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Original Research

Assessment of Bidirectional Relationship between Polycystic Ovary Syndrome and Depression: A Two-Sample Mendelian Randomization Study

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Abstract

Background: Evidence from observation studies has implied an association between polycystic ovary syndrome (PCOS) and risk of depression. Nevertheless, it remains elusive if the identified correlation is causal or owing to biases in observation researches. Hence, we utilized a bidirectional two-sample Mendelian randomization (MR) method to evaluate the potential causal relationship between PCOS and depression. **Methods**: Genetic instruments for PCOS and depression were acquired from two large genome-wide association studies (GWASs). MR analyses were completed via the inverse-variance weighted (IVW) method and weighted median approaches. The underlying pleiotropy was tested by MR-Egger regression, and leave-one-out method was used to evaluate the stability of MR results. **Results**: Using the IVW analyses (odds ratio (OR) = 1.07, 95% confidence interval (CI) = 1.01–1.06, $p < 0.01$) and weighted median approach (OR = 1.04, 95% CI = 1.00–1.08, $p < 0.05$), we found that PCOS was related to an elevated risk of depression. MR-Egger regression did not identify potential horizontal pleiotropy. Sensitivity analyses using leave-one-out method also provided supportive evidence. In the reverse MR analyses, we did not observe causal effect of depression on PCOS ($p > 0.05$). **Conclusions**: The present study provides evidence to support a potential causal association between PCOS and an elevated risk of depression. Hence, early psychological intervention for PCOS might show anti-depression benefits.

Keywords: causal association; polycystic ovary syndrome; depression; Mendelian randomization

1. Introduction

Polycystic ovary syndrome (PCOS) is a commonly seen endocrine disturbance which is the major cause of anovulatory infertility and affects up to 15% of women of reproduction age. It is characterized by androgenism, ovulatory dysfunction, obesity, menstrual dysfunction, metabolic and psychiatric abnormalities [1,2]. Hyperandrogenemia is present in 15%–45% of patients with PCOS [3], such as acne, hairiness, and increased level of free testosterone in peripheral blood. Moreover, it is known that women with PCOS are more likely to suffer from psychological problems, especially anxiety and depression [4].

The pathogenesis of PCOS remains unclear. Clinical observations and animal experiment data suggest the assumption that PCOS is inherited and induced by developmental programming of normal genetic mutations. Those genes would be magnified by exposing to in-utero androgen and stimulated by various post-natal life-style and environment factors. Chemistry substances that disrupt endocrine harbor the possibility to affect the developmental programming of PCOS susceptible genes [5].

Depression is a more and more commonly seen disease which constitutes remarkable health-care challenge. In 2008, WHO considered severe depression the 3rd cause of disease burden across the globe and forecasted that the problem will rank first by 2030 [6]. Depression influences females more than males [7] and is the most commonly seen psychological issue for females with PCOS. Females with PCOS present an 8-fold greater incidence of depression in contrast to females with no PCOS [8]. The different pathophysiologic causal links inducing depression are insulin resistance (IR), disturbances in the hypothalamic pituitary adrenal (HPA) axis and hyperandrogenism [2].

Although previous studies provided a suggestive link between PCOS and the risk of depression, residual confounding and reverse causation are difficult to eliminate in observational studies. Recently, there is an alternative method to investigate the potential causal association unbiasedly, two-sample Mendelian randomization, which depends on gene mutations as instrumental variables (IVs) to assess the causal association between an exposure and a result [9]. After random location in the process of meiosis, single-nucleotide polymorphisms (SNPs) used as in-

