

The Effect of Circulating Inflammatory Proteins on Endometriosis: A Mendelian Randomization Study

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Background: Endometriosis is a complex gynecological condition in which endometrial fragments are implanted outside the uterus, causing pain and infertility. Although immune mediators play a vital role in endometriosis, their exact etiology remains elusive. Using Mendelian randomization (MR), this study aimed to assess the causal relationship between inflammatory proteins and endometriosis.

Methods: Genetic variants associated with inflammatory proteins were filtered from a genome-wide protein quantitative trait locus study under stringent thresholds. These variants were used as instrumental variables (IVs) to evaluate the causal effects of these inflammatory proteins on endometriosis. A two-sample MR analysis was performed with endometriosis from the UK Biobank as the outcome, and a sensitivity analysis was performed to mitigate potential confounding factors. Analyses were replicated in an independent endometriosis cohort from the FinnGen, followed by a meta-analysis of MR results from both cohorts. Finally, we assessed the causality between inflammatory proteins and the endometriosis subtypes.

Results: Independent MR analysis revealed that the genetically higher levels of CXCL5 were linked to a lower chance of having endometriosis. The causal link remained significant in the meta-analysis. Furthermore, the causality of CXCL5 expression has been identified in ovarian and pelvic peritoneal endometriosis.

Conclusion: Our MR analysis indicated that CXCL5 was associated with a decreased risk of endometriosis, suggesting that CXCL5 might have a protective effect against endometriosis. This enhances our understanding of the involvement of chemokines in endometriosis pathology and provides insights for future studies to explore the detailed mechanisms underlying CXCL5 in endometriosis.

Keywords: endometriosis, inflammatory proteins, Mendelian randomization, CXCL5, causal inference

Introduction

Endometriosis (EMs) is a prevalent disorder characterized by endometrium-like tissues located outside the uterus.¹ It afflicts individuals with persistent pelvic pain, dysmenorrhea and infertility, impacting around 10% of women of childbearing age worldwide.^{1,2} Despite multifactorial contributions to its pathogenesis, including hormonal, immunological, genetic and epigenetic factors, the precise etiology of EMs remains elusive.^{3,4}

Numerous hypotheses have been proposed to explain endometriosis onset and progression. Among these, retrograde menstruation, in which endometrial fragments are shed into the pelvic cavity, is widely acknowledged to be a causative factor.⁵ This ectopic debris attaches to distant tissues, circumvents immune clearance and proliferates into endometriotic lesions.⁶ Recently, the immunological origins of endometriosis have gained increasing interest, as endometriotic fragments provoke a pro-inflammatory response in ectopic tissues.⁷ Even under a heightened inflammatory response, endometriosis patients are unable to remove these lesions, hinting at deeper immune dysfunction underlying this phenomenon. Notably, the plasma from patients with endometriosis demonstrates dysregulation of inflammatory proteins.⁸ For example, increased concentrations of pro-inflammatory cytokines, including IL-1 β , TNF- α , and IL-6, have been observed in the peritoneal fluids and ectopic lesions of endometriotic individuals, thereby contributing to

inflammation and fibrosis.^{9–12} Conversely, cytokines produced in stressed tissues lead to perturbations at the endocrine, neuronal and immune levels, thus exerting an inevitable influence on the pathogenesis of endometriosis.⁷ For instance, the Th1 cytokine milieu, which includes cytokines such as interferon-gamma (IFN- γ), has been shown to suppress the progression of endometriosis in murine models.¹³ However, causal links between inflammatory mediators and endometriosis have not yet been determined. This inconsistency may stem from insufficient sample size, flaws in the research design and unmeasured confounding variables.

