

Causal Relationship Between Endometriosis and Pelvic Inflammatory Diseases: Mendelian Randomization Study

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Objective: This study explores the causal relationship between endometriosis and pelvic inflammatory diseases (PID).

Methods: The study utilized genome-wide association study (GWAS) datasets for endometriosis ("finn-b-N14_ENDOMETRIOSIS") and PID ("finn-b-N14_OTHFEMPELINF"). Subsequently, two-sample Mendelian randomization (MR) analyses were conducted using inverse variance weighting (IVW), Egger regression (MR-Egger), and weighted median (WM) methods. Heterogeneity was evaluated using Cochran's Q test, and in case of detected outliers, they were removed for re-evaluation of MR causality.

Results: From the endometriosis GWAS dataset, 33 single nucleotide polymorphisms (SNPs) were selected as instrumental variables. All three methods, IVW ($OR = 1.39$, $P < 1 \times 10^{-8}$), MR-Egger ($OR = 1.41$, $P = 0.003$), and WM ($OR = 1.37$, $P = 1.16 \times 10^{-5}$) confirmed a causal relationship between endometriosis and PID. The association between endometriosis and pelvic inflammation remained unaffected by the exclusion of individual SNPs. Lastly, Cochran's Q test and funnel plots showed no evidence of SNP asymmetry.

Conclusion: The results of the MR analysis support a potential causal relationship between endometriosis and an increased risk of PID.

Keywords: endometriosis, pelvic inflammatory diseases, genome-wide association study, Mendelian randomization

Introduction

Pelvic inflammatory disease (PID) is an infection affecting the endometrium, fallopian tubes, ovaries, and pelvic peritoneum.^{1,2} The patient's clinical symptoms mainly include pelvic pain, abnormal vaginal discharge, fever and chills, and painful urination.^{3,4} Due to its nonspecific symptoms, misdiagnosis or delayed diagnosis are usually happened which can lead to inflammatory sequelae including infertility, ectopic pregnancy, and chronic pelvic pain.^{1,2} According to 2013–2014 data, there were 110,000 cases of PID among women aged 18–44.^{5,6} Considering the estimated treatment cost of \$1995 per patient in previous years, this undeniably poses a significant healthcare concern.¹ Sexually transmitted infections and bacterial vaginosis have been considered as predominantly causes of PID. However, research shows that as society evolves, a variety of factors may be associated with this disease. In the 1950s, PID was associated with Mycobacterium tuberculosis and Neisseria gonorrhoeae, while in the 1980s, Chlamydia trachomatis became linked to PID.⁷ Recent clinical trial results for PID in American women showed that only 25% of cases were due to sexually transmitted infections.^{8,9} Advances in clinical screening technology have led to the recognition of certain factors, such as postpartum or postabortion infection, intrauterine devices, endometrial surgery, and endometriosis, as predisposing factors for PID.

Endometriosis is a disease in which tissue similar to the lining of the uterus (endometrium) grows on the ovaries, fallopian tubes, and other pelvic structures. It affects 6–10% of reproductive-aged women, causing symptoms such as dysmenorrhea, dyspareunia, chronic pelvic pain, irregular uterine bleeding, and/or infertility, significantly impacting their quality of life.^{10,11} Moreover, endometriosis is linked to various diseases including ovarian cancer, breast cancer, autoimmune disorders, cardiovascular diseases, and asthma.^{12,13} PID and endometriosis can share common symptoms

and pathogenesis factors. An increasing number of researchers are turning their attention to the connection between PID and endometriosis. Lei Wan et al analyzed public data from the National Health Insurance Research Database (NHIRD) and demonstrated that patients with PID had a three-fold increase in the risk of developing endometriosis.¹⁴ On the other hand, studies confirmed that having endometriosis is a high-risk factor for PID and PID recurrence.^{10,15} However, traditional observational studies have some limitations, and the associations between endometriosis and PID reported in previous studies may still be explained by reverse causality and residual confounding. Thus, whether there is a causal relationship between endometriosis and PID remains uncertain.

