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ORIGINAL RESEARCH

Causal Relationship Between Mood Swing and Gynecological Disorders: A Mendelian Randomization Study

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Background: Gynecological disorders are a wide range of health problems affecting the female reproductive system, which poses substantial health challenges worldwide. Increasing number of observational studies have associated mood instability to common female diseases, but the underlying causal relationship remains unclear. In this work, Mendelian randomization (MR) analysis was applied to explore the genetically predicted causal relationship of mood swings and several prevalent gynecological disorders.

Methods: Instrumental variables (IVs) of mood swings were selected from UK Biobank (UKB), with 204,412 cases and 247,207 controls being incorporated. The genetic variants for female disorders were obtained from genome-wide association studies (GWASs) and FinnGen consortium. To avoid biases caused by racial difference, only European population was included here. Five strong analytical methodologies were used to increase the validity of the results, the most substantial of which was the inverse variance weighting (IVW) method. Pleiotropy, sensitivity, and heterogeneity were assessed to strengthen the findings.

Results: We found mood swings was significantly positively associated with risk of endometrial cancer (OR= 2.60 [95% CI= 1.36, 4.95], P= 0.0037), cervical cancer (OR= 1.01[95% CI= 1.00,1.02], P= 0.0213) and endometriosis (OR= 2.58 [95% CI= 1.18, 5.60], P= 0.0170) by IVW method. However, there was no causal relationship between mood swing and ovarian cancer. No pleiotropy and heterogeneity existed and sensitivity tests were passed.

Conclusion: This study reveals that mood swing may serve as a genetically predicted causal risk factor for endometrial cancer, cervical cancer, and endometriosis in the European population, while no such association was observed for ovarian cancer. These findings make up for observational research's inherent limitations and may improve patient outcomes in the field of gynecological health. However, the study's focus on European populations may limit the applicability of these results globally.

Keywords: Mendelian randomization, mood swing, genetic relationship, gynecological disorders

Introduction

Gynecological disorders encompass a diverse group of conditions that affect the female reproductive system, posing substantial health challenges worldwide.[1,2] Among these disorders, endometrial cancer, cervical cancer, ovarian cancer, and endometriosis stand out due to their high prevalence, significant morbidity and mortality rates, and long-term consequences.[3–5] Gaining a comprehensive understanding of the distinct characteristics, risk factors, and underlying mechanisms of these gynecological disorders is imperative for effective prevention, early detection, and targeted treatment strategies.

Gynecologic cancers are among the leading types of cancer affecting women and significantly contribute to cancer-related deaths, particularly in countries with high socioeconomic status. The three most common types of these cancers are endometrial, cervical, and ovarian carcinomas.[6–9] Endometrial cancer, originating in the endometrium, is the most common gynecological malignancy in developed nations, predominantly afflicting postmenopausal women.[6,7] Cervical cancer, primarily caused by persistent high-risk human papillomavirus (HPV) infection, remains a global health concern, particularly in low- and middle-income countries.[10] Ovarian cancer, a heterogeneous disease, represents the most lethal gynecological malignancy, often detected at advanced stages due to a lack of specific symptoms and effective screening

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methods.[11] Endometriosis, characterized by ectopic endometrial-like tissue growth, affects a substantial proportion of reproductive-aged women and is associated with significant pain and infertility.[12,13] Currently, effective screening methods for EC detection are scarce. Preventing gynecologic cancers involves a multifaceted strategy, including screenings, vaccinations, healthy living, and risk factor management. Greater awareness of these cancer risks and preventive measures are crucial to enhance public understanding, potentially reducing incidence, boosting survival, and lowering mortality, with a focus on high-risk individuals.[9]