Mendelian randomization (MR) offers an alternative method for establishing causal relationships that are not easily discerned through conventional observational studies, particularly in cases where randomized controlled trials are impractical.¹⁴ By utilizing randomly allocated genetic variants as instrumental variables (IVs), MR investigates the causal link between two factors, thereby mitigating confounding bias and reverse causality.^{15,16} Here, we performed comprehensive MR analysis to elucidate the causal connections between inflammatory proteins and endometriosis. Our findings implicate CXCL5 in the etiology of endometriosis, with genetically elevated levels of CXCL5 inversely correlated with the risk of endometriosis.

Methods

Study Design

We performed two-sample MR analysis to assess the causal connections between inflammatory mediators and endometriosis. Single nucleotide polymorphisms (SNPs) were used as IVs based on three criteria: 1) direct association with exposure, 2) lack of association with potential confounding factors, and 3) effect on the outcome solely through exposure.¹⁵ Figure 1 summarized the overall study design. Initially, the IVs for each inflammatory protein were extracted using a stringent threshold ($p < 5 \times 10^{-7}$, $r^2 = 0.001$, $kb = 10000$). Subsequently, we acquired endometriosis GWAS summary statistics from independent sources (UK Biobank and FinnGen) and performed separate MR analyses to explore causal associations. To enhance the robustness of the causal relationships between CXCL5 and endometriosis, we meta-analyzed MR results from both sources. Finally, we assessed the causal relationship between CXCL5 and five subtypes

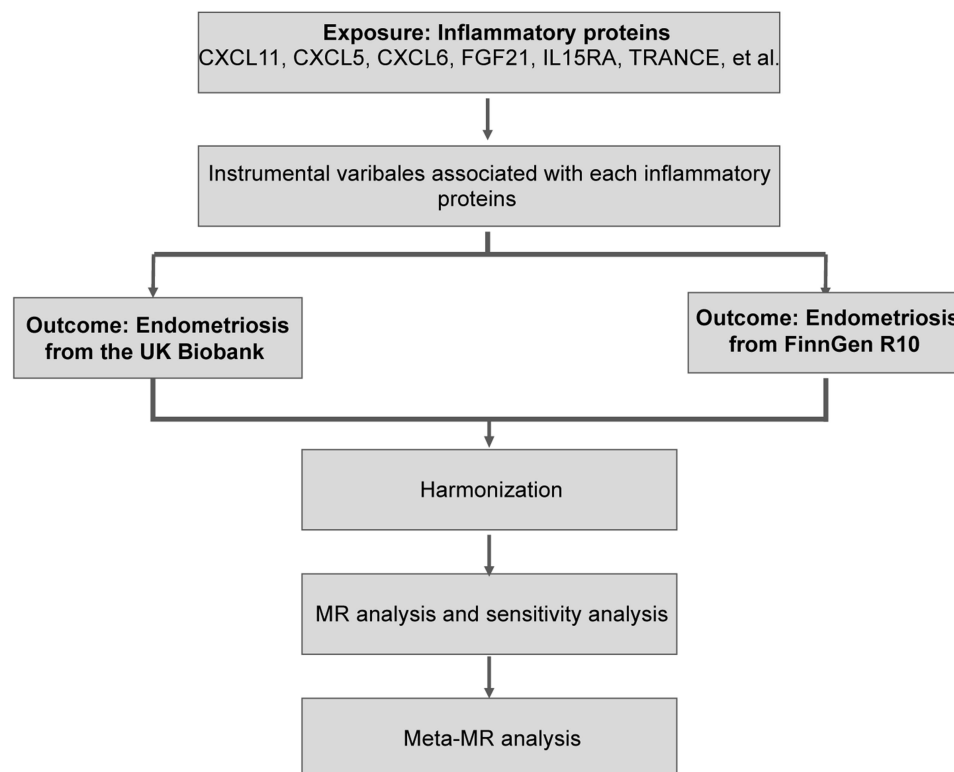


Figure 1 Overall design of this study in the form of a flow chart. The flowchart depicts how the MR analysis was conducted in a step-by-step manner.

of endometriosis: endometriosis of the ovary, intestine, pelvic peritoneum, fallopian tube, rectovaginal septum, and the vagina. This study adhered to STROBE-MR (Strengthening the reporting of observational studies in epidemiology using mendelian randomization) guideline^{17,18} ([Supplemental Table 1](#)).