To study the cause-and-effect link between endometriosis and PID, we can employ Mendelian randomization (MR). MR is a method that uses genetic variants as instrumental variables to estimate the causal impact of risk factors on health outcomes.¹⁶ In comparison to traditional multivariate observational analysis, Mendelian Randomization (MR) is less susceptible to the influence of confounding variables and measurement errors, and it avoids biases arising from reverse causation. Therefore, MR has become a reliable method for obtaining robust estimates of the causal effects of various risk factors on health outcomes, often yielding results similar to those of randomized controlled trials.

In the present study, we employ a two-sample MR approach to evaluate the influence of endometriosis on PID risk, revealing potential associations between the two conditions. Our results support a potential causal relationship between endometriosis and an increased risk of PID.

Methods

Study Design

The study utilized the Integrative Epidemiology Unit Open Genome-Wide Association Studies database (IEU openGWAS, <https://gwas.mrcieu.ac.uk/>), which aggregates data from various studies involving genetic variations related to endometriosis (GWAS ID: finn-b-N14_ENDOMETRIOSIS, a European database has 16,377,306 SNPs from 77,257 samples.)¹⁷ and pelvic inflammatory disease (GWAS ID: finn-b-N14_OTHFEMPELINF, a European database has 16,379,585 SNPs from 114,771 samples.). We selected genetic variants associated with endometriosis and pelvic inflammatory disease, ensuring a minimum minor allele frequency (MAF) greater than 0.01 in the European population (Figure 1). The study adhered to the three core assumptions of MR research: (1) the selected genetic variants SNPs should be closely related to the exposure, (2) the selected genetic variants SNPs should be independent of confounding factors, and (3) the selected genetic variants SNPs should affect the outcome only through the exposure, but not directly related. This study was based on publicly available pooled data, and the protocol and data collection were approved by the ethics committee of each original association study, following the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) guidelines.¹⁸

Pelvic Inflammatory Disease GWAS Summary Statistics

To investigate the causal relationship between endometriosis and pelvic inflammatory disease risk, we systematically retrieved summary data from the pelvic inflammatory disease GWAS. The IEU OpenGWAS database's pelvic inflammatory disease GWAS data (finn-b-N14_OTHFEMPELINF) consisted of summary statistics from a study involving 2913 cases and 111,858 female controls, encompassing 16,379,585 SNP loci.

Genetic Instrument Variable Selection

To study the causal relationship between endometriosis and pelvic inflammatory disease risk, we employed instrumental variables to assess the relationship between the two conditions. We identified the endometriosis GWAS to identify genetic variants associated with endometriosis. Initially, we selected SNPs associated with endometriosis as candidate instrumental variables for MR analysis ($P < 5e-06$). Subsequently, to ensure exposure-related instrumental variables were independent, we used linkage disequilibrium (LD) clumping to exclude SNPs in LD ($r^2 = 0.01$, clumping window = 10Mb). Finally, to avoid bias from weak instrumental variables, we calculated the strength of instrumental variables using the F-statistic, with an F-statistic greater than 10 indicating a low likelihood of weak instrumental variables. Instrumental variable selection and quality control were conducted using the R package TwoSampleMR (v 0.5.6).