The relationship between mood swings and the risk of developing gynecological disorders has become an area of interest within the field of women's health. Mood swings, characterized by rapid and intense fluctuations in emotional states, may have implications for the occurrence of gynecological conditions.[14,15] Evidence suggests that mood swings may influence the risk of certain gynecological disorders.[16] Endometrial cancer, cervical cancer, ovarian cancer, and endometriosis are among the conditions that have been investigated in this context. Psychological distress, hormonal imbalances, and altered immune function associated with mood swings could potentially contribute to the development of these disorders. Conversely, the presence of gynecological conditions may also impact mood stability due to the associated physical and emotional distress.[17,18]

Mendelian randomization (MR) is a statistical technique used to investigate causal relationships between risk factors and health outcomes by applying principles of genetics and Mendelian inheritance.[19] This method employs genetic variants as instrumental variables to determine whether an observed association between an exposure and an outcome reflects a true causal relationship. MR is based on the concept of random gene assortment during meiosis, which results in a generally random distribution of genetic variations within a population. Genetic variants, particularly single nucleotide polymorphisms (SNPs), serve as proxies for modifiable risk factors or exposures.[20] Since these variants are randomly distributed at conception, they are inherently less prone to confounding by environmental or lifestyle factors—a common source of bias in observational studies. This natural randomization simulates the conditions of a controlled experiment, offering a robust framework for causal inference.

The findings from this MR study have the potential to enhance our understanding of the etiological factors contributing to gynecological disorders and inform strategies for prevention and intervention. Overall, this MR study aims to elucidate the causal relationship between mood swing and the risk of endometrial cancer, cervical cancer, ovarian cancer, and endometriosis. By employing robust analytical methods and leveraging genetic data, we seek to provide evidence for the potential impact of mood swing on these gynecological disorders and contribute to the broader knowledge of their etiology. In clinical practice, this approach could translate into more personalized treatment plans that include psychological assessments as part of routine gynecological care. Additionally, public health initiatives could focus on raising awareness about the link between mental health and gynecological conditions, encouraging early intervention and holistic management strategies for mental health problem.

Material and Method

Study Design

The study design is depicted in Figure 1, providing an overview of the research methodology. To identify suitable instrumental variables (IVs) associated with mood swings, a rigorous selection process was undertaken. Subsequently, a two-sample MR analysis was conducted to ascertain the genetic causal effects of mood swings on four prevalent gynecological disorders, namely endometrial cancer, cervical cancer, ovarian cancer, and endometriosis. Robust sensitivity analyses, including assessments of pleiotropy and heterogeneity, were performed to ensure the validity and reliability of the findings. It is important to note that the genetic data utilized in this study is openly accessible to researchers worldwide, thus obviating the need for additional ethical review or informed consent.

Data Sources

The genetic variants associated with mood swings and the four gynecological disorders (endometrial cancer, cervical cancer, ovarian cancer, and endometriosis) were obtained from publicly available genetic databases and large-scale genome-wide association studies (GWAS). The specific data sources used in this study include but are not limited to the

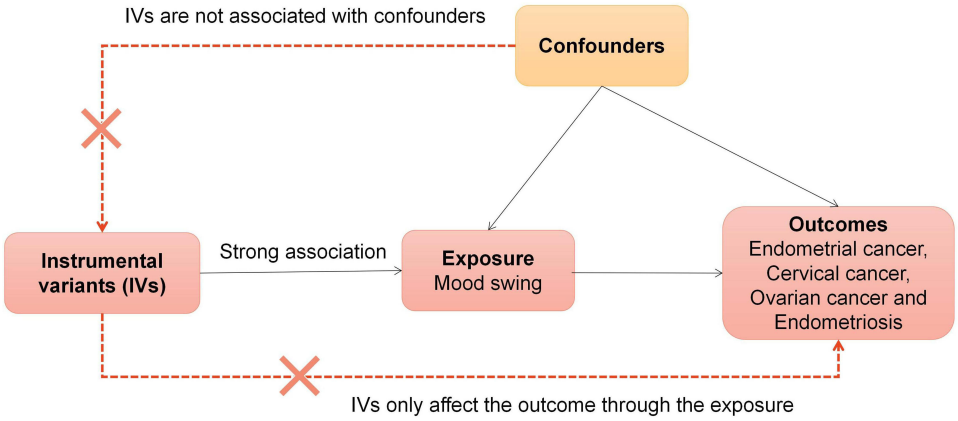

Figure 1 Overview of study design. Schematic showing how MR was applied to evaluate a causal association between mood swing and four common gynecological disorders in this study. Three assumptions should be satisfied here: (1) instrumental variables (IVs) are strongly related to exposure; (2) IVs are independent of any confounders; (3) IVs only affect the outcome through exposure.