Data Sources

Genome-wide protein quantitative trait locus (pQTL) data for circulating inflammatory mediators were sourced from a recent study by Zhao et al, who identified multiple genetic variants influencing protein levels.¹⁹ The GWAS data for endometriosis in European population (ukb-saige-615) was retrieved from Pheweb under the term of “endometriosis”, a UK Biobank Single Variant Association Analysis by LeeLab.²⁰ Accordingly, endometriosis data in the FinnGen were obtained with the ID “finnGen-n14-endometriosis”.²¹ GWAS data from ukb-saige-615 comprised 4053 cases and 399757 controls, whereas the data from the FinnGen included 16588 cases and 111583 controls. Additionally, we acquired five different subtypes of endometriosis from the FinnGen: endometriosis of the intestine (492 cases and 111583 controls), ovary (6444 cases and 111583 controls), pelvic peritoneum (6237 cases and 111583 controls), fallopian tubes (239 cases and 111583 controls) and the rectovaginal septum and vagina (2687 cases and 111583 controls).

Detailed information on each phenotypic exposure and outcome is presented in [Supplementary Table 2](#).

Selection of Instrumental Variables

At a threshold of $p < 5e-7$, SNPs were selected for further analysis of 91 plasma inflammatory proteins. Linked disequilibrium clumping was performed to verify the independence of each SNPs under the stringent criteria ($r^2 = 0.001$, window size = 10000). Non-concordant and palindromic alleles were excluded during the harmonization of exposure and outcome. The remaining SNPs were considered instrumental variables. The PhenoScanner demonstrated no potential association between these instrumental variables and confounding factors. Furthermore, F-statistics were calculated for these instrumental variables, and none exhibited weak instrumental variable bias.^{22,23} Detailed information on the eligible instrumental variables used for the MR analysis was provided in [Supplementary Table 3](#).

Mendelian Randomization and Sensitivity Analysis

Two-sample Mendelian randomization analyses were performed between each inflammatory protein and endometriosis using the UK Biobank (UKB). We employed inverse variance weighting (IVW),²⁴ weighted median (WM),²⁵ and MR-Egger methods²⁶ to calculate the odds ratio, with IVW as the primary approach. Among the factors with P_{IVW} less than 0.05, six inflammatory proteins were identified, and their causal directions were consistent across the different methods ([Supplementary Table 4](#)). Statistical power was calculated to assess the robustness of each factor by using an online source (<https://sb452.shinyapps>). Cochran's Q was used to identify heterogeneity among the instrumental variables of these six factors, with a P-value > 0.05 , indicating heterogeneity.²⁷ To address the potential effect of pleiotropy, MR-Egger was employed with P-value for intercept term below 0.05 suggesting significance. Furthermore, MR-PRESSO was employed to eliminate any outliers.²⁸ Steiger tests were incorporated to examine causal directions.²⁹ All MR analyses were performed using RStudio with TwoSampleMR (0.5.7).

Results

Screening of Inflammatory Proteins Associated with Endometriosis

To explore the effects of inflammatory mediators on endometriosis, two-sample MR analyses were performed. Briefly, we extracted SNPs from GWAS summary statistics of each inflammatory protein under a well-recognized threshold ($p < 5e-7$, $r^2 = 0.001$, kb = 10000) and removed palindromic SNPs and those related to confounding factors according to the PhenoScanner. After excluding inflammatory proteins without qualified SNPs, 86 inflammatory proteins were identified as exposures, the instrumental variables of which all showed F-statistics > 10 ([Supplementary Table 3](#)). Subsequent two-sample MR analysis of these proteins and endometriosis revealed six inflammatory proteins at a significant P_{IVW} of 0.05, including CXCL11, CXCL5, CXCL6, FGF21, IL15RA and TNF-related activation induced cytokine (TRANCE).

