Assessing the Potential Causal Relationship between Polycystic Ovary Syndrome and Post-Traumatic Stress Disorder: A Bidirectional Mendelian Randomization Study

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Abstract

Background: Observational studies have reported that individuals diagnosed with polycystic ovary syndrome (PCOS) face a heightened vulnerability to developing post-traumatic stress disorder (PTSD). However, it is unclear whether this relationship is causal. Consequently, we implemented a bidirectional Mendelian randomization (MR) analysis to examine the empirical causal association of PCOS and PTSD. **Methods**: We acquired genetic association data for PCOS through a comprehensive meta-analysis from several large-scale genome-wide association studies (GWASs), which enrolled 10,074 cases and 103,164 controls. For PTSD, we obtained data from a GWAS performed by the Psychiatric Genomics Consortium Posttraumatic Stress Disorder (PGC-PTSD) group. The study included a total of 23,212 cases of PTSD and 151,447 controls of European ancestry. For both PCOS and PTSD, we carefully selected genetic instruments that met the rigorous significance threshold ($p < 5 \times 10^{-8}$, $r^2 < 0.01$). To investigate the causal association between PCOS and PTSD, we conducted bidirectional Mendelian randomization (MR) analyses. The primary analysis employed the inverse-variance weighted (IVW) method, complemented by alternative MR approaches such as the maximum-likelihood method, MR-Egger regression, Mendelian randomization-Robust Adjusted Profile Score (MR-RAPS), and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test. Sensitivity analyses were also carried out to verify the robustness of this association. **Results**: In this study, we identified and utilized 14 genetic variants as instruments for PCOS, while 2 genetic variants were selected as instruments for PTSD. Our findings demonstrated that a genetic predisposition to PCOS was significantly associated with an elevated risk of developing PTSD (odds ratio (OR) = 1.11, 95% confidence interval (CI): 1.03–1.19, $p = 7.27 \times 10^{-3}$ for IVW). MR-Egger regression analysis was performed, and the results did not provide evidence of directional pleiotropy (p intercept = 0.187). Sensitivity analyses utilizing alternative MR methods consistently yielded similar results, supporting the robustness of our findings. Furthermore, in the reverse MR analysis, we observed no significant association between genetic predisposition to PTSD and the risk of developing PCOS (OR = 1.15, 95% CI: 0.69–1.91, $p = 0.586$ for IVW). Comparable null associations were also observed when alternative MR methods were employed. **Conclusions**: Through a genetic epidemiological approach, we found that genetic predisposition to PCOS was associated with an increased risk of PTSD, suggesting a potential causal relationship between PCOS and PTSD. Nonetheless, further investigation is necessary to elucidate the underlying mechanism through which PCOS contributes to the development of PTSD.

Keywords: genetic instruments; Mendelian randomization; polycystic ovary syndrome; post-traumatic stress disorder

1. Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine condition that primarily affects women during their reproductive years. It is characterized by several typical clinical features, including hyperandrogenism (acne, hirsutism, and alopecia), menstrual irregularity (long menstrual cycles, oligo/anovulation), and the presence of polycystic ovaries [1,2]. It has been estimated that in 2019, approximately 66.0 (95% uncertainty interval (UI): 46.0–86.3) million individuals were affected by PCOS worldwide, with an overall prevalence rate of 829.6 per 100,000 [3].

Despite the precise etiology and pathogenesis of PCOS remaining uncertain, available evidence suggests that its occurrence is shaped by a blend of genetic and environmental factors. Established risk factors for PCOS encompass genetic susceptibility [4], obesity [5] and insulin resistance (IR) [6,7]. Vink *et al.* [4] conducted a study revealing that the similarity of PCOS among monozygotic twin sisters (tetrachoric r^2 0.71) was approximately twice as pronounced compared to dizygotic twins or other sisters (tetrachoric r^2 0.38). In recent times, there has been a heightened recognition of the detrimental effects of PCOS on psychological well-being [8]. In a meta-analysis con-

ducted by Brutocao *et al.* [9], which included 57 studies and a total of 172,040 patients, it was discovered that women diagnosed with PCOS had a higher likelihood of experiencing clinical depression (odds ratio (OR) = 2.79; 95% confidence interval (CI): 2.23–3.50), anxiety (OR = 2.75; 95% CI: 2.10–3.60), bipolar disorder (OR = 1.78; 95% CI: 1.43–2.23), and obsessive-compulsive disorder (OR = 1.37; 95% CI: 1.22–1.55). Likewise, in a meta-analysis conducted by Cooney *et al.* [10], which covered 30 cross-sectional studies across 10 countries, it was observed that women diagnosed with PCOS had a higher probability of experiencing moderate to severe symptoms of depression and anxiety compared to non-PCOS controls.