GWAS Catalog, UK Biobank, and the FinnGen dataset. These sources provide comprehensive genetic information, including single nucleotide polymorphisms (SNPs) and their corresponding effect sizes, which were utilized as instrumental variables in the MR analysis. The utilization of publicly available genetic data ensures transparency, reproducibility, and adherence to ethical standards in genomic research.

Genetic association with the mood swings was obtained from the GWAS pipeline using Phesant derived variables from UKB, consisting of 451,619 European cases and 9,851,867 SNPs. Summary data of association with endometrial cancer were derived from GWAS, with 12,906 cases and 108,979 controls.[21] Besides, the genetic statistics of cervical cancer were concluded from MRC-IEU (563 cases / 198,523 controls). Genetic variants of ovarian cancer were extracted from the study of Phelan et al.[22] FinnGen consortium provided the genetic data of endometriosis (8,288 cases / 68,969 controls).

Selection of Genetic Instruments

The instrumental variables (IVs) were carefully selected based on rigorous criteria. Firstly, single-nucleotide polymorphisms (SNPs) showing a strong association with mood swings ($P < 5\times10\text{-}8$) were included. Secondly, genetic variants in linkage disequilibrium (LD) ($r2 > 0.001$) were excluded to avoid redundancy. Furthermore, the F-statistics, calculated using the formula $F=beta^2/se^2$, were utilized to assess the strength of the selected IVs. A threshold of F-statistics > 10 was applied to ensure an adequate statistical power. IVs with lower F-statistics were considered to have reduced statistical power.[23] The comprehensive information regarding the selected IVs employed in this MR study can be found in Supplementary Table 1.

Statistical Analysis

In our study, two-sample Mendelian randomization (MR) analyses were conducted using the TwoSampleMR package (version 0.5.6) in R software (version 4.3.1).[24] The inverse-variance-weighted (IVW) method was employed as the primary approach for two-sample MR analysis. This method employs weighted regression of SNP-specific Wald ratios to estimate the causal effects of the exposure on the outcomes. Additionally, four other assessment approaches, namely Weighted median, Simple mode, MR Egger, and Weighted mode, were simultaneously performed to assess the consistency of our results.[25,26] The MR-PRESSO method was applied to identify and remove potential outliers and examine the sensitivity of the analysis.[27] The leave-one-out method was utilized to assess the sensitivity of the MR analyses. Moreover, pleiotropy and heterogeneity were evaluated to strengthen the robustness of our conclusions.

Result

Selected Genetic Instruments (IVs)

In accordance with the aforementioned criteria, a rigorous selection process was undertaken to identify IVs for mood swings. Following stringent criteria, a total of 57 independent SNPs were selected as the IVs (Supplementary Table 1

provides detailed information). Importantly, the selected IVs demonstrated no evidence of weak instrumental bias as indicated by the F statistics, all of which exceeded the threshold of 10. The F statistics, serving as a measure of the strength of the selected IVs, were included in the Supplementary Table 1 for reference. By adhering to these criteria and ensuring robustness in the selection of IVs, the study maintains the integrity and validity of the Mendelian randomization analysis. These carefully selected IVs form the foundation for assessing the causal relationship between mood swings and the gynecological disorders under investigation.

