyperandrogenism and psychiatric disorders. Finally, for the first time, we found that clinical manifestations of hyperandrogenism are associated with an increased risk of psychiatric disorders using a nationwide population-based cohort study design, which to the best of our knowledge, has not been established in previous studies.

The present study had several limitations that warrant consideration. First, we did not use the test results for the exact amount of androgens as the basis for the discussion. Therefore, the results may have been inaccurate. Only three diseases have been used to explain this phenomenon. Second, other genetic, psychosocial, and environmental factors were not considered. Third, the lack of data on the severity of psychiatric disorders limits the generalizability of the results. Fourth, the NHI program started in 1995; however, in this study, the NHIRD that we used contained a database of only 16 years. We strongly recommend a more comprehensive follow-up study in the future. Fifth, some individuals with characteristics of hyperandrogenism during development may not express any of these traits. These patients were not included in our study. Finally, the results of this study were limited to Taiwan and may not necessarily represent other countries or regions. Hence, further studies are needed to investigate the association between the three clinical manifestations of hyperandrogenism and the risk of psychiatric disorders.

Conclusions

The results showed an association between the clinical characteristics of hyperandrogenism and psychiatric disorders. Additionally, this study demonstrated that women aged 20–29 years were more likely to develop subsequent psychiatric disorders. Nevertheless, this study is limited by the lack of exact data on serum androgen levels, as the three clinical symptoms are inferred from hyperandrogenism. Further studies are needed to elucidate the underlying pathophysiological

mechanisms of the relationship between hyperandrogenism and psychiatric disorders in women. These findings should be timely reminders for clinicians to pay attention to women who might suffer from psychiatric disorders.

Data Sharing Statement

Data are available from the National Health Insurance Research Database (NHIRD) published by the Taiwan National Health Insurance (NHI) Administration. Due to legal restrictions imposed by the government of Taiwan concerning the "Personal Information Protection Act", data cannot be made publicly available. Data requests can be sent as formal proposals to the NHIRD (http://www.mohw.gov.tw).

Ethics Approval

The study was conducted per the Declaration of Helsinki guidelines and approved by the Institutional Review Board of the Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan (TSGH IRB No.B-111-15).

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Disclosure

The authors report no conflicts of interest in this work.

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