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that arises and persists after an individual personally experiences, witnesses, or is confronted with one or more traumatic events. These events can involve the individual themselves or others, and the resulting symptoms can endure for a significant period of time, affecting their mental and emotional well-being [11]. The presence of comorbid mental disorders, including major depression, is commonly observed in individuals with PTSD. Moreover, those affected by PTSD face an elevated risk of suicidal ideation, substance abuse, and impaired occupational functioning [12]. Multiple medical conditions have been associated with a heightened vulnerability for developing PTSD. A recent meta-analysis revealed that the combined prevalence rate of PTSD among children and adolescents diagnosed with cancer was about 20.90% (95% CI: 13.28–29.73%) [13]. Among adult patients, in turn, there is a higher prevalence of post-traumatic stress disorder (PTSD) observed in those with chronic heart diseases (CHDs) when compared to those without CHDs (0.8% vs. 0.5%; adjusted prevalence ratio (Apr): 1.5, 95% CI: 1.2–1.8). [14]. In addition, a study conducted by Tay *et al.* [15] revealed that women with PCOS had a notably higher prevalence of PTSD compared to women without PCOS (adjusted odds ratio (OR) = 1.5, 95% confidence interval (CI): 1.1–1.9). Nevertheless, as this finding stems from a conventional observational epidemiological study, it is susceptible to potential biases, including confounding and reverse causation. Therefore, the causal relationship of the observed association remains ambiguous.

Mendelian randomization (MR) is a genetic epidemiological method that leverages single nucleotide polymorphisms (SNPs) strongly associated with the exposure of interest as instrumental variables (IVs). This approach enables the estimation of potential causal relationships between the exposure and the outcome in question [16]. Assuming that genotypes are randomly allocated during gamete formation and disease onset, the application of the IV approach effectively addresses the problems of confounding and reverse causation commonly encountered in observational studies. This approach helps address these concerns to a considerable extent [17,18]. Therefore, the present study implemented a two-sample Mendelian randomization (MR) analysis to investigate the possible causal relationship between PCOS and PTSD.

2. Materials and Methods

2.1 Data Sources

The study design, as presented in Fig. 1, used a bidirectional MR analysis to identify the causality between PCOS and PTSD. To accomplish this, we utilized summary data obtained from published genome-wide association studies (GWAS). To ensure the robustness of the MR study, it is essential to fulfill the following critical assumptions: (i) the genetic variants chosen as instrumental variables (IVs) must exhibit strong associations with the exposure of interest; (ii) the IVs employed should not be linked to any confounding factors; and (iii) the IVs should solely influence the outcome through the exposure being investigated [18].

We acquired summary-level genetic association data for PTSD from the Psychiatric Genomics Consortium Posttraumatic Stress Disorder (PGC-PTSD) group. This dataset consisted of 23,212 individuals diagnosed with PTSD and 151,447 controls of European ancestry [19]. The determination of PTSD status was based on established criteria, while the controls primarily consisted of individuals who had experienced trauma but did not meet the diagnostic criteria for PTSD. Genotyping was carried out using Illumina genotyping arrays, and the association between SNPs and PTSD was assessed using logistic regression in PLINK 1.9 (National Institutes of Health, Bethesda, MD, USA) , incorporating the first five principal components as covariates, under an additive model.

We obtained genetic association data for PCOS from a meta-analysis of genome-wide association studies (GWAS), which encompassed a total of 10,074 cases and 103,164 controls of European ancestry [20]. This represents the most extensive GWAS meta-analysis conducted on PCOS thus far, comprising participants from seven distinct cohorts, including Rotterdam, Estonian Genome Center of the University of Tartu (EGCUT), deCODE, the UK (London/Oxford), Chicago, Boston, and 23andMe. Diagnosis of PCOS among cases was established based on the criteria outlined by the National Institute of Health (NIH) or the Rotterdam Criteria. Due to the unavailability of publicly accessible data from 23andMe, the study population ultimately consisted of 4138 individuals diagnosed with PCOS and 20,129 controls. The comprehensive details regarding the data sources utilized in this study are provided in **Supplementary Table S1**. As this study solely relied on published summary-level GWAS datasets, no further ethical approval was deemed necessary.