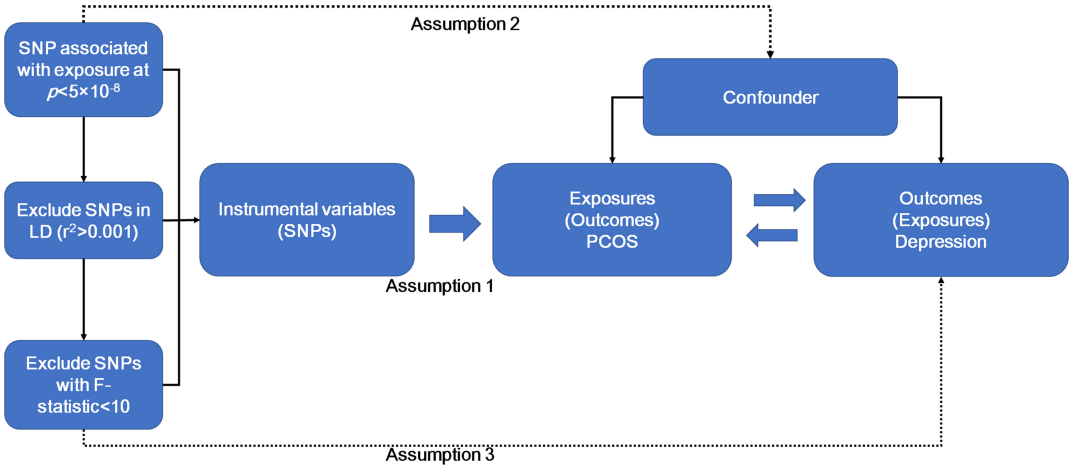

Fig. 1. Principles of mendelian randomization study for PCOS and depression. SNP, single nucleotide polymorphisms; PCOS, polycystic ovary syndrome.

strumental variables (IVs) remains stable and non-modified throughout a life-time of environment exposure, which makes them independent of confounding factors or reverse causation [10].

Based on gene mutations, Mendelian randomization (MR)-offered proofs of PCOS-related causality pertaining to several physical disorders have been found [11]. Moreover, previous Mendelian randomized study also explored the causal associations between PCOS and psychiatrical disorder and discovered that PCOS increased the risk of obsessive-compulsive disorder, but was not associated with the other four psychiatric disorders (anxiety disorders, bipolar disorders, severe depression disorders, or schizophrenia) [12]. On the basis of the release of a new database with a larger sample size, we conducted this updated bidirectional Mendelian randomized analyses to assess whether the underlying causality between PCOS and depression could have different outcomes.

2. Materials and Methods

2.1 Data Source and Study Samples of PCOS and Depression

The genome-wide association study (GWAS) dataset of PCOS was retrieved from the European ancestry. Using a meta-analysis technique, an adequate sample size from seven original datasets was obtained (10,074 cases and 103,164 controls) [13], which yielded better statistical power in identifying the associated SNPs. The diagnosis criteria of PCOS were on the foundation of the NIH or Rotterdam standards, or self-reporting in different original datasets. More specific information regarding the cohorts, genotyping, quality control, and imputation can be viewed in previous studies [13].

The gene correlation estimates of depression were acquired from a meta-analysis [14]. It enrolled a total of 807,553 participants (246,363 cases and 561,190 controls) from three cohorts: 23andMe [15] (75,607 cases & 231,747 controls), UK Biobank [16] (127,552 cases & 233,763 controls), and PGC_139k [17] (43,204 cases & 95,680 controls), after excluding overlapping samples. All the samples were of European descent. In the 23andMe cohort, individuals with depression were defined via self-reporting using on-line investigation. Detailed description of these questions can be accessed in the publication by Hyde CL *et al.* [15]. In the UK Biobank cohort, depression was defined according to the self-report using a touchscreen survey. Participants with bipolar disorder, schizophrenia or personality disorder were excluded. Additionally, the enrolled samples were strictly confined to the "White British" to reduce the population architecture bias. The PGC_139k cohort used samples from the earlier released data of 23andMe and UK Biobank cohorts. The overlapping samples were removed from the combined cohort.

2.2 Genetic Instruments Selection

The genetic instruments of PCOS and depression were identified with a genome-wide statistical threshold of $p < 5 \times 10^{-8}$. By further calculating the linkage disequilibrium (LD) of related SNPs, independent SNPs (LD r^2 <0.001, kb <1 Mb) were retained. Additionally, we also selected steiger-MR approach [18] to verify if the SNPs elucidated remarkably more variance in exposure in contrast to result. The opposite might reveal reverse causation and violate the basic MR assumptions. In addition, the strength of gene instruments was assessed via F-statistics to avoid the weak instrument variables bias. F-statistics were calculated via the formula below: F-statistics = $(\text{Beta/Se})^2$, and its mean was regarded as the overall statistics. F-statistics >10 indicates strong statistical power [19]. Eventually, a total of 13 and 50 SNPs were selected as instrument variables for PCOS and depression, respectively. Detailed information of the IVs for PCOS and depression is summarized in Tables 1,2, separately.

Table 1. Summary characteristics for SNPs of PCOS.