Causal Effects of Inflammatory Mediators on Endometriosis

Based on GWAS summary statistics from the UKB, MR analysis was performed to estimate the effect of the six inflammatory mediators on endometriosis. All three approaches, IVW, MR-Egger, and weighted median, demonstrated the same causal direction, as presented in [Figure 2](#). Surprisingly, the levels of three chemokines, CXCL11, CXCL5, and CXCL6, are associated with a reduced risk of endometriosis. Specifically, genetically elevated levels of CXCL5 (1 SD increase) were casually associated with 11.2% lower odds for the risk of endometriosis (IVW: OR=0.888, 95% CI: 0.797–0.989, P: 3.06e-2; WM: 0.906, 95% CI: 0.801–1.026, P: 1.20e-1; MR-Egger: 0.903, 95% CI: 0.761–1.072, P: 0.298) ([Figure 2](#), and [Supplementary Table 5](#)). In addition, three other inflammatory factors were identified to be significantly associated with the risk of endometriosis via the IVW method, with FGF21 and TRANCE exhibiting a positive causal relationship, and IL15RA showing the opposite ([Figure 2](#), and [Supplementary Table 5](#)). Among the sensitivity tests, Cochran's Q test revealed no heterogeneity in the risk of endometriosis for all six factors ($P_{\text{heterogeneity}} > 0.05$), and the MR-Egger test did not identify any pleiotropy ($P_{\text{pleiotropy}} > 0.05$) ([Supplementary Table 5](#)). Moreover, the leave-one-out analysis demonstrated no potentially influential instrumental variables for CXCL5 ([Supplementary Figure 1](#) and [Supplementary Table 6](#)). Through MR Steiger tests, we confirmed the consistency in causal directions of all six factors on endometriosis (All $P_{\text{steiger}} < 0.0001$) ([Supplementary Table 5](#)). The leave-one-out analysis and scatter plots for 6 inflammatory proteins were visualized in [Supplementary Figures 1](#) and [2](#).

In the replication analysis, GWAS data for endometriosis were acquired using the FinnGen R10. Circulating CXCL5 was confirmed to negatively affect endometriosis (IVW: OR=0.914, 95% CI: 0.862–0.968, P: 2.18e-3; WM: 0.912, 95% CI: 0.855–0.973, P: 5.13e-3; MR-Egger: 0.893, 95% CI: 0.814–0.981, P: 0.064) ([Figure 3](#)). No significant associations were found between CXCL11, CXCL6, FGF21, IL-15A, or TRANCE and the risk of endometriosis ([Figure 3](#)). We observed no heterogeneity or pleiotropy for CXCL5 and endometriosis using Cochran's Q and MR-Egger tests ([Supplementary Table 7](#)). The leave-one-out analysis did not identify any potentially influential SNP ([Supplementary Table 8](#)). The directionality of causal estimations was confirmed using the MR-Steiger test ([Supplementary Table 7](#)). Leave-one-out forest plots and scatter plots were constructed to illustrate the findings ([Supplementary Figures 3](#) and [4](#)). In conclusion, genetically predicted CXCL5 levels demonstrated a causal association with a reduced incidence of endometriosis, supported by both datasets.