2.2 Selection of Instrumental Variables

To ascertain independent SNPs associated to PCOS risk, we employed a rigorous significance threshold ($p < 5 \times 10^{-8}$). Only SNPs with an $r^2 < 0.01$ were selected to ensure independence and avoid linkage disequilibrium
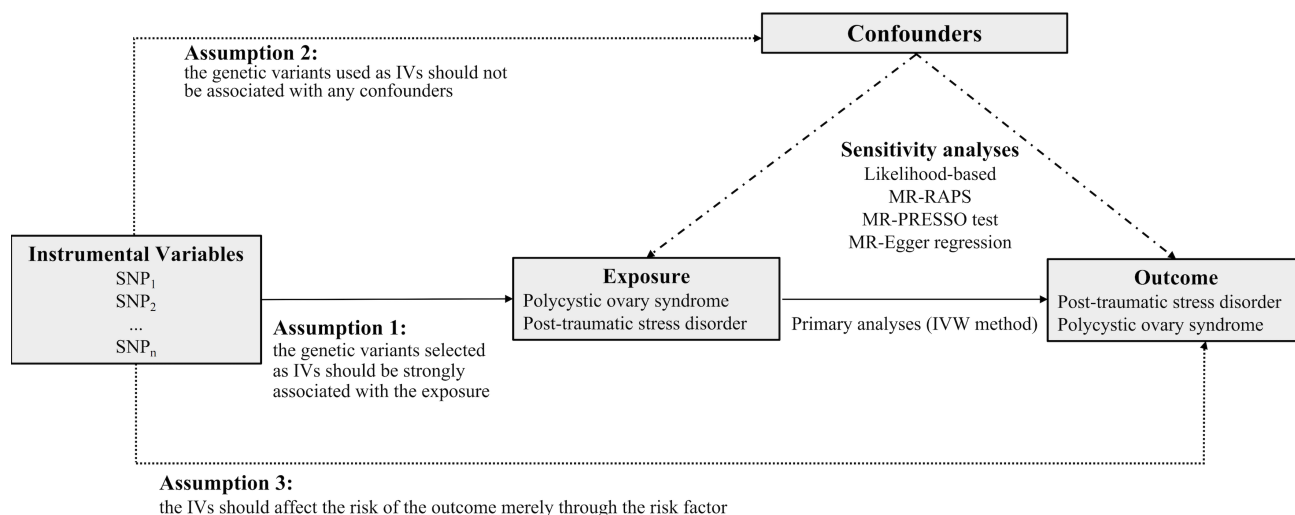
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Fig. 1. The overall design of the present MR study. MR, Mendelian randomization; SNP, single nucleotide polymorphism; IVs, instrumental variables; MR-RAPS, Mendelian randomization-Robust Adjusted Profile Score; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; IVW, inverse-variance weighted.

(LD) issues. In the current study, a total of 14 independent SNPs were carefully chosen as IVs for the exposure analysis of PCOS. These IVs, which accounted for approximately 0.27% of the variance in PCOS risk, were utilized in the analysis. Moreover, we obtained two SNPs associated with the risk of PTSD, reaching genome-wide significance, from the Psychiatric Genomics Consortium Posttraumatic Stress Disorder (PGC-PTSD) group. The comprehensive information regarding the SNPs used as IVs is provided in Table 1.

2.3 Statistical Analysis

To evaluate the strength of the instrumental variables (IVs), we calculated F-statistics using the formula: $F = r^2 (N - k - 1) / k (1 - r^2)$. Here, r^2 represents the coefficient of determination, N represents the sample size, and k represents the number of IVs utilized in the analysis [21]. Subsequently, we conducted the inverse-variance weighted (IVW) method as the primary analysis in the MR study to examine the causality between genetic predisposition to PCOS and the risk of PTSD, as well as the reverse association. To ensure the reliability and robustness of our findings, we performed a range of sensitivity analyses. These included alternative MR methods such as the likelihood-based method, Mendelian randomization-Robust Adjusted Profile Score (MR-RAPS), MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test, and MR-Egger regression. These additional analyses allowed us to evaluate the stability and consistency of our results across different statistical approaches, helping to validate the causal relationship between PCOS and PTSD.

Specifically, the IVW approach was presented, which combines the effects of IVs and provides a weighted effect estimate. This approach assumes the validity of all IVs and aims to yield a consistent estimate by consider-

ing the inverse of their variances [22]. To assess the heterogeneity of the IVs used in the analysis, we performed Cochran's Q test to assess heterogeneity. If heterogeneity was present ($p < 0.05$), we utilized the random-effects IVW method. Conversely, if no significant heterogeneity was detected, the fixed-effects IVW method was applied. These approaches allowed for appropriate consideration of the potential variability among the IVs and ensured robustness in our analysis [23]. Furthermore, we conducted the likelihood-based method to investigate the causal impact of changes in PCOS risk on the risk of PTSD. This method assumes a linear relationship between the two conditions and models their association using a bivariate normal distribution. By utilizing this approach, we aimed to estimate the magnitude and direction of the causal effect, taking into account the underlying statistical assumptions of the relationship between PCOS and PTSD [22]. To account for the potential influence of pleiotropic IVs, we conducted the Robust Adjusted Profile Score (MR-RAPS) analysis with the Huber loss function. This method allows for the estimation of causal effects while considering the presence of measurement error in single nucleotide polymorphism exposure (SNP-exposure) effects. Importantly, MR-RAPS is robust to both systematic and idiosyncratic pleiotropy, ensuring the reliability of our findings in the presence of potential confounding factors [24]. To identify and address potential outliers in the data, we conducted the MR-PRESSO test. This analysis allowed us to detect any horizontal pleiotropic outlier variants and subsequently provide corrected causal estimates by excluding these outliers from the analysis. By implementing the MR-PRESSO test, we aimed to ensure the robustness and accuracy of our causal estimates by mitigating the potential influence of any influential variants that could bias the results [25]. To examine the possibility of directional pleiotropy, we applied MR-Egger re-

Table 1. Characteristics of the genetic variants associated with PCOS and PTSD.

