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ORIGINAL RESEARCH

Relationship Between the Ovarian Cyst and Depression: A Two-Sample Mendelian Randomization Study

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Objective: Explore the causal relationship between the ovarian cyst and depression using a two-sample Mendelian randomization approach (MR).

Methods: Based on data pooled from genome-wide association studies, genetic variants of the ovarian cyst and depression were selected as instrumental variables, as well as the Mendelian randomization analysis was conducted using inverse variance weighted (IVW) as the main analysis method and MR-Egger regression analysis, MR-PRESSO and other sensitivity analysis methods as supplements.

Results: The IVW analysis showed a direct causal association between ovarian cysts and depression (OR=1.040; 95% CI: 1.003, 1.078; p=0.031). Meantime, there was a causal effect of genetically predicted depression on ovarian cysts (OR=1.327.; 95% CI: 1.197, 1.470; p<0.001). Sensitivity analyses such as MR-Egger regression analysis and MR-PRESSO indicated that the IVW results were robust and reliable.

Conclusion: This study suggested since ovarian cysts and female depression are mutually causal, the comorbidity of ovarian cysts and depression in women should be actively attended to and given appropriate prevention and treatment besides the diagnosis and treatment of depression or ovarian cysts.

Keywords: Mendelian randomization, depression, ovarian cyst, genetic variation

Introduction

Ovarian cyst is a common gynecological disease that can occur at any age, with typical symptoms including abdominal masses and pain.[1] The prevalence of ovarian cysts in women has been reported to range from 5% to 17%.[2,3] Furthermore, it has been discovered that ovarian cysts can cause endocrine system dysfunction in women, which has a negative impact on their physical and mental health.[4]

Studies have found that endocrine dysfunction, inflammation, stressful environments and genetics are the main causes of ovarian cysts in women.[5,6] Moreover, ovarian cysts have been linked to a variety of psychological disorders. For instance, the research revealed that ovarian cysts affect the synthesis and secretion of hormones, thereby triggering depression.[7] Additionally, significant pro-inflammatory and endocrine system dysfunction has been discovered in depressed people.[8–10] Meanwhile, chronic inflammation could induce ovarian cysts.[11] This implies that depression may also be a risk factor for the development of ovarian cysts in women. However, depression has long been considered a comorbidity of ovarian cysts rather than a risk factor.[12] This could be due to poorly documented studies on the effect of depression on ovarian cysts, as well as the fact that causal inferences from available observational studies can be challenged by potential confounding bias and reverse causality. Therefore, the bidirectional causal relationship between depression and ovarian cysts remains to be further elucidated.

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Mendelian randomization (MR) analysis is a promising tool for causal inference in the context of the rapid development of large-scale Genome-wide association studies (GWAS).[13] It explores the causal relationship between exposure and outcome using genetic variants that are closely related to exposure as instrumental variables. Meanwhile, given that genetic variants for exposure and outcome are randomly assigned, they are relatively independent of environmental factors and the relationship exists before disease occurrence, thus reducing problems such as confounding and reverse causality to a minimum.[14] Two-sample MR analysis refers to the exposure and outcome from GWAS databases of different or non-overlapping populations, while bidirectional MR analysis attempts to explore reverse causality.[15]

Therefore, this study proposed a two-sample bivariate MR with publicly available GWAS summary statistics explore the causal relationship between depression and ovarian cysts, intending to provide some implications for the prevention and treatment of depression, ovarian cysts and their co-morbid diseases.

Methods and Materials

Data Sources

The summary single nucleotide polymorphism (SNP)–phenotype association data for depression, ovarian cyst and female infertility were obtained on the MR-Base platform. Specifically, genetic association estimates for ovarian cyst were obtained from FinnGen biobank analysis round 5, including 79,817 European ancestry. Patients with ovarian cysts were diagnosed with International Classification of Diseases-10 (ICD-10), including follicular cysts of ovary, corpus luteum cysts, as well as other and unspecified ovarian cysts. The genetic associations for depression were obtained from Psychiatric Genomics Consortium (PGC) and UK Biobank (excluding 23andme) which includes 170,756 cases and 329,443 control of European participants.[16]