Chr	Position	SNP	Effect Allele	Other Allele	EAF	Beta	SE	Gene	*p* value	F-statistic
2	43561780	rs7563201	A	G	0.4507	–0.1081	0.0172	THADA	3.68E-10	39.49976
2	2.13E+08	rs2178575	A	G	0.1512	0.1663	0.0219	ERBB4	3.34E-14	57.66287
3	1.32E+08	rs13164856	T	C	0.7291	0.1235	0.0193	IRF1/RAD50	1.45E-10	40.94674
8	11623889	rs804279	A	T	0.2616	0.1276	0.0184	GATA4/NEIL2	3.76E-12	48.09121
9	5440589	rs10739076	A	C	0.3078	0.1097	0.0197	PLGRKT	2.51E-08	31.0085
9	97723266	rs7864171	A	G	0.4284	–0.0933	0.0168	FANCC	2.95E-08	30.84216
9	1.27E+08	rs9696009	A	G	0.0679	0.202	0.0311	DENND1A	7.96E-11	42.18732
11	30226356	rs11031005	T	C	0.8537	–0.1593	0.0223	ARL14EP/FSHB	8.66E-13	51.02956
11	1.02E+08	rs11225154	A	G	0.0941	0.1787	0.0272	YAP1	5.44E-11	43.16297
11	1.14E+08	rs1784692	T	C	0.8237	0.1438	0.0226	ZBTB16	1.88E-10	40.48563
12	56477694	rs2271194	A	T	0.416	0.0971	0.0166	ERBB3/RAB5B	4.57E-09	34.21545
12	75941042	rs1795379	T	C	0.2398	–0.1174	0.0195	KRR1	1.81E-09	36.24657
16	52375777	rs8043701	A	T	0.815	–0.1273	0.0208	TOX3	9.61E-10	37.45675

SNP, single nucleotide polymorphisms; EAF, effect allele frequency; PCOS, polycystic ovary syndrome; Chr, chromosome; SE, standard error.

2.3 Statistical Analyses

Three methods including the inverse variance weighted (IVW), weighted median value, and MR Egger regression were utilized to assess the bilateral causal association between PCOS and depression (Fig. 1). The IVW approach hypothesizes that all the IVs are effective. It combines the effects of IVs and then yields an overall weighted effect. The weighted median estimator [20] can produce stable causality estimates even when 50% IVs are not valid. Two methods were undertaken to identify potential pleiotropy. First, we applied MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method to identify potential pleiotropic outliers, and MR-PRESSO conducts a global test of heterogeneity to identify potential horizontal pleiotropy [21]. Then, the intercept test from MR-Egger [22] was also applied to assess the directional pleiotropy. The intercept term significantly away from zero in statistics indicates the presence of pleiotropy and violation of basic MR assumptions.

Leave-one-out (LOO) analysis was used to identify the potential influential SNPs in the causality estimates between PCOS and depression. $p < 0.05$ (two-sided) was set as the threshold of statistical significance. The entire analytical process and figures were made via the R software (version 3.6.5) (https://www.r-project.org/).

3. Results

3.1 Genetically Predicted PCOS on Depression

As shown in Fig. 2, genetically predicted PCOS was associated with a 1.04-fold increased risk of depression by the IVW method (95% confidence interval (CI) = 1.01–1.06, $p = 0.003$). This increased risk was also replicated by the weighted median approach (OR = 1.04, 95% CI = 1.00–1.08, $p = 0.03$), suggesting a potential risky role of PCOS in the suffering of depression. No pleiotropic signs (MR-Egger intercept = –0.004, $p = 0.733$; MR-PRESSO global test $p = 0.179$) were observed (Table 3).

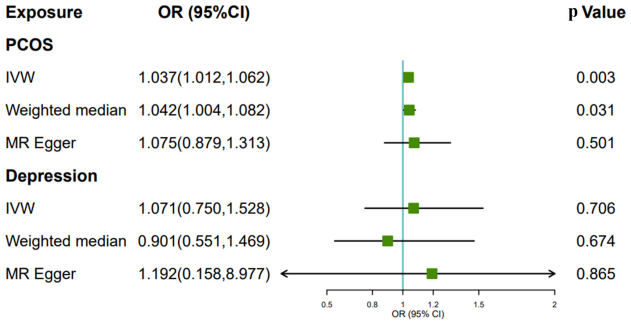

Fig. 2. The forest plot for bidirectional Mendelian randomization. PCOS, polycystic ovary syndrome; OR, odds ratios; IVW, inverse-variance-weighting; CI, confidence interval.