SNP	Chr	Position	Effect allele	β	SE	p-value	Variance explained (r^2)	F-statistic
PCOS								
rs7563201	2	43561780	A	−0.108	0.017	3.68×10^{-10}	0.000348	39.43
rs2178575	2	213391766	A	0.166	0.022	3.34×10^{-14}	0.000507	57.45
rs13164856	5	131813204	T	0.124	0.019	1.45×10^{-10}	0.000364	41.28
rs804279	8	11623889	A	0.128	0.018	3.76×10^{-12}	0.000427	48.39
rs10739076	9	5440589	A	0.11	0.02	2.51×10^{-8}	0.000275	31.18
rs7864171	9	97723266	A	−0.093	0.017	2.95×10^{-8}	0.000271	30.64
rs9696009	9	126619233	A	0.202	0.031	7.96×10^{-11}	0.000372	42.19
rs11031005	11	30226356	T	−0.159	0.022	8.66×10^{-13}	0.000449	50.84
rs11225154	11	102043240	A	0.179	0.027	5.44×10^{-11}	0.000382	43.31
rs1784692	11	113949232	T	0.144	0.023	1.88×10^{-10}	0.000358	40.6
rs2271194	12	56477694	A	0.097	0.017	4.57×10^{-9}	0.000301	34.14
rs1795379	12	75941042	T	−0.117	0.02	1.81×10^{-9}	0.000318	36
rs8043701	16	52375777	A	−0.127	0.021	9.61×10^{-10}	0.000329	37.28
rs853854	20	31420757	A	−0.098	0.016	2.36×10^{-9}	0.000319	36.15
PTSD								
rs34517852	6	157789333	A	0.11	0.02	3.10×10^{-9}	0.000173	30.25
rs9364611	6	162163506	T	−0.124	0.02	4.30×10^{-8}	0.00022	38.44

Chr, chromosome; PCOS, polycystic ovary syndrome; PTSD, post-traumatic stress disorder; SE, standard error; SNP, single nucleotide polymorphism.

gression. This method incorporates an intercept term into the regression model, allowing us to assess the presence of pleiotropy. If the intercept term significantly deviates from zero in statistical analysis, it suggests the existence of pleiotropy and potential violation of fundamental MR assumptions. By utilizing MR-Egger regression, we aimed to gain insights into the presence and impact of pleiotropic effects on our causal inference [26]. To explore potential secondary phenotypes associated with the IVs used in our analysis, we conducted a manual search of the SNPs in the GWAS Catalog (http://www.ebi.ac.uk/gwas, accessed on April 6, 2022). This allowed us to investigate any additional phenotypic associations related to the IVs. Additionally, we conducted sensitivity analyses by excluding any SNPs that displayed pleiotropic effects, in order to evaluate the consistence of our findings and the potential impact of these variants on the results.

All statistical analyses were conducted using R software version 3.6.3 (R Project for Statistical Computing, Vienna, Austria), using the Mendelian randomization, Two-Sample MR, and MRPRESSO packages. A two-sided p-value threshold of 0.05 was considered statistically significant for all analyses.

3. Results

The F-statistics for the IVs chosen for PCOS ranged from 30.64 to 57.45, while for PTSD they ranged from 30.25 to 38.44. These values $>$10 indicate that the IVs were less susceptible to weak instrument bias (Table 1).

Genetic predisposition to PCOS was found to be associated with an elevated risk of developing PTSD (OR = 1.11, 95% CI: 1.03–1.19, $p = 7.27 \times 10^{-3}$ for IVW)

(Fig. 2). Sensitivity analyses using alternative MR methods consistently showed a statistically significant association, with similar effect estimates. Specifically, the maximum-likelihood method yielded an odds ratio (OR) of 1.11 (95% CI: 1.02–1.21, $p = 0.021$), and the MR-RAPS method yielded an OR of 1.12 (95% CI: 1.03–1.21, $p = 6.76 \times 10^{-3}$). The absence of outlier SNPs detected through the MR-PRESSO test strengthens the reliability of our findings. Moreover, the estimation between genetic predisposition to PCOS and the increasing risk of PTSD remained consistent, with comparable results (OR = 1.11, 95% CI: 1.02–1.21, $p = 0.039$). These additional findings further support the robustness of the observed relationship between PCOS genetics and the development of PTSD. MR-Egger regression analysis did not provide significant evidence of directional pleiotropy (p intercept = 0.187). This indicates that the basic assumption of Mendelian randomization is upheld and suggests that there is no substantial bias due to pleiotropic effects in our study (Fig. 3).

During our scan of the SNPs assigned as IVs in the GWAS Catalog, we obtained three SNPs (rs11031005, rs13164856, and rs2271194) that showed associations with other traits or phenotypes (**Supplementary Table S2**). After excluding these SNPs, the association between PCOS and PTSD remained statistically significant (OR = 1.09, 95% CI: 1.00–1.20, $p = 0.044$) using the IVW method, indicating that the relationship between PCOS and PTSD is robust even without these particular SNPs.