Genetic Instruments

Genetic instruments for depression or ovarian cyst were selected as single-nucleotide polymorphisms (SNPs) that were associated with the exposure at genome-wide significance ($P < 5*10^{-6}$) and were independent, ie, pairwise linkage disequilibrium ($r2 < 0.001$ and distance >10,000 kb). Moreover, the *F*-statistics of each exposure was calculated to assess instrument strength, of which more than 10 were considered valid instruments.[17]

Mendelian Randomization Analysis

The TwoSampleMR and Mendelian Randomization R packages were used to perform Mendelian randomization analysis (MR). Firstly, the MR analyses were performed for depression and ovarian cyst separately to estimate the bi-directional causality. Briefly, the inverse-variance weighted method (IVW) was used as the main MR analysis. Additionally, a bilateral $p<0.05$ was considered indicative of significance.

Sensitivity Analyses

Sensitivity analysis has been pivotal in MR studies to assess the robustness of the findings. Specifically, the IVW and MR Egger approaches were used to evaluate the heterogeneity. While the directional pleiotropy was estimated by MR-PRESSO[18] and the intercept obtained from the MR-Egger regression.[14] Moreover, the leave-one-out analysis was conducted to assess whether MR estimates were driven or biased by a single SNP. The $p<0.05$ of indicators for sensitivity analysis was considered acceptable.

Results

Genetic Instruments

In total, 175 and 14 independent SNPs were used as genetic instrumental variables for depression and ovarian cyst, respectively (Table S1). The F-statistic values of individual SNPs ranged from 21 to 75, which the means of 27.86 and 25.67 for depression and ovarian cyst, respectively. All greatly surpass the limited value ($F > 10$), further suggesting that causal associations are less likely to be affected by weak instrumental variable bias.

Mendelian Randomization

The IVW analysis indicated a direct causal association between ovarian cyst and depression (*OR*=1.040; 95% *CI*: 1.003, 1.078; *p*=0.031). Meantime, there was a causal effect of genetically predicted depression on ovarian cyst (*OR*=1.327.; 95% *CI*: 1.197, 1.470; *p*<0.001). These were similar to the estimates from the weighted median, simple mode and weighted mode analyses (Table 1). Concerning the effect values of individual SNPs, the rs17641524 and rs12967143 loci had the most significant effect on the causal relationship between depression and ovarian cysts, while the most important loci affecting the causal relationship between ovarian cysts and depression were rs1853279 and rs10204333 (Figure 1).

Sensitivity Analysis

Although the IVW approach is effective for inferring exposure causality for complicated outcomes, a well-known vulnerability to weak instrumental biases. Sensitivity analyses (the IVW, MR Egger, leave-one-out analysis and MR-PRESSO approaches) were performed to overcome these biases. Concerning the relationship among depression and ovarian cyst, the direction of effect of the inverse variance weighted and other methods was mainly consistent (Figure 2). Although the CI of MR-Egger included 0 (Figure S1), indicating a possible violation of the assumption of no measurement error,[19] the funnel plot is overall symmetrical indicating less heterogeneity of the included SNP loci (Figure S2), the MR-Egger intercept analysis did not indicate horizontal pleiotropy (Table S2) and the results of leave-one-out analysis (Table S3) and MR-PRESSO (Table S4) could be accepted.

Discussion

Large-scale GWAS data were used to investigate the genetically predicted relationship between depression and ovarian cyst within an MR framework, providing genetic evidence to support a bidirectional causal relationship between depression and ovarian cyst.

The key finding of this study was that ovarian cysts could cause depression in women, which is consistent with previous research that patients with ovarian cysts frequently have symptoms of depression and anxiety.[20,21] As a common gynecological disease, ovarian cyst could impair the ovarian reserve function of an individual, manifested by the disturbance of E_2 (estradiol)and anti-müllerian hormone (AMH) levels, as well as a reduction in ovarian volume and follicle density.[1,22,23] Furthermore, E_2 was discovered to have a potential role in regulating 5-hydroxytryptamine (5-HT) receptor mRNA, implying that E2 deficiency could cause depression.[24] Furthermore, Gordon et al discovered that ovarian cysts affect the ovarian cortex, causing a continuous decrease in follicular release, which affects hormone synthesis and secretion. Additionally, pregnanolone could effectively promote the role of gamma-amino-butyric acid (GABA) and changes in pregnanolone derived GABAergic neurosteroids may induce dysfunction of the GABAergic system, which in turn causes disorders of the hypothalamic-pituitary-adrenal (HPA) axis and mood disorders.[7,25] In general, these may indicate that ovarian cysts also induce depression by affecting the changes of E_2 and progesterone in women.