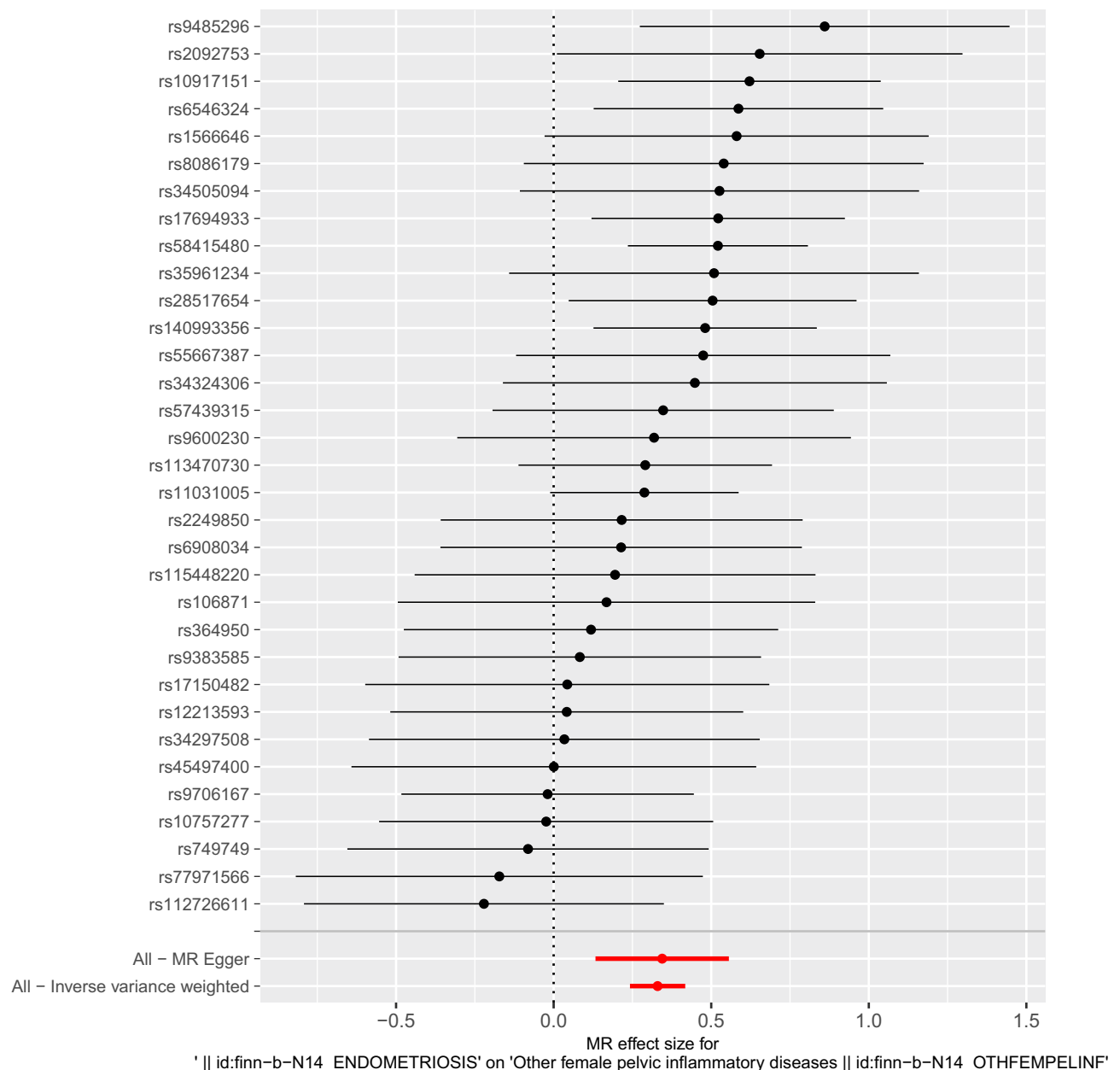


Figure 1 Forest plot illustrating the causal relationship between single nucleotide polymorphisms (SNPs) associated with endometriosis and pelvic inflammatory disease (PID) using Inverse Variance Weighting (IVW), MR-Egger, and Weighted Median (WM) analyses. Red lines represent MR results from IVW and MR-Egger.

Mendelian Randomization Estimation

The study employed the inverse variance weighting (IVW) method to assess the effect size of each instrumental variable, estimating the causal impact of exposure on outcomes using the Wald ratio. The MR Egger regression intercept was utilized to assess pleiotropy, and if $p > 0.05$, it was determined that there was no evidence of pleiotropy. MR-Egger and weighted median (WM) results further confirmed the causal relationship between endometriosis and pelvic inflammatory disease. The primary distinction between MR-Egger and IVW is that MR-Egger considers the presence of an intercept and fits using the inverse of the outcome variance as weights, while IVW does not consider the presence of an intercept. Furthermore, Cochran's Q test was used to assess heterogeneity, and if outliers were detected, they were removed, and MR causality was reassessed. Statistical analysis and data visualization were performed using R software version 4.1.3 (<https://www.r-project.org/>).