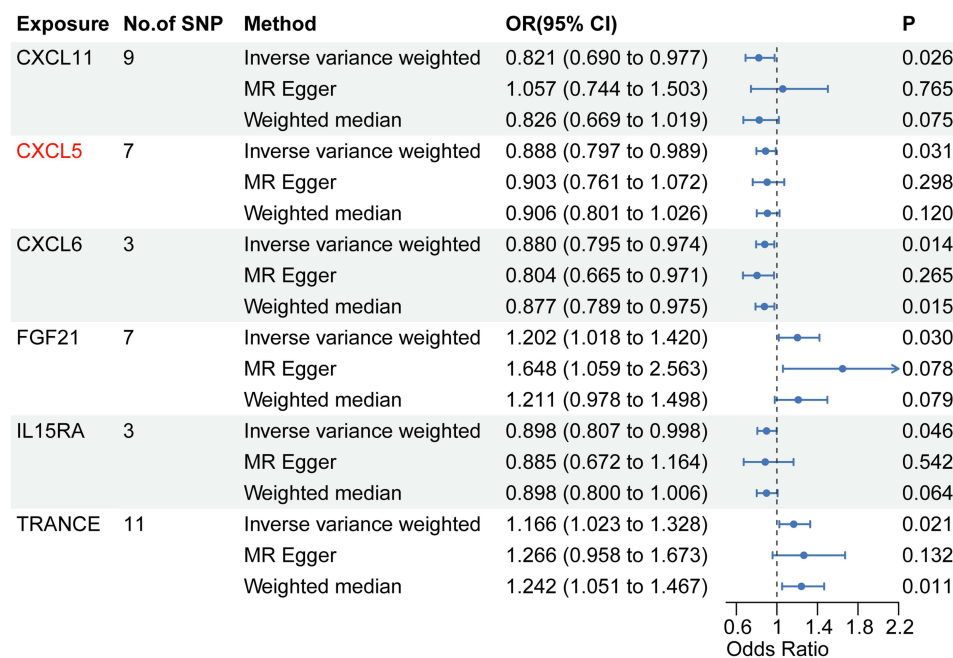


Figure 2 Causal estimates of six inflammatory proteins on endometriosis in the UK Biobank. Forest plots showing causal estimates of CXCL11, CXCL5, CXCL6, FGF21, IL15RA and TRANCE in endometriosis in the UK Biobank of European ancestry. The odds ratio (OR) was estimated using the IVW, MR-Egger, and weighted median methods. Horizontal bars represent 95% confidence intervals (CI). CXCL5 was highlighted in red text.

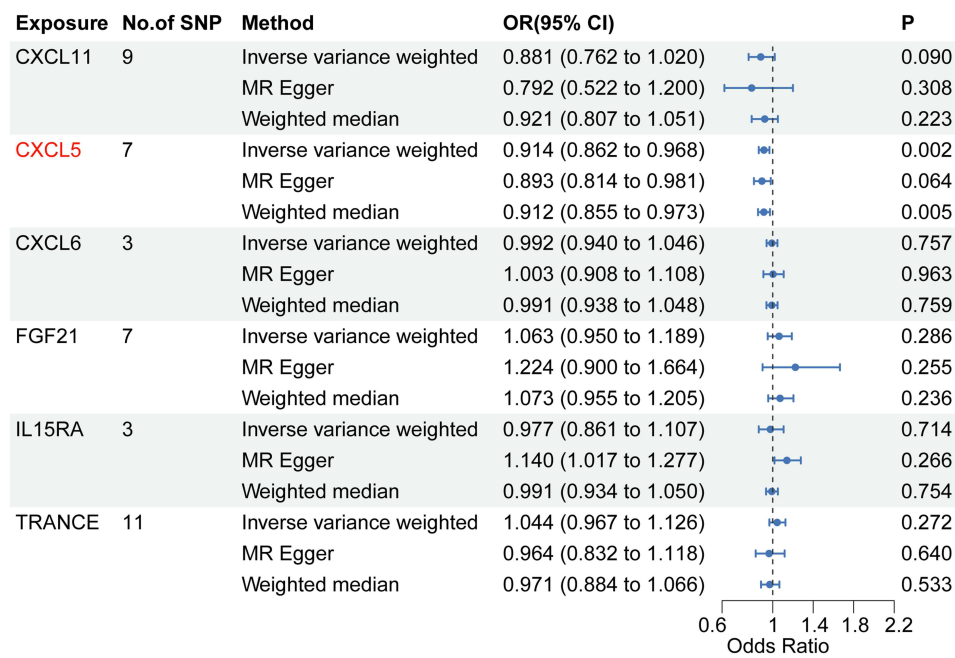


Figure 3 Causal estimates of six inflammatory proteins on endometriosis in the FinnGen. Forest plots showing causal estimates of CXCL11, CXCL5, CXCL6, FGF21, IL15RA and TRANCE in endometriosis in the FinnGen of European ancestry. The OR was estimated using the IVW, MR-Egger, and weighted median approaches. The horizontal bars represent 95% CI. CXCL5 was highlighted in red text.