As displayed in Fig. 3A, with the increase of the SNP effect on PCOS, the SNP effect on depression increased as well. The LOO analyses disclosed that no influential SNP existed in the PCOS-depression causal association.

3.2 Genetically Predicted Depression on PCOS

The estimates of genetically forecasted depression on PCOS were displayed in Fig. 2. In the IVW analyses, the OR was 1.07 (95% CI = 0.76–1.50, $p = 0.706$), which did not suggest a risky role of depression in the occurrence of PCOS. The estimate from the weighted-median method (OR = 0.90, 95% CI = 0.55–1.47) was also insignificant ($p = 0.674$). There were no signs of pleiotropy (MR-Egger intercept = –0.003, $p = 0.961$; MR-PRESSO global test $p = 0.319$) in Table 3.

The scatter plot visualizing the SNPs-depression association against SNPs-PCOS association is displayed in Fig. 3B. The LOO analyses indicated that no influential SNP existed in the depression-PCOS association.

Table 2. Summary characteristic of IVs of depression.

Chr	Position	SNP	Effect allele	Other allele	Beta	Se	EAF	*p* value
1	52274078	rs7551758	G	T	0.0283	0.0043	0.5329	5.11E-11
1	72765116	rs2568958	A	G	0.0382	0.0044	0.6042	2.90E-18
1	175913828	rs10913112	T	C	–0.0262	0.0045	0.378	4.53E-09
1	197704717	rs17641524	T	C	–0.03	0.0053	0.2101	1.50E-08
1	49675276	rs354155	C	G	–0.0449	0.0075	0.0923	1.75E-09
1	67132262	rs7538938	C	T	0.0251	0.0043	0.5599	7.29E-09
1	18122009	rs4141983	C	T	–0.0264	0.0046	0.326	9.69E-09
2	208049581	rs2111592	A	G	0.0263	0.0046	0.3141	1.35E-08
2	212618440	rs72948506	A	G	0.0265	0.0047	0.2975	1.71E-08
3	158171455	rs35469634	G	A	–0.0241	0.0044	0.5774	3.28E-08
3	61255413	rs843812	A	G	0.0248	0.0044	0.4117	1.41E-08
3	49214303	rs9831648	T	G	–0.0292	0.0052	0.7739	1.59E-08
3	117515519	rs66511648	C	T	0.0297	0.0048	0.284	6.03E-10
3	115977242	rs76954012	A	T	0.0412	0.0074	0.0931	2.41E-08
5	103972357	rs30266	A	G	0.0366	0.0046	0.3271	1.43E-15
5	87630769	rs247910	G	A	0.0237	0.0043	0.457	4.71E-08
5	164487555	rs7725715	A	G	0.029	0.0043	0.5343	1.61E-11
6	27182377	rs150186873	C	A	0.0704	0.012	0.0327	4.51E-09
6	28366151	rs2232423	G	A	–0.062	0.007	0.1056	1.14E-18
6	165117329	rs9364755	G	A	0.0283	0.0051	0.2262	3.49E-08
6	67000001	rs2214123	G	A	–0.0261	0.0045	0.6466	8.56E-09
6	142996618	rs2876520	G	C	0.026	0.0043	0.4688	2.24E-09
7	82448100	rs2522831	C	T	0.024	0.0043	0.4739	2.11E-08
7	109100414	rs4730387	A	T	0.0238	0.0043	0.4659	4.12E-08
7	117625599	rs150346963	T	C	0.0283	0.0044	0.4118	1.16E-10
7	12250402	rs3807865	A	G	0.031	0.0044	0.4105	1.09E-12
7	2086814	rs10235664	C	T	–0.027	0.0049	0.2529	4.68E-08
7	38724868	rs59082935	T	C	0.0363	0.0066	0.1342	3.07E-08
9	37182655	rs62535714	A	G	0.0339	0.0058	0.1639	4.69E-09
9	11203149	rs1931388	G	A	–0.0295	0.0044	0.4042	1.68E-11
9	25232978	rs59283172	A	G	–0.039	0.007	0.1081	2.41E-08
9	119731359	rs2418449	C	T	–0.0281	0.0048	0.281	4.25E-09
10	106610839	rs1021363	G	A	–0.03	0.0045	0.6434	2.29E-11
11	61471678	rs198457	T	C	–0.0315	0.0056	0.1886	1.90E-08
11	88756779	rs4497414	C	T	0.0291	0.0044	0.44	2.93E-11
11	113365141	rs4936276	C	G	0.0278	0.0044	0.622	3.57E-10
12	52352301	rs61914045	A	G	0.0309	0.0054	0.2034	7.96E-09
13	31790053	rs9529218	T	C	–0.034	0.0054	0.2031	2.23E-10
13	53860655	rs9536381	T	C	0.0255	0.0046	0.3259	2.62E-08
13	80921519	rs508502	T	C	–0.0264	0.0048	0.2992	3.56E-08
14	42097937	rs1950829	G	A	–0.0297	0.0043	0.5173	4.74E-12
14	103997525	rs754287	A	T	–0.0289	0.0045	0.3664	1.31E-10
14	75125540	rs7152906	C	T	0.0258	0.0043	0.5196	1.87E-09
15	88945878	rs28541419	G	C	–0.0292	0.0052	0.2308	1.76E-08
16	13800430	rs12919291	C	G	0.0327	0.0055	0.1884	3.09E-09
18	35155910	rs4799949	T	C	–0.0292	0.0046	0.6684	1.40E-10
18	53099012	rs12967143	C	G	–0.0345	0.0047	0.7012	2.53E-13
18	77580712	rs7241572	A	G	0.0323	0.0054	0.2047	2.43E-09
18	50861409	rs1367635	C	T	0.0253	0.0043	0.5148	4.35E-09
20	44692598	rs13037326	T	C	0.031	0.0049	0.2597	2.40E-10