The Causal Relationship of Mood Swing on Common Gynecological Disorders

In the present MR study, the MR-PRESSO method was employed to identify and exclude outlier SNPs. Consequently, the final set of SNPs used for the two-sample MR analysis was reduced in comparison to the initial number of IVs as described earlier. The results of the two-sample MR analysis, employing five different methods, along with the corresponding SNP numbers, are presented in Table 1. Scatter plots illustrating the relationship between mood swing and the four gynecological disorders are displayed in Figure 2.

The scatter plots indicate a positive genetic impact of mood swing on all four gynecological disorders under investigation. Notably, mood swing demonstrated statistically significant associations with endometrial cancer (OR = 2.60 [95% CI = 1.36, 4.95], P = 0.0037), cervical cancer (OR = 1.01 [95% CI = 1.00, 1.02], P = 0.0213), and endometriosis (OR = 2.58 [95% CI = 1.18, 5.60], P = 0.0170). However, the genetic predicted effect of mood swing on ovarian cancer was not statistically significant (OR = 1.46 [95% CI = 0.81, 2.62], P = 0.2041). Therefore, based on these findings, it can be concluded that mood swing may serve as a genetically predicted causal risk factor for endometrial cancer, cervical cancer, and endometriosis in the European population, while no such association was observed for ovarian cancer.

Sensitivity Analysis

To assess the potential weak IV bias in the selected IVs for mood swing and the four gynecological disorders (endometrial cancer, cervical cancer, ovarian cancer, and endometriosis), we calculated the F-statistic and ensured that

Table 1 Mendelian Randomization Analysis of Causal Relationship Between Mood Swing and Four Common Gynecological Disorders

Outcome	Case/Control	nSNP	MR methods	Beta	SE	OR (95% CI)	P	P_h	P_p
Endometrial cancer	12,906/108,979	57	MR Egger	0.0151	1.8663	1.0152 (0.0262,39.3712)	0.9936	0.2249	0.6110
			Weighted median	1.1677	0.4379	3.2147(1.3628,7.5832)	**0.0077**		
			IVW	0.9547	0.3285	2.5978(1.3644,4.9461)	**0.0037**		
			Simple mode	1.3624	1.0171	3.9057(0.5320,28.6740)	0.1858		
			Weighted mode	1.2276	0.9455	3.4130(0.5350,21.7752)	0.1995		
Cervical cancer	563/198,523	52	MR Egger	0.0012	0.0192	1.0012(0.9643,1.0395)	0.9519	0.7870	0.7170
			Weighted median	0.0094	0.0050	1.0094(0.9995,1.0194)	0.0633		
			IVW	0.0080	0.0035	1.0081(1.0012,1.0150)	**0.0213**		
			Simple mode	0.0139	0.0124	1.0140(0.9897,1.0389)	0.2653		
			Weighted mode	0.0139	0.0126	1.0140(0.9892,1.0394)	0.2750		
Ovarian cancer	25,509/40,941	52	MR Egger	2.5590	1.8130	12.9226(0.3699,451.4137)	0.1643	0.2478	0.2287
			Weighted median	0.4577	0.4029	1.5805(0.7175,3.4816)	0.2559		
			IVW	0.3793	0.2987	1.4613(0.8137,2.6244)	0.2041		
			Simple mode	0.7623	0.9226	2.1432(0.3513,13.0748)	0.4125		
			Weighted mode	0.8489	0.8969	2.3372(0.4029,13.5574)	0.3484		
Endometriosis	8,288/68,969	54	MR Egger	1.2606	2.4904	3.5275(0.0268,464.9008)	0.6149	0.2458	0.8987
			Weighted median	0.9157	0.5368	2.4986(0.8724,7.1557)	0.0880		
			IVW	0.9461	0.3964	2.5756(1.1843,5.6013)	**0.0170**		
			Simple mode	0.7238	1.3565	2.0623(0.1444,29.4465)	0.5959		
			Weighted mode	0.6832	1.2874	1.9801(0.1588,24.6936)	0.5979		

Notes: P values less than 0.05 are highlighted in **bold** to emphasize their statistical significance.
Abbreviations: nSNP,non-synonymous single nucleotide polymorphism; CI, confidence interval; SE, standard error; OR, odds ratio; P_h, P value of heterogeneity test; P_p, P value of pleiotropy test; IVW, Inverse variance weighted method.