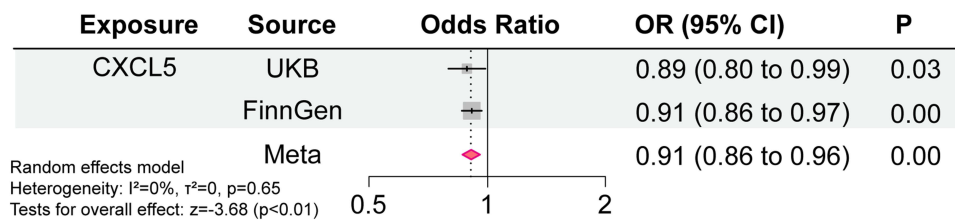


Figure 4 Causal estimates of six inflammatory proteins on endometriosis in a meta-analysis. Forest plots showing causal estimates of CXCL5 in endometriosis in a meta-analysis of the UK Biobank and FinnGen. The OR was estimated using IVW. The horizontal bars represent 95% CI.

To verify our findings, we meta-analyzed the MR results with outcomes from the UKB and FinnGen databases. These results corroborated the significant causal effects of CXCL5 on endometriosis (OR: 0.91, 95% CI: 0.86–0.96, $P<0.01$) (Figure 4). Based on these results, we concluded that genetically elevated CXCL5 levels are negatively associated with endometriosis.

Causal Effects of CXCL5 on Different Subtypes of Endometriosis

From the FinnGen R10 database, we obtained GWAS summary statistics for the five subtypes of endometriosis. Subsequently, an MR analysis was conducted to investigate the causality of CXCL5 expression in various endometriosis subtypes. The findings demonstrated significant negative effects of CXCL5 on ovarian and pelvic peritoneal endometriosis (OR: 0.879, 95% CI: 0.790–0.977, $P: 0.017$ for endometriosis of ovary; OR: 0.894, 95% CI: 0.801–0.997, $P: 0.045$ for endometriosis of pelvic peritoneum), as presented in the forest plot in Figure 5. In the Cochran's Q test, we observed no heterogeneity in the SNPs associated with CXCL5 and endometriosis of both ovary and pelvic peritoneum (Supplementary Table 9).

Discussion

Based on the published large-scale GWAS studies of European ancestry from independent sources, we investigated the causality between inflammatory mediators and endometriosis. Our findings uncovered a notable inverse relationship