SNP, single nucleotide polymorphisms; EAF, effect allele frequency; PCOS, polycystic ovary syndrome; Chr, chromosome; SE, standard error; IV, instrumental variants.

Table 3. The test of pleiotropy in bidirectional Mendelian randomization.

Exposure	Outcome	MR-Egger intercept		MR-PRESSO global test
		The estimates of egger intercept	*p*	*p*
PCOS	Depression	–0.004	0.733	0.179
Depression	PCOS	–0.003	0.961	0.319

PCOS, polycystic ovary syndrome.

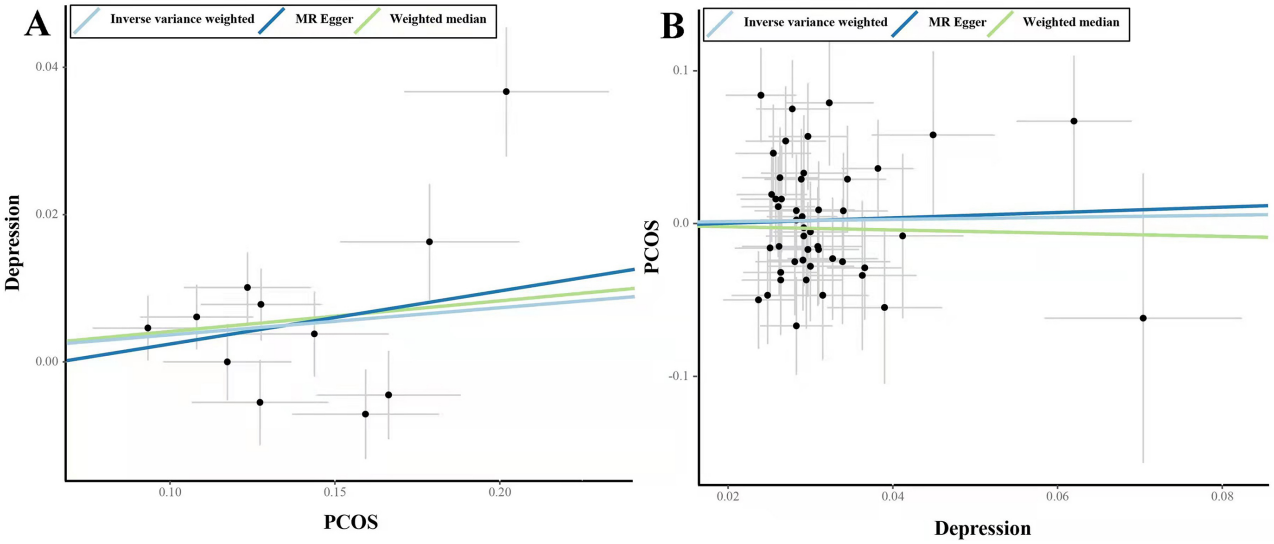

Fig. 3. The scatter plot for bidirectional Mendelian randomization. The subplots (A) represents the causal effects of PCOS on depression; The subplots (B) represents the causal effects of depression on PCOS.