The reverse MR analysis indicated that genetic predisposition to PTSD was not significantly associated with the risk of PCOS (OR = 1.15, 95% CI: 0.69–1.91, $p = 0.586$) using the IVW method. The sensitivity analyses, includ-
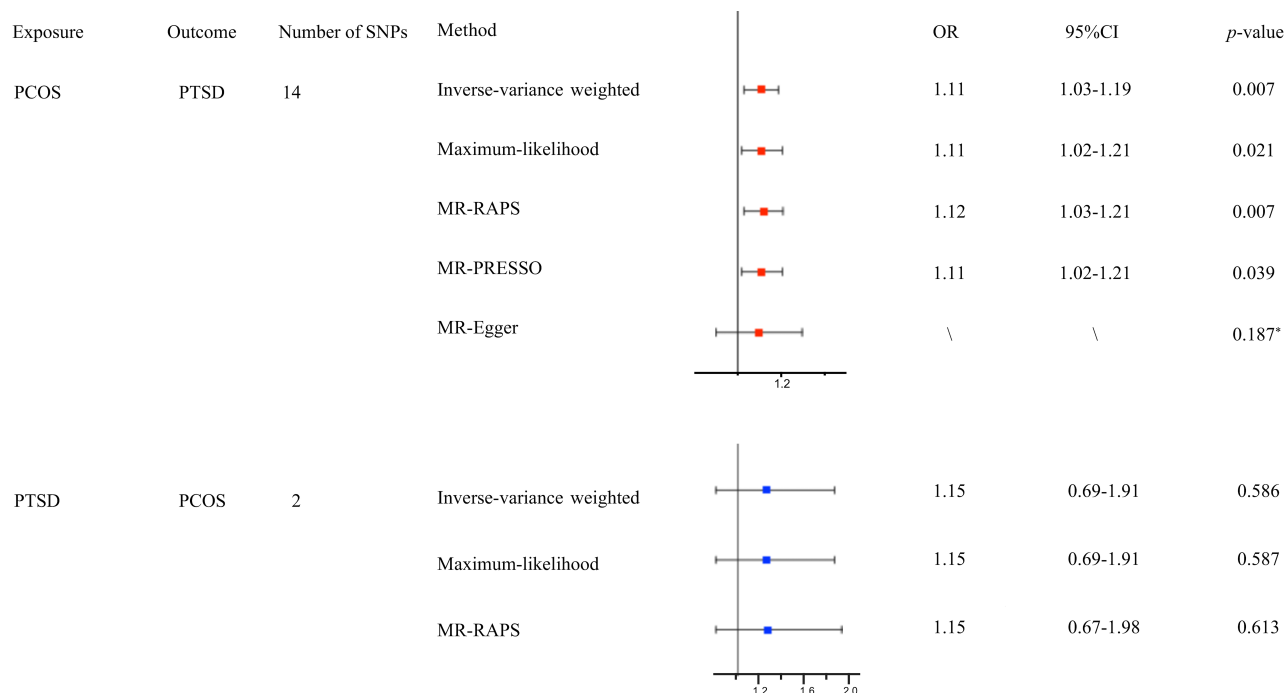
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Exposure	Outcome	Number of SNPs	Method		OR	95%CI	*p*-value
PCOS	PTSD	14	Inverse-variance weighted		1.11	1.03-1.19	0.007
			Maximum-likelihood		1.11	1.02-1.21	0.021
			MR-RAPS		1.12	1.03-1.21	0.007
			MR-PRESSO		1.11	1.02-1.21	0.039
			MR-Egger		\	\	0.187*
PTSD	PCOS	2	Inverse-variance weighted		1.15	0.69-1.91	0.586
			Maximum-likelihood		1.15	0.69-1.91	0.587
			MR-RAPS		1.15	0.67-1.98	0.613