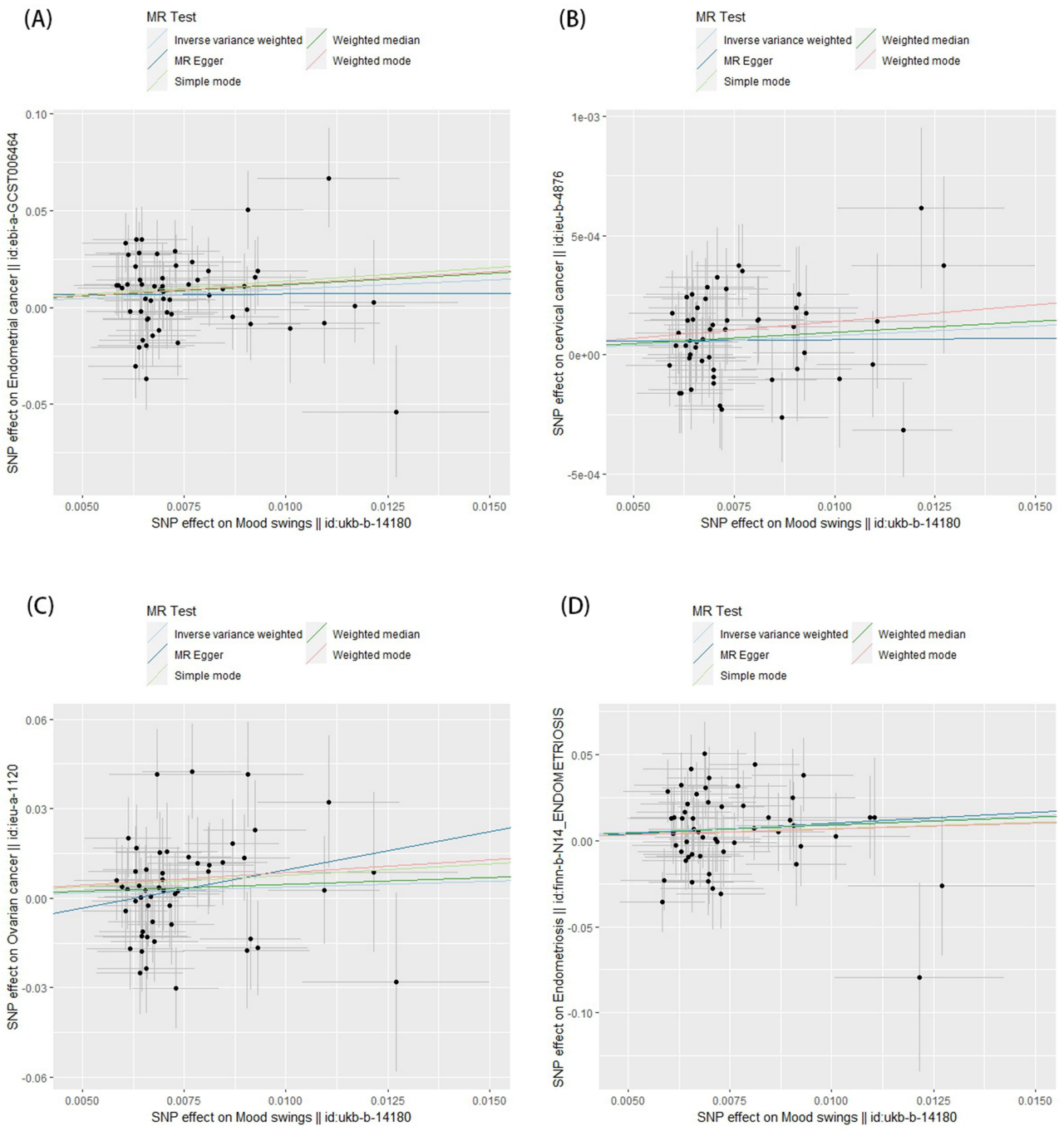

Figure 2 Scatter plots to assess causal associations between mood swing and each of the following four gynecological disorders: (**A**) endometrial cancer; (**B**) cervical cancer; (**C**) ovarian cancer and (**D**) endometriosis. All of these scatter plots showing a positive genetic causal relationship between mood swing and four gynecological disorders above.