Results

Characteristics of Instrumental Variable SNPs

The study initially selected 35 SNPs highly associated with endometriosis ($P < 5e-06$, $r^2 = 0.01$, clumping window = 10Mb). Subsequently, SNPs with inconsistent alleles and those with irreparable palindromic SNPs (rs9482771) were discarded, leaving 33 remaining SNPs. These 33 SNPs were rs112726611, rs77971566, rs749749, rs10757277, rs9706167, rs45497400, rs34297508, rs12213593, rs17150482, rs9383585, rs364950, rs106871, rs115448220, rs6908034, rs2249850, rs11031005, rs113470730, rs9600230, rs57439315, rs34324306, rs55667387, rs140993356, rs28517654, rs35961234, rs58415480, rs17694933, rs34505094, rs8086179, rs1566646, rs6546324, rs10917151, rs2092753, rs9485296. To assess the strength of each instrumental variable, we calculated the F-statistic for each instrumental variable. In our study, the F-statistic was substantially greater than 10, indicating these SNPs are strong instrumental variables (Table 1).

Causal Relationship Between Endometriosis and Pelvic Inflammatory Disease

Based on summary data from the pelvic inflammatory disease GWAS (2913 cases and 111,858 female controls), MR analysis was conducted to evaluate the causal impact of endometriosis on pelvic inflammatory disease. MR estimates from various methods all indicated a causal relationship between endometriosis and pelvic inflammatory disease (Figure 1, Table 2). The

Table 1 Information on Single Nucleotide Polymorphism (SNP) Loci Associated with Endometriosis

Name	SNP	EAF	Beta	SE	N	R2	F
1	rs106871	0.444	-0.0805	0.0176	77,257	2.71E-04	20.91969
2	rs10757277	0.4203	-0.1013	0.0178	77,257	4.19E-04	32.38677
3	rs10917151	0.1706	0.1685	0.0232	77,257	6.82E-04	52.7488
4	rs11031005	0.1676	-0.2379	0.0239	77,257	1.28E-03	99.07905
5	rs112726611	0.06078	0.1953	0.037	77,257	3.61E-04	27.86056
6	rs113470730	0.05153	0.3055	0.0404	77,257	7.40E-04	57.18057
7	rs115448220	0.005281	0.5926	0.1257	77,257	2.88E-04	22.22499
8	rs12213593	0.2431	0.1106	0.0204	77,257	3.80E-04	29.39265
9	rs140993356	0.05875	0.3247	0.0379	77,257	9.49E-04	73.39643
10	rs1566646	0.1931	-0.1116	0.0225	77,257	3.18E-04	24.60096
11	rs17150482	0.3743	-0.0856	0.0182	77,257	2.86E-04	22.12043
12	rs17694933	0.4243	0.1331	0.0177	77,257	7.31E-04	56.54554
13	rs2092753	0.04426	-0.2016	0.0432	77,257	2.82E-04	21.77721
14	rs2249850	0.3658	0.0959	0.0182	77,257	3.59E-04	27.76407
15	rs28517654	0.2432	-0.1356	0.0205	77,257	5.66E-04	43.75225
16	rs34297508	0.1623	-0.1176	0.0242	77,257	3.06E-04	23.61417
17	rs34324306	0.01216	0.3896	0.0802	77,257	3.05E-04	23.59815
18	rs34505094	0.2003	0.1049	0.0219	77,257	2.97E-04	22.94307
19	rs35961234	0.05312	0.1863	0.0398	77,257	2.84E-04	21.9103
20	rs364950	0.002201	0.9335	0.1964	77,257	2.92E-04	22.59095
21	rs45497400	0.003704	0.7068	0.1534	77,257	2.75E-04	21.22908
22	rs55667387	0.3381	0.0944	0.0185	77,257	3.37E-04	26.0369
23	rs57439315	0.3779	-0.101	0.0181	77,257	4.03E-04	31.13683
24	rs58415480	0.2315	0.2216	0.021	77,257	1.44E-03	111.3499
25	rs6546324	0.6921	-0.125	0.019	77,257	5.60E-04	43.28143
26	rs6908034	0.1573	0.1261	0.024	77,257	3.57E-04	27.60555
27	rs749749	0.4789	0.0923	0.0175	77,257	3.60E-04	27.81737
28	rs77971566	0.006435	0.518	0.1109	77,257	2.82E-04	21.81651
29	rs8086179	0.09891	-0.1412	0.0296	77,257	2.94E-04	22.75489
30	rs9383585	0.1229	0.1421	0.0268	77,257	3.64E-04	28.11301
31	rs9485296	0.1978	0.1136	0.022	77,257	3.45E-04	26.66245
32	rs9600230	0.07633	0.1635	0.0333	77,257	3.12E-04	24.10659
33	rs9706167	0.1454	0.1622	0.0249	77,257	5.49E-04	42.43183