Fig. 2. MR effect estimates for associations of exposures with the risk of outcomes. **p*-value of the intercept from MR-Egger regression. SNP, single nucleotide polymorphism; MR-RAPS, Mendelian randomization-Robust Adjusted Profile Score; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; PCOS, polycystic ovary syndrome; PTSD, post-traumatic stress disorder; OR, odds ratio; CI, confidence interval.
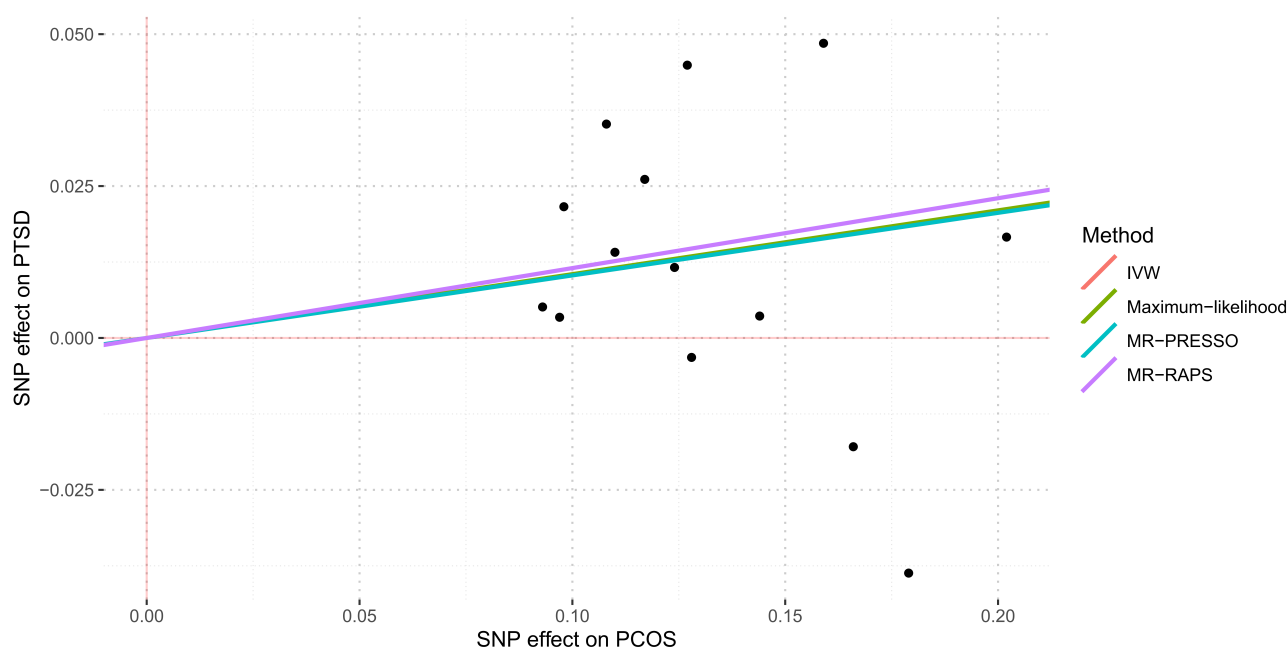

Fig. 3. Plot of the effect size and 95% CIs of each SNP on PCOS and PTSD risk. The x-axis plots the previously published b-estimate for the association of each SNP with PCOS. The y-axis plots the bestimate for the association of each SNP with risk of PTSD. Error bars indicate 95% CIs of the effect estimates. Slopes of the orange green blue and purple lines represent the combined causal effect estimates using the IVW method, maximum-likelihood method, MR-PRESSO test and MR-RAPS method. IVW, inverse-variance weighted; SNP, single nucleotide polymorphism; MR-RAPS, Mendelian randomization-Robust Adjusted Profile Score; MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; PCOS, polycystic ovary syndrome; PTSD, post-traumatic stress disorder.

ing the maximum-likelihood method (OR = 1.15, 95% CI: 0.69–1.91, p = 0.587) and MR-RAPS (OR = 1.15, 95% CI: 0.67–1.98, p = 0.613), consistently yielded similar causal effect estimates (Fig. 2). The results from leave-one-out method illustrated that the combined effect estimates were consistent after removing SNPs in turn (**Supplementary Fig. S1**).

4. Discussion

In this study, we employed a bidirectional MR approach to examine the potential causal link between PCOS and PTSD. Our findings revealed a significant causality between genetic susceptibility to PCOS and the developing risk of PTSD. The results remained consistent and robust across various sensitivity analyses utilizing different MR methods and alternative instrumental variable sets. These results indicate the stability of our findings. Conversely, we observe non-significant evidence between genetic predisposition to PTSD and the increasing risk of PCOS.

Previous observational studies have demonstrated a significant association of PCOS condition and PTSD onset. For instance, a cross-sectional analysis including 89 women with PCOS and 456 women without PCOS revealed that PCOS was strongly associated with an increased risk of PTSD (OR = 2.2, 95% CI: 1.7–2.8, p < 0.001). Even when consider multiple important factors such as body mass index (BMI), education, employment, smoking status, alcohol use, physical activity level, adverse childhood experience, social support, and perceived stress, the association between PCOS and PTSD remained robust. After adjusting for these confounding variables, the odds of developing PTSD were still significantly higher in individuals with PCOS (adjusted odds ratio = 1.5, 95% CI: 1.1–1.9, p = 0.008). This suggests that PCOS is independently associated with an increased likelihood of experiencing PTSD [15]. Our findings consistently demonstrated that genetically predicted PCOS was associated with a heightened risk of developing PTSD. By leveraging the assumption that exposure-related genetic variants are randomly allocated during conception, we utilized genetic variants associated with PCOS risk as instrumental variables. This approach allowed us to assess the impact of PCOS on the likelihood of developing PTSD, while minimizing the influence of confounding factors such as socioeconomic status or education level, as well as the potential bias from reverse causation.