it exceeded the threshold of 10. Robustness of the MR analyses was validated through multiplicity, heterogeneity, and sensitivity analyses, as outlined in Table 1. The MR-Egger intercept and MR-PRESSO tests indicated no evidence of horizontal pleiotropy in any of the aforementioned analyses, with all corresponding p-values exceeding 0.05. Furthermore, heterogeneity was detected in the heterogeneity tests of MR-Egger and IVW methods in certain analyses, which is considered acceptable within the context of MR studies. Funnel plots and forest plots of MR analysis were shown in Supplementary Figure 1–8. Leave-one-out sensitivity analyses were performed to evaluate the stability of the

estimated causal effects of mood swing on endometrial cancer, cervical cancer, ovarian cancer, and endometriosis, and the results indicated robustness (Supplementary Figure 9–12).

Discussion

In the present two-sample MR study, our aim was to investigate the potential causal relationship between mood swing and the risk of gynecological disorders. By utilizing genetic variants as instrumental variables, we sought to uncover insights into the impact of mood swing on endometrial cancer, cervical cancer, ovarian cancer, and endometriosis. The study design included the selection of instrumental variables based on strict criteria, followed by two-sample MR analysis and various sensitivity and robustness assessments.

Psychological distress has long been suspected to influence cancer incidence and mortality. The observed causal relationship between mood swing and endometrial cancer is consistent with existing evidence highlighting the potential role of psychological factors in the development of gynecological disorders.[16] It remains largely unknown whether and how stress affects the efficacy of anticancer therapies. Psychological distress and mood[28] disturbances have been associated with hormonal imbalances and alterations in immune function, which might influence cancer risk.[28–31] Yang et al found that stress elevated plasma corticosterone and upregulated the expression of Tsc22d3, which blocked type I interferon (IFN) responses in dendritic cell (DC) and IFN-γ+ T cell activation.[29–31] This study contributes to the understanding of the multifactorial etiology of endometrial cancer and emphasize the importance of addressing psychological well-being in prevention and management strategies.

The identification of a causal relationship between mood swing and cervical cancer underscores the potential impact of psychological factors on the development of this gynecological malignancy. Psychological distress and mood swings may contribute to immune dysfunction, compromising the body's ability to clear high-risk human papillomavirus (HPV) infections, thus increasing the risk of cervical cancer.[32] These findings highlight the need for comprehensive approaches that address both physical and mental health aspects in the prevention and control of cervical cancer.

The observed causal relationship between mood swing and endometriosis suggests that psychological factors may play a role in the development or progression of this chronic condition. Chronic pain, fertility challenges, and reduced quality of life associated with endometriosis can lead to psychological distress and mood swings.[33] The bidirectional relationship between mood swings and endometriosis could potentially exacerbate symptom severity and impact disease progression.[34,35] These findings emphasize the importance of integrating psychological support and mental health interventions in the management of endometriosis.

In our study, the absence of a significant causal relationship between mood swing and ovarian cancer suggests that other factors may play a more prominent role in the development of this gynecological malignancy. While psychological stress and mood disorders have been broadly associated with alterations in immune function and hormonal balance, which could theoretically influence cancer risk, empirical evidence directly linking mood swings to the development of ovarian cancer is limited.[36] Epidemiological studies often face methodological challenges, including the accurate assessment of mood swings and the potential for confounding variables, which may partly explain the inconsistent findings across different studies.[37] Ovarian cancer is a complex disease influenced by multiple genetic and environmental factors.[38,39] Genetic factors, such as mutations in the BRCA1 and BRCA2 genes, have been established as having a profound impact on the risk of developing ovarian cancer.[37] Additionally, environmental factors like chemical exposures, diet, and lifestyle choices are considered to play a significant role, potentially through their effects on cellular processes like proliferation, apoptosis, and DNA repair mechanisms.[40] Future research should continue to explore the multifactorial etiology of ovarian cancer and elucidate the interplay between various risk factors, including psychological factors, to better understand its pathogenesis.