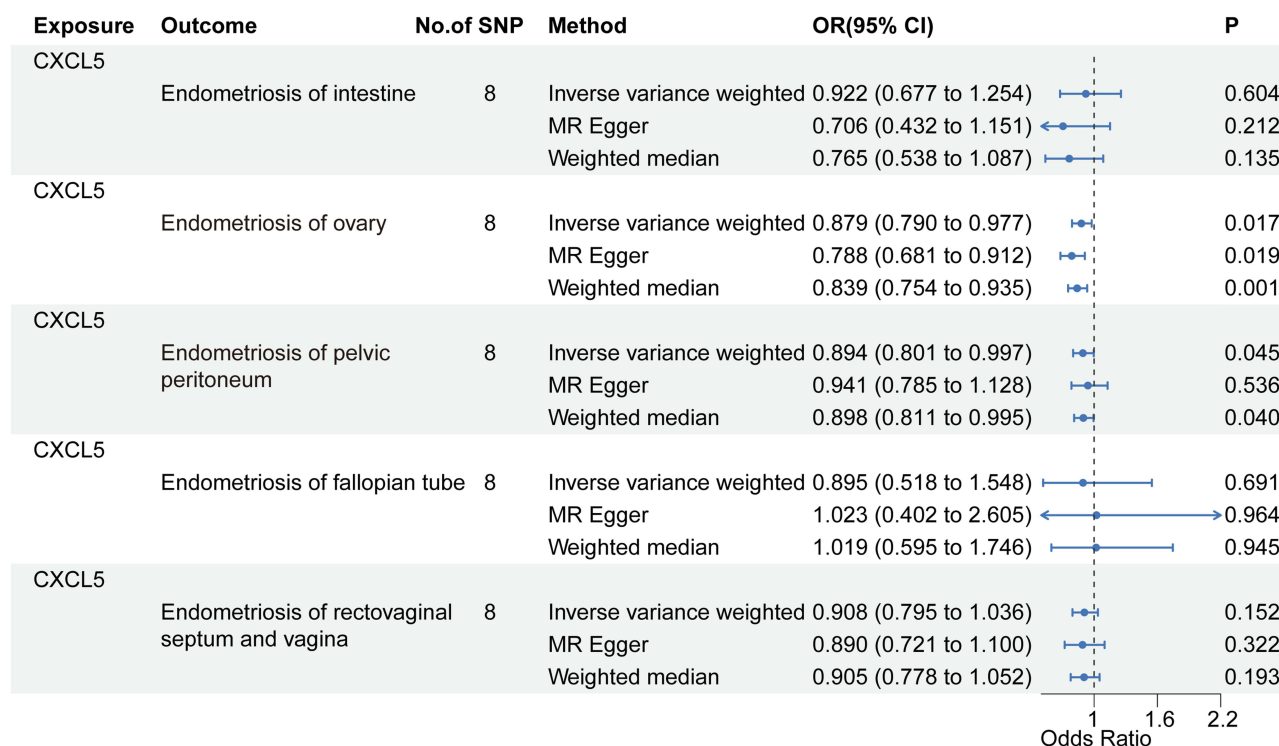


Figure 5 Causal estimates of six inflammatory proteins on endometriosis in a meta-analysis. Forest plots showing causal estimates of CXCL5 in different subtypes of endometriosis in the FinnGen of European ancestry. The OR was estimated using the IVW, MR-Egger, and weighted median approaches. The horizontal bars represent 95% CI.

between circulating CXCL5 levels and endometriosis. The causality was robustly validated through a meta-analysis of two independent MR analyses. Additionally, the investigation on the role of CXCL5 across the five subtypes of endometriosis showed a consistent causal direction, which further confirmed its protective effect. Our findings underscored the significance of modulating CXCL5 levels in the prevention and treatment of endometriosis.

Emerging evidence implies that an imbalanced interplay of immune cells and inflammatory proteins contributes to the formation of blood vessels and fibrous tissues in ectopic lesions, thereby hastening their implantation and progression.³⁰ Despite contradictory discoveries regarding immune factors in endometriosis, there is consensus that chemokines of the CXC family modulate immune cell recruitment and activation, thereby exerting a pivotal influence on the formation of ectopic lesions. The CXC chemokines encompass 17 types of cytokines, the majority of which have been implicated in endometriosis.⁸ For instance, Ruiz et al discovered the involvement of the CXCL12-CXCR4/7 axis in endometriosis, with enhanced proliferation and movement of endometriotic cells.³¹ Additionally, CXCL16 was found to be upregulated in women with endometriosis, and blocking the CXCL16/CXCR6 axis was shown to reduce the motility of endometriotic cells.³² Similarly, an antagonist of the CXCL12 receptor (CXCR4), AMD3100, reduced endometriosis progression both in vitro and in vivo.^{31,33} Consequently, an imbalance in inflammatory protein levels may reflect an overall change in the inflammatory status of endometriosis patients. However, the etiology and causal relationships underlying these correlations remain unclear.