Psychiatric disorders in individuals with PCOS are influenced by intricate mechanisms. One contributing factor is the presence of PCOS-related manifestations, including acne, hirsutism, obesity, and infertility. These physical features can potentially diminish self-esteem and amplify psychological distress among affected women. Furthermore, hormonal imbalances associated with PCOS can also impact mental well-being. A study by Marsh *et al.* [27] demonstrated that individuals with PCOS exhibited lower levels of positive mood and higher levels of trait anxiety in comparison to control groups. Moreover, elevated levels

of total testosterone and insulin, as well as insulin resistance, were found to be associated with increased scores in trait anger and anger expression [28]. The hormonal imbalance in individuals with PCOS can also impact the microstructure of white matter, thereby affecting cognitive function [29] and work efficiency [30] in PCOS patients. Furthermore, hyperparathyroidism is a significant clinical manifestation observed in PCOS, and it can influence mood disorders and impulsivity in both women with and without PCOS [28,31,32]. Lastly, there is evidence suggesting that women with PCOS may exhibit an increased responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, which could contribute to the development of psychiatric disorders through disrupted stress responses [33,34]. While these explanations offer biologically plausible connections, additional research is needed to elucidate the precise underlying mechanisms through which PCOS contributes to the development of PTSD.

The application of genetic variants as IVs in MR analyses greatly addresses the challenge of confounding present in conventional observational studies. Nevertheless, it is important to acknowledge several limitations in our study. Certain limitations should be considered when interpreting the results of our study. Firstly, the participants were predominantly of European descent, which raises the question of generalizability to other ethnic populations. Additional research is warranted to assess the generalizability of our findings across diverse populations. Furthermore, it is worth noting that the lack of a statistically significant association between PTSD and PCOS in our study may be influenced by the limited statistical power and the relatively small size of the instrumental variable used in the Mendelian randomization analysis. Thus, additional studies with larger sample sizes are warranted to further investigate the potential relationship between PTSD and PCOS. To address concerns regarding the validity of the MR study, we took measures to ensure the selection of appropriate instrumental variables (IVs). Specifically, we included independent SNPs that reached the genome-wide significance level ($p < 5 \times 10^{-8}$) and demonstrated strong instrument strength (i.e., F-statistic >10) in our analysis. Additionally, we applied a linkage disequilibrium (LD) threshold of $r^2 < 0.01$ to avoid the inclusion of SNPs in high LD. These rigorous criteria were implemented to enhance the reliability of our results and minimize potential biases associated with instrumental variable selection. Finally, one potential limitation of our MR study is the presence of pleiotropy. To address this concern, we conducted various MR approaches to examine the possibility of pleiotropic effects. Fortunately, our findings did not indicate any evidence of pleiotropy affecting the causal relationship between PCOS and the risk of developing PTSD. Moreover, we took an additional step to mitigate potential pleiotropic effects by specifically selecting SNPs that were solely associated with the exposures of interest. We accomplished this by excluding SNPs associated with other phenotypes, as determined through the

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GWAS Catalog. By employing these strategies, we aimed to minimize the impact of pleiotropy on our results and enhance the validity of our findings.

5. Conclusions

Through the utilization of a genetic epidemiological approach, our study revealed a potential causality between genetic predisposition to PCOS and an increasing odd of PTSD. This finding indicates a potential causal relationship between PCOS and PTSD. Nevertheless, it is crucial to delve deeper into the underlying mechanisms that link PCOS to the development of PTSD. Further investigation in this area will provide valuable insights and contribute to a comprehensive understanding of the interplay between PCOS and PTSD.

Abbreviations

CI, confidence interval; GWAS, genome-wide association studies; IV, instrumental variable; IVW, inverse-variance weighted; LD, linkage disequilibrium; MR, mendelian randomization; OR, odds ratio; PCOS, polycystic ovary syndrome; PGC-PTSD, Psychiatric Genomics Consortium Post-traumatic Stress Disorder; PRESSO, Pleiotropy RESidual Sum and Outlier; PTSD, post-traumatic stress disorder; RAPS, Robust Adjusted Profile Score; SNPs, single nucleotide polymorphisms.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available in the genome-wide association studies repository. (PCOS: https://doi.org/10.17863/CAM.36024. PTSD: https://www.med.unc.edu/pgc/download-results/)

Author Contributions

XZ and JS performed the literature review, conducted data analysis, interpreted findings, and drafted the manuscript. BL and MCD carried on data analysis and interpreted findings. BXW, XWC and YFH mainly conducted on the data collation and checked the manuscript. YYM and FQ directed analytic strategy, supervised the study from conception to completion and revised drafts of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Since this project is based on the statistical analysis of publicly available databases and published studies, ethics approval and consent to participate is not applicable.

Conflict of Interest

The authors declare no conflict of interest. Fan Qu is serving as one of the Guest editors of this journal. We declare that Fan Qu 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 Michael H. Dahan.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5009193.

References

[1] Meier RK. Polycystic Ovary Syndrome. The Nursing Clinics of North America. 2018; 53: 407–420.

[2] Louwers YV, Laven JSE. Characteristics of polycystic ovary syndrome throughout life. Therapeutic Advances in Reproductive Health. 2020; 14: 2633494120911038.

[3] GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England). 2020; 396: 1204–1222.

[4] Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. The Journal of Clinical Endocrinology and Metabolism. 2006; 91: 2100–2104.

[5] Barbieri RL, Sluss PM, Powers RD, McShane PM, Vitonis A, Ginsburg E, *et al.* Association of body mass index, age, and cigarette smoking with serum testosterone levels in cycling women undergoing *in vitro* fertilization. Fertility and Sterility. 2005; 83: 302–308.