Table 1 The MR Results for the Relationship Among Depression and Ovarian Cyst

Exposure vs Outcome	Method	SNPs	OR (95% CI)	*p*
Ovarian cyst vs Depression	MR Egger	14	1.009(0.928, 1.098)	0.824
	Weighted median	14	1.044(1.000, 1.091)	0.046
	IVW	14	1.040(1.003, 1.078)	0.031
	Simple mode	14	1.094(0.994, 1.204)	0.087
	Weighted mode	14	1.078(0.992, 1.170)	0.097
Depression vs Ovarian cyst	MR Egger	175	1.340(0.881, 2.037)	0.172
	Weighted median	175	1.405(1.216, 1.642)	<0.001
	IVW	175	1.327(1.197, 1.470)	<0.001
	Simple mode	175	1.645(1.021, 2.651)	0.042
	Weighted mode	175	1.543(1.001,2.378)	0.05

Abbreviation: IVW, the inverse-variance weighted method.

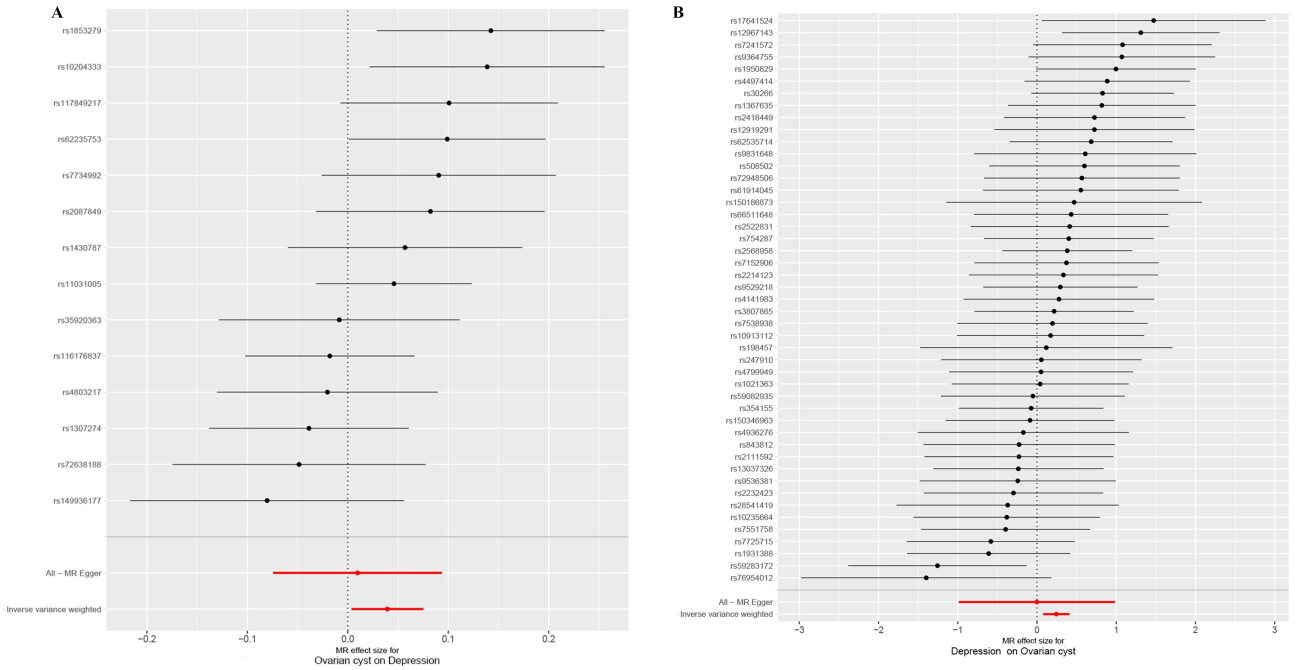

Figure 1 Mendelian Randomization (MR) Plots for Relationship between ovarian cyst and depression. (**A**), Mendelian Randomization summary effects for the risk of ovarian cyst associated with depression. (**B**), Mendelian Randomization summary effects for the risk of depression associated with ovarian cyst. Summary effects were computed using an inverse-variance weighted (IVW) method from each individual SNP. Dots represent the coefficient and the extremities represent the 95% confidence interval of the odds ratio.