Table 2 Evaluation of the Impact of Endometriosis on the Causal Relationship with Pelvic Inflammatory Disease Using Inverse Variance Weighting (IVW), MR-Egger, and Weighted Median (WM) Methods

Method	nsnp	Beta	SE	pval	OR	Low 95%	Up 95%
MR Egger	79	0.3444	0.108	0.003251	1.411143	1.14193	1.743823
Weighted median	79	0.3129	0.07136	1.16E-05	1.367385	1.188907	1.572656
Inverse variance weighted	79	0.3298	0.04475	1.71E-13	1.39069	1.273909	1.518177
Weighted mode	79	0.4945	0.1221	0.000303	1.639678	1.290699	2.083014

specific results were as follows: IVW, OR = 1.39, $P < 1 \times 10^{-8}$; MR-Egger, OR = 1.41, $P = 0.003$; WM, OR = 1.37, $P = 1.16 \times 10^{-5}$; Weighted mode, OR = 1.64, $P = 0.0003$. Furthermore, the intercept represents the average pleiotropic effect of genetic variation, and IVW, MR-Egger, WM, and Weighted mode all indicated minimal presence of confounding factors within the data (Figure 2).

Heterogeneity and Sensitivity Analysis

Heterogeneity refers to the variability of causal estimates obtained from each SNP. Low heterogeneity suggests increased reliability of MR estimates. Cochran's Q test indicated low heterogeneity for IVW and MR-Egger, further confirming the increased reliability of the causal relationship between endometriosis and pelvic inflammatory disease (Table 3). After