[6] Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocrine Reviews. 1997; 18: 774–800.

[7] Traub ML. Assessing and treating insulin resistance in women with polycystic ovarian syndrome. World Journal of Diabetes. 2011; 2: 33–40.

[8] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, *et al.* Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human Reproduction (Oxford, England). 2018; 33: 1602–1618.

[9] Brutocao C, Zaiem F, Alsawas M, Morrow AS, Murad MH, Javed A. Psychiatric disorders in women with polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine. 2018; 62: 318–325.

[10] Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of

moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Human Reproduction (Oxford, England). 2017; 32: 1075–1091.

[11] Shalev A, Liberzon I, Marmar C. Post-Traumatic Stress Disorder. The New England Journal of Medicine. 2017; 376: 2459–2469.

[12] Yehuda R. Post-traumatic stress disorder. The New England Journal of Medicine. 2002; 346: 108–114.

[13] Al-Saadi LS, Chan MF, Al-Azri M. Prevalence of Anxiety, Depression, and Post-Traumatic Stress Disorder among Children and Adolescents with Cancer: A Systematic Review and Meta-Analysis. Journal of Pediatric Hematology/oncology Nursing. 2022; 39: 114–131.

[14] Simeone RM, Downing KF, Bobo WV, Grosse SD, Khanna AD, Farr SL. Post-traumatic stress disorder, anxiety, and depression among adults with congenital heart defects. Birth Defects Research. 2022; 114: 124–135.

[15] Tay CT, Teede HJ, Loxton D, Kulkarni J, Joham AE. Psychiatric comorbidities and adverse childhood experiences in women with self-reported polycystic ovary syndrome: An Australian population-based study. Psychoneuroendocrinology. 2020; 116: 104678.

[16] Katan MB. Commentary: Mendelian Randomization, 18 years on. International Journal of Epidemiology. 2004; 33: 10–11.

[17] Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. JAMA. 2007; 297: 278–285.

[18] Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ (Clinical Research Ed.). 2018; 362: k601.

[19] Nievergelt CM, Maihofer AX, Klengel T, Atkinson EG, Chen CY, Choi KW, et al. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. Nature Communications. 2019; 10: 4558.

[20] Day F, Karaderi T, Jones MR, Meun C, He C, Drong A, et al. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. PLoS Genetics. 2018; 14: e1007813.

[21] Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genetic Epidemiology. 2016; 40: 304–314.

[22] Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genetic Epidemiology. 2013; 37: 658–665.

[23] Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Human Molecular Genetics. 2018; 27: R195–R208.

[24] Zhao QWJ, Hemani G, Bowden J. Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. The Annals of Statistics. 2018; 48: 1742–1769.

[25] Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nature Genetics. 2018; 50: 693–698.

[26] Bowden J, Del Greco M F, Minelli C, Davey Smith G, Sheehan NA, Thompson JR. Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I2 statistic. International Journal of Epidemiology. 2016; 45: 1961–1974.

[27] Marsh CA, Berent-Spillson A, Love T, Persad CC, Pop-Busui R, Zubieta JK, et al. Functional neuroimaging of emotional processing in women with polycystic ovary syndrome: a case-control pilot study. Fertility and Sterility. 2013; 100: 200–207.e1.

[28] Özdil Demiryürek E, Tekin A, Çakmak E, Temizkan O, Karamustafalıoğlu O, Gökova S, et al. Correlations between impulsiveness and biochemical parameters in women with polycystic ovary syndrome. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2016; 207: 5–10.

[29] Rees DA, Udiawar M, Berlot R, Jones DK, O'Sullivan MJ. White Matter Microstructure and Cognitive Function in Young Women with Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology and Metabolism. 2016; 101: 314–323.

[30] Soleman RS, Kreukels BPC, Veltman DJ, Cohen-Kettenis PT, Hompes PGA, Drent ML, et al. Does polycystic ovary syndrome affect cognition? A functional magnetic resonance imaging study exploring working memory. Fertility and Sterility. 2016; 105: 1314–1321.e1.

[31] Lambrinoudaki I, Bouziou G, Armeni E, Spyropoulou A, Koundi K, Rizos D, et al. Circulating androgens are associated with mood disturbances in young postmenopausal women. Climacteric: the Journal of the International Menopause Society. 2015; 18: 205–213.

[32] Weiner CL, Primeau M, Ehrmann DA. Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls. Psychosomatic Medicine. 2004; 66: 356–362.

[33] Benson S, Arck PC, Tan S, Hahn S, Mann K, Rifaie N, et al. Disturbed stress responses in women with polycystic ovary syndrome. Psychoneuroendocrinology. 2009; 34: 727–735.

[34] Benson S, Hahn S, Tan S, Janssen OE, Schedlowski M, Elsenbruch S. Maladaptive coping with illness in women with polycystic ovary syndrome. Journal of Obstetric, Gynecologic, and Neonatal Nursing: JOGNN. 2010; 39: 37–45.