In summary, our analysis clearly indicates a significant correlation between psychological distress and gynecological disorders. This suggests that proactive intervention is essential, whether in the prevention or management of gynecological conditions. As a growing number of therapeutic interventions, including music therapy, are being employed to enhance psychological and physical health, it is imperative that the medical community leverages these approaches.[41] From this perspective, healthcare providers should focus on the psychological well-being of their patients. It is better to actively address the emotional distress associated with gynecological disorders, providing support that extends beyond

the physical symptoms.[42] This holistic approach not only treats the physical aspects of disease but also supports the emotional and psychological resilience of patients, ultimately contributing to better health outcomes and a more compassionate healthcare system.

This study demonstrates several strengths in its approach to investigating the potential causal relationship between mood swing and four gynecological disorders. The utilization of MR analysis, a robust methodological framework, allows for the assessment of causal relationships, enhancing the validity of the findings. Additionally, the inclusion of large-scale genetic datasets adds to the strength of the study, ensuring a broader representation of populations and increasing the generalizability of the results. The comprehensive discussion of the potential causal links between mood swing and endometrial cancer, cervical cancer, ovarian cancer, and endometriosis contributes to the existing literature in this field, offering valuable insights into the etiology of these gynecological disorders.

Despite its strengths, this essay also exhibits some limitations. One such limitation is the focus on European populations, which may restrict the generalizability of the findings to other ethnic groups or geographical regions. Additionally, the reliance on genetic data as instrumental variables assumes no pleiotropic effects, potentially introducing bias into the analysis. While sensitivity analyses were mentioned, providing further details on potential sources of bias and confounding would have strengthened the overall analysis. Taking these limitations into consideration, future research should strive to include diverse populations and employ comprehensive sensitivity analyses to enhance the robustness of the findings.

The findings of this MR study contribute to our understanding of the complex interplay between mood swing and gynecological disorders. The observed causal relationships underscore the importance of addressing psychological factors and mental health in the prevention and management of endometrial cancer, cervical cancer, and endometriosis. Future research should further explore the underlying mechanisms linking mood swing to gynecological disorders and investigate the potential effectiveness of interventions targeting psychological well-being in reducing disease risks. These findings provide a basis for personalized interventions and improved patient outcomes in the field of gynecological health.

Conclusion

In conclusion, this MR study establishes a significant causal relationship between mood swing and increased risks of endometrial cancer, cervical cancer, and endometriosis in European populations. However, no significant causal association was observed for ovarian cancer. These findings emphasize the relevance of considering psychological factors in the prevention and management of gynecological disorders, informing the development of comprehensive care approaches. Further research is warranted to investigate the underlying mechanisms and validate these findings in diverse populations.

Data Sharing Statement

All of the genetic data used in this work was publicly available. The original contributions presented in the study are included in the article and supplementary materials, further inquiries can be directed to the corresponding author (nbjiabian@126.com).

Ethical Approval

All participating studies involved in the GWAS obtained informed consent from the study populations. As we utilized publicly available datasets to conduct MR, no additional ethics approval was required. An certification of ethics approval waiver was consented to by the ethics committee of the Affiliated People's Hospital of Ningbo University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

This paper has been uploaded to Research Square as a preprint: https://www.researchgate.net/publication/373282230_Causal_relationship_between_mood_swing_and_gynecological_disorders_a_Mendelian_randomization_study-preprint.

The authors report no conflicts of interest in this work.

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