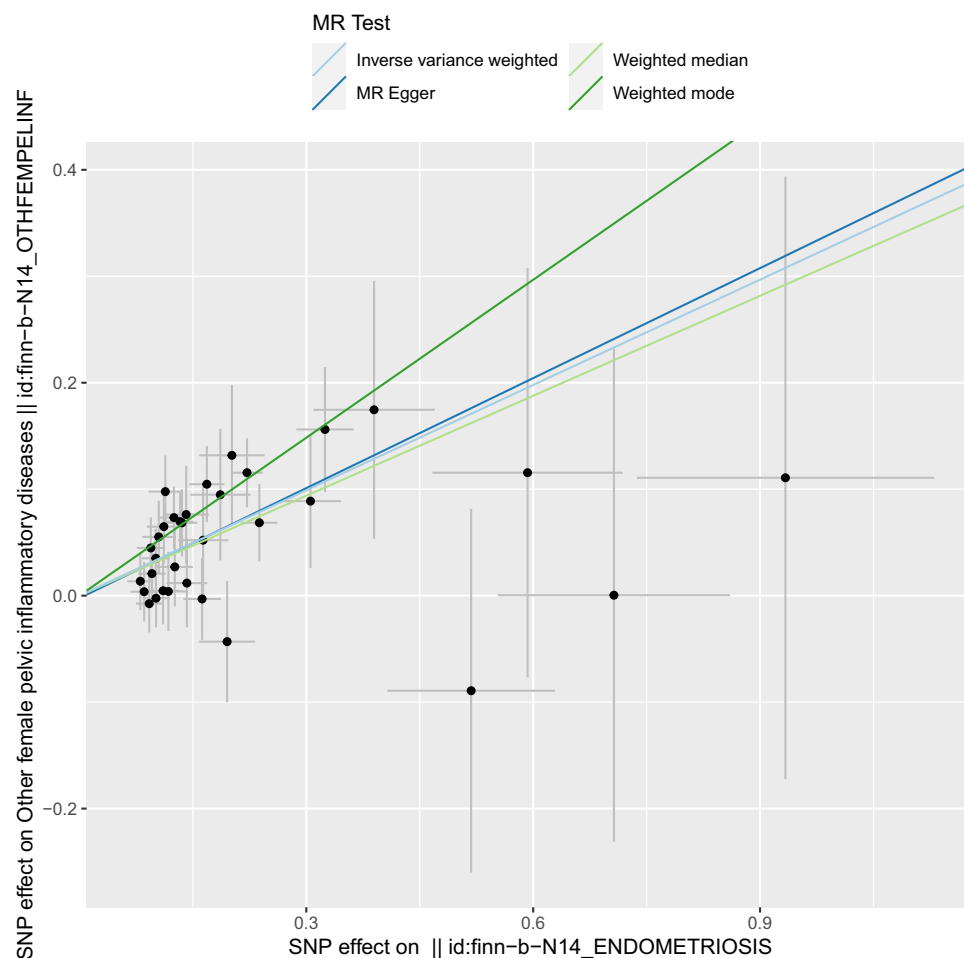


Figure 2 Scatter plot depicting the genetic associations between endometriosis and pelvic inflammatory disease. Blue represents Inverse Variance Weighting (IVW), dark blue represents MR-Egger, and green represents Weighted Median (WM) analyses.

Table 3 Cochran's Q Assessment of Heterogeneity for Inverse Variance Weighting (IVW) and MR-Egger Results in the Relationship Between Endometriosis and Pelvic Inflammatory Disease

Method	Q	df	I ²
Inverse variance weighted	30.6	32	0.045752
MR Egger	30.58	31	0.013734

performing individual SNP exclusion tests, the association between endometriosis and pelvic inflammatory disease remained unaffected by any single SNP (Figure 3A). Subsequently, the funnel plot revealed no evidence of asymmetric SNP distribution (Figure 3B).

Discussion

In this study, we employed extensive GWAS data from publicly available databases and conducted an unbiased two-sample MR analysis to investigate the causal associations between endometriosis and PID. Following rigorous quality control measures, we obtained the results to confirm that there is a causal relationship between endometriosis and PID. Our results provide a new theoretical basis for clinical diagnosis and prevention of PID.

Endometriosis and PID are two distinct gynecological conditions, sometimes they may have interconnect and impact on reproductive health.¹⁹ More and more researchers are paying attention to the relationship between endometriosis and PID. Current reports suggest that endometriosis may affect PID through multiple potential pathways. Firstly, the infiltration of macrophages and abnormal activation of vascularization in endometriosis lead to adhesions and structural changes in pelvic organs.^{20–22} Subsequently, these altered structures make it easier for bacteria to thrive, thus increasing the risk of PID. Secondly, the presence of stagnant blood in endometriotic lesions may raise the pH of surrounding organs, impacting the local microbial environment, lead to bacterial infection, and subsequently induce PID.^{23,24} Furthermore, the cyclic renewal of the lesion site during the menstrual cycle creates a favorable nutritional environment