This study represents the first comprehensive evaluation of the association between overall alterations in the inflammatory protein profile and endometriosis, using Mendelian randomization. The protective role of CXCL5 in endometriosis has been validated in two independent cohorts. Yet, these findings contradict earlier researches indicating that CXCL5 levels increase in both peritoneal fluid and blood in cases of deep infiltrating endometriosis (DIE).³⁴ Mice deficient in *Cxcr2*, the receptor for *Cxcl5*, exhibited diminished endometriotic lesions, suggesting a disease-promoting effect of the *Cxcl5/Cxcr2* axis in endometriosis.³⁵ Interestingly, the contradictory role of CXCL5 was in line with two independent MR studies on ulcerative colitis (UC), in which genetically heightened CXCL5 was correlated with a lower disease risk despite its strong upregulation in serum samples from patients with UC.^{19,36} The protective role of CXCL5

extends beyond that in endometriosis and UC. Cui et al revealed CXCL5 as a protective factor in breast cancer.³⁷ Therefore, it would be intriguing to investigate the underlying mechanism of CXCL5 in the inhibition of multiple diseases characterized by enhanced inflammatory responses. CXCL5, initially known as a neutrophil-activating peptide, is secreted by various cell types including epithelial cells,³⁸ endothelial cells,³⁹ macrophages,⁴⁰ smooth muscle cells.⁴¹ CXCL5 attracts neutrophils and monocytes through its receptors CXCR1 and CXCR2, and modulates neutrophil homeostasis at mucosal sites.⁴² Additionally, CXCL5 is also critical for B cell accumulation in inflamed tissues.⁴³ The seemingly paradoxical role of CXCL5 could be explained by neutrophils which maintain innate immune surveillance under normal conditions, but contribute to tissue damage once inflammation initiates. In the case of endometriosis, we propose that reduced CXCL5 levels impair neutrophil homeostasis and facilitates immune evasion of endometriotic cells, leading to their subsequent implantation. However, the exact etiology of CXCL5 in endometriosis requires further investigation.

Nonetheless, some limitations have to be addressed for this study. Firstly, the number of instrumental variables used in the analysis ranged from three to nine, which could potentially impact the robustness of the MR findings. However, this is unlikely to mislead the study, as the F-statistics of all instrumental variables exceeded 10, suggesting a minimal risk of weak instrumental bias. Secondly, it is worth mentioning that the GWAS study on inflammatory proteins included both female and male volunteers. Thus, it is important to acknowledge potential bias, given that our two-sample MR study was conducted on a population background that may not be consistent across genders. Finally, our findings are not representative of other populations, as they were based solely on European ancestry. Therefore, cautions should be exercised when extending our conclusions to populations of different ancestral backgrounds.

Conclusions

In conclusion, our study have provided evidence of causality between inflammatory mediators and endometriosis through an extensive two-sample MR analysis, punctuating the intricacy between immune system and endometrium. Specifically, our findings support the causal inference that circulating CXCL5 levels reduce endometriosis risk. Further research is warranted to deepen our understanding of the involvement of CXCL5 in the pathogenesis of endometriosis and its therapeutic implications.

Data Sharing Statement

The GWAS summary statistics for inflammatory proteins can be accessed via the supplementary materials of the article.¹⁹ The GWAS summary statistics for endometriosis was available on Leelab Pheweb (<https://pheweb.org/UKB-TOPMed/pheno/615>) for the UK Biobank cohort and on the FinnGen R10 (<https://r10.ristey.s.finnngen.fi/>) for the FinnGen cohort.

Ethics Statement

According to item 1 and 2 of Article 32 of “the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects”, this study is exempt from ethical review and approval, as it utilized summary statistics from public GWAS studies.

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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

The authors declare that they have no competing interest for this work.

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