4. Discussion

Herein, our team completed a two-sample MR and identified a potential causal association of PCOS with depression via the biggest GWAS data set to date. This study suggested that PCOS might increase the risk of depression. In contrast, we did not find evidence that depression may increase the risk of PCOS.

Previously, observational researches have unveiled the underlying correlation between depression and PCOS. Açmaz *et al.* [23] discovered that PCOS group (n = 86) with infertility had higher depression scores. Altinkaya *et al.* [24] found that Beck Depression Inventory scoring was remarkably greater in patients with PCOS (n = 83) in contrast to normal controls [24]. An Iranian case control study found that there existed a remarkable diversity between PCOS (n = 742) and controls (n = 798) in depression (18.9% vs. 7.9%; $p < 0.001$) [25]. A cross-sectional study showed that females with PCOS displayed severer anxiety ($p = 0.007$) and depression ($p = 0.048$) in contrast to females without PCOS [26]. A study in Southwest China involved 120 out-patients with PCOS and 100 normal controls showed that the prevalence of depression (27.5% vs. 3.0%) was greater in PCOS sufferers in contrast to controls ($p < 0.05$) [27]. Coherent with those aforesaid observation researches, data from this study herein backed the assumption that PCOS might be related to an elevated risk of depression.

Despite the fact that the biofunction of PCOS in the depression progression remains elusive, some researches have offered reasonable elucidation in this regard, one of which is hyperandrogenism [28,29]. Second, a positive association between insulin resistance and depression was found [30,31]. The randomized control trial (RCT) of Greenwood *et al.* [32] (738 PCOS females) potently reveals that insulin resistance is a causation factor for PCOS-related depression. In addition, PCOS is considered a proinflammation status featured by elevated contents of proinflammation biomarkers. Hence, there exists a probability of an inflammation association between depression and PCOS [33]. It is probable that the inflammation biomarkers in PCOS can cross the blood-brain barrier, inducing the progression of depression [33]. While the above theory-wise elucidation is reasonable, more researches are needed to reveal the potential causal link between PCOS and depression.

The major contribution of the present research is the utilization of the MR method, which has been extensively utilized to explore the causality of PCOS with the risks of other diseases. In addition, our team obtained the SNPs of depression and PCOS via the biggest GWAS datasets to date. The SNPs herein were remarkably related to PCOS at genome-wide significance, hence decreasing potential breach of the first hypothesis of MR. In addition, the F-statistics for the IVs all satisfied the liminal value of F-statistics >10, revealing that the analyses were not likely

to be influenced by weak instrument bias [34]. The MR-Egger regression analyses were completed to study the data and did not observe the existence of directional pleiotropy [22]. Those coherent outcomes revealed the stability of the discoveries in the present paper.

Nonetheless, there are certain limitations of our research. Firstly, as our analyses were limited by European individuals, the results might not be extended to other races. Nevertheless, this remarkably decreased the underlying influences of population stratification bias as well. Secondly, while the MR method may offer a non-biased outcome because of the diminished confounders, the gene–milieu and gene–gene interplay might influence the progression of depression or PCOS inevitably. Thirdly, the MR analyses of PCOS and depression were on the foundation of summary statistics with comparatively smaller sample size, and the underlying side effects of PCOS on the risks of depression ought to be further investigated in bigger sample size. In addition, as the related data of all PCOS phenotypes were unavailable, our team merely investigated the correlation between PCOS and depression, and our team did not stratify the outcomes herein as per the diverse PCOS phenotypes. More researches highlighting the correlation of PCOS with depression are still needed.

5. Conclusions

To sum up, the present research offered evidence to suggest potential causality between PCOS and an elevated risk of depression amongst European individuals. Nevertheless, the accurate roles and the potential biology processes of PCOS in the progression of depression require deeper explorations.

Author Contributions

FQ and YF designed the study. XZ and YT conducted data collection. XZ and YG conducted data analysis. XZ and MD carried out table arrangement and picture drawing. YM conducted the supervision of data analysis. YF conducted supervision. XZ and YT wrote the original draft. YF and FQ reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. FQ is serving as one of the Guest editors of this journal. We declare that FQ had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

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