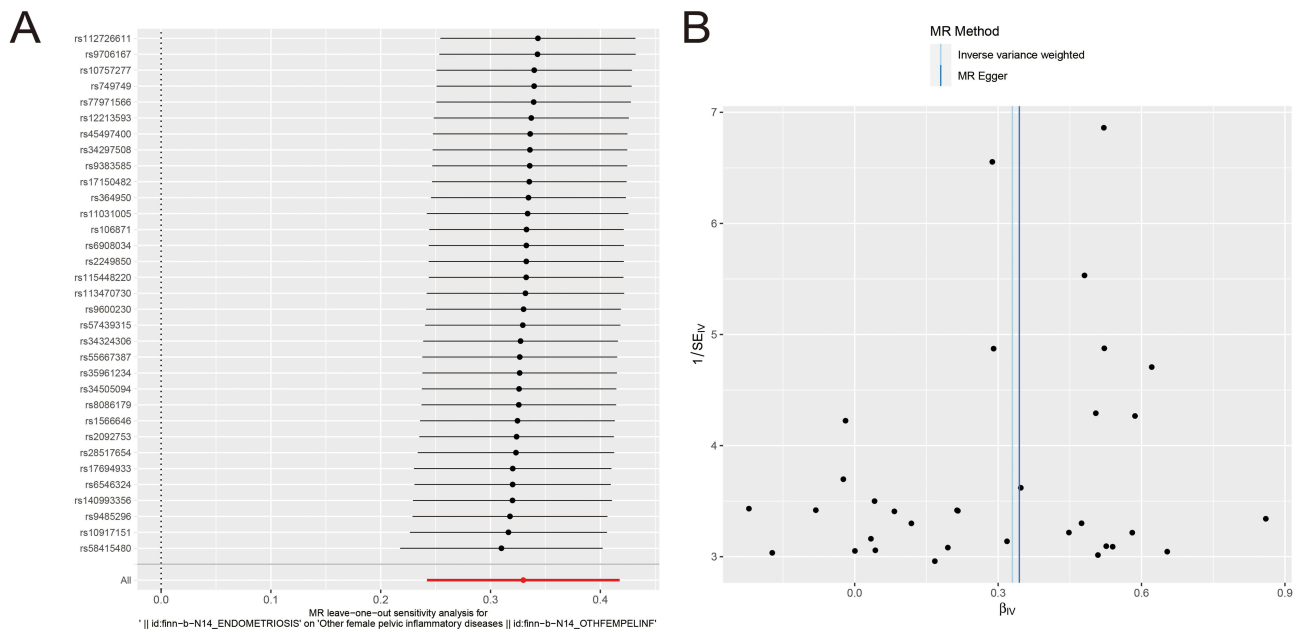


Figure 3 Sensitivity and heterogeneity assessment for the relationship between endometriosis and pelvic inflammatory disease. (A) Forest plot illustrating the impact on pelvic inflammatory disease by sequentially excluding single nucleotide polymorphisms (SNPs). Red dots represent IVW estimates for all SNPs. (B) Funnel plot evaluating heterogeneity, with blue line representing IVW and dark blue line representing MR-Egger.

for bacterial proliferation, promoting the spread of infection.^{25,26} Thirdly, the microbiota normally regulates inflammation, immunity, and metabolism, forming a protective barrier against pathogen invasion and eliminating pathogenic microbes.^{27–29} Changes in the microbiota around endometriotic lesions—specifically, decreased abundance of lactobacilli in the lower reproductive tract and diverse anaerobic bacteria in the upper reproductive tract, peritoneum, and endometriotic lesions, including *Gardnerella*, *Streptococcus*, *Enterococcus*, and *Escherichia coli*—facilitate the propagation of pathogens associated with bacterial vaginosis, leading to the development of PID.^{30–32} Fourthly, dysregulation of the local immune system in patients with endometriosis, such as increased number and activation of peritoneal macrophages and dysregulation of T lymphocytes, can further lead to changes in local and systemic inflammatory mediators.^{33–36} Abnormally levels of inflammatory factors can lead to persistent inflammation, impeding timely clearance of bacteria and leading to PID.^{2,37} Additionally, endometriosis exhibits abnormal DNA methylation, histone modifications, and non-coding RNA expression, inducing further changes in immune cell function, quantity, and phenotype, compromising the immune defense mechanisms and exacerbating PID progression.^{38–40}

Consistent with previous observational studies. Our study employed MR analysis to assess the causal relationship between endometriosis and PID. Given that MR studies can be influenced by genetic variation and associations with multiple variables, we used the weighted median (WM) method to address pleiotropy, conducted MR-Egger for assessing directional pleiotropy, and conducted sensitivity analysis to examine the robustness of our MR study. The results from IVW, MR-Egger, and WM methods consistently confirmed the causal relationship between endometriosis and PID.

This study has its own limitations: (1) The GWAS data are derived exclusively from European populations. Therefore, the findings may not be extrapolated to other ethnic groups and regions. More comprehensive studies across different ethnic groups are needed; (2) Although utilizing the largest available large-scale GWAS data, follow-up research efforts should focus on further expanding the sample size to produce more precise assessments.

Conclusion

In conclusion, our study findings demonstrate that endometriosis is a risk factor for PID, suggesting a potential causal relationship between endometriosis and increased PID risk. This sheds new light on the underlying mechanisms of the potential association between endometriosis and PID, providing a novel direction for further exploration.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors declared that they have no conflicts of interest in this work.

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