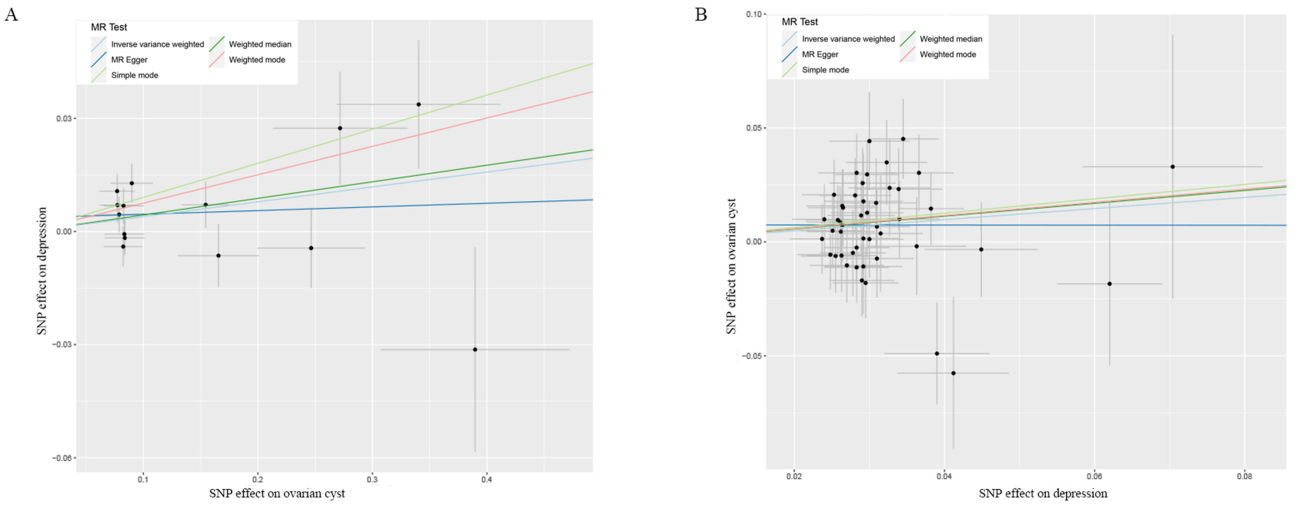

Figure 2 Scatter plots for MR analyses of the bi-directional causality between ovarian cyst and depression. (**A**), scatter plot of single-nucleotide polymorphism (SNP) potential effects on ovarian cyst vs depression. (**B**), scatter plot of single-nucleotide polymorphism (SNP) potential effects on depression vs ovarian cyst.

Additionally, this study expanded on prior research that indicated depression was a risk factor for ovarian cysts.[26] Depressed patients have been found to have a dysregulation of natural and acquired immunity.[27] Meanwhile, numerous studies have shown that early depression can induce late inflammation in individuals.[8–10] Inflammation also contributes to the development of ovarian cysts, having a significant negative impact on women's endocrine systems[11] and a direct impact on ovarian function,[28] oocyte quality[29] and endometrial receptivity.[30] Furthermore, individuals with ovarian cysts have a persistent state of pro-inflammation,[31] which may also affect normal ovarian function, impairing sex hormone

synthesis and release, as well as follicular maturation and subsequent ovulation.[11] This imply that depression causes ovarian cysts in women by inducing an inflammatory response.

In conclusion, this study suggested since ovarian cysts and female depression are mutually causal, the comorbidity of ovarian cysts and depression in women should be actively attended to and given appropriate prevention and treatment besides the diagnosis and treatment of depression or ovarian cysts. Furthermore, as the GWAS data included in this study were all of European ancestry, future studies to investigate the relationship between ovarian cysts and depression across different ancestries or ethnicities are warranted.

Ethics Statement

This study is part of a research project on neurobiological mechanisms in patients with psychiatric disorders, which has been reviewed by the Ethics Committee of Hainan An Ning Hospital in 2022 (No. 202205).

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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