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The correlation between immune cells and endometriosis: a bidirectional two-sample mendelian randomization study

Lele Pan^{1,2†}, Yuying Chen^{1†}, Ziwei Zhou^{1†}, Song Ma¹, Yuzhen Cao¹ and Ying Ma^{1*}

Abstract

Objectives Endometriosis (EM), a prevalent estrogen-dependent inflammatory disorder affecting women of reproductive age, is characterized by the presence of endometrial-like tissue outside the uterus, resulting in pelvic scarring, pain, and infertility. Although the pathogenesis of EM remains poorly understood, there is growing evidence suggesting the involvement of the immune system in its etiology, pathophysiology, and associated morbidities such as pain, infertility, and adverse pregnancy outcomes. While previous studies have indicated a close relationship between the immune system and EM, the specific underlying mechanism remains incompletely elucidated.

Methods Through the utilization of publicly available genetic data, a two-sample Mendelian randomization (MR) analysis was conducted to establish an association between 731 immune cell phenotypes and EM. Comprehensive sensitivity analyses were performed to validate the robustness, heterogeneity, and potential horizontal pleiotropy of the findings.

Results The MR analysis revealed potential associations between 22 immune cell phenotypes and EM. Conversely, reverse MR analysis identified 11 immune phenotypes demonstrating potential associations between genetic liability in the immune phenotypes and EM.

Conclusion This study provides evidence of a potential correlation between immune cell phenotypes and EM, including the existence of reverse causation. These findings open up new avenues for investigating the underlying mechanisms of EM.

Keywords Endometriosis, Mendelian randomization, Immune cell traits, GWAS, Bidirectional mendelian randomization analysis, Two-sample mendelian randomization

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Introduction

Endometriosis (EM) is a prevalent gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, affecting approximately 10% of reproductive-aged women (190 million) worldwide [1]. The most commonly affected organs are located within the pelvic cavity, including the ovaries, fallopian tubes, urinary bladder, intestines, or peritoneum; In rare cases, it can also be localized in other organs outside the pelvis, such as the diaphragm, pleura, abdominal wall, or central and peripheral nervous systems [2, 3]. It is associated with debilitating symptoms such as chronic pelvic pain, dysmenorrhea, and infertility, significantly impacting the quality of life for affected individuals. Recent studies increasingly advocate for the recognition and management of EM as a multisystem disorder, rather than limiting it to an obstetric and gynecological issue [4]. Clinically, it manifests with a broad spectrum of symptoms extending beyond the reproductive system, including migraine, depression, and eating disorders [4]. Furthermore, individuals with EM are at an elevated risk for a range of pelvic and extrapelvic comorbidities, such as cancer, autoimmune diseases, allergic conditions, and cardiovascular complications [4]. Despite the significant impact of EM on women's physical and mental health, the underlying mechanisms driving its pathogenesis remain poorly understood. The etiology of EM is complex and multifactorial, involving factors such as retrograde menstruation, immune system dysregulation, benign metastasis, hormonal imbalances, coelomic metaplasia, stem cell contributions, changes in epigenetic regulation, and environmental influences [1, 5]. The recent identification of kisspeptin as a key mediator of internal and external signals on the hypothalamic-pituitary-gonadal axis has provided new insights into the neuroendocrine regulation of the human reproductive system, suggesting its potential involvement in processes such as metabolism, inflammation, and pain sensitivity in EM [6]. Currently, no single pathophysiological or molecular mechanism has been identified that fully explains all cases.

In recent years, there has been growing interest in exploring the role of the immune system in the development and progression of EM [7–13]. Dysregulation of immune responses, particularly involving various immune cell populations, has been implicated in the pathophysiology of EM [2, 7, 10, 13, 14].

The complex interplay between the immune system and endometriotic lesions involves intricate cellular and molecular mechanisms. Among the diverse immune cell types, B cells, CDCs (complement-dependent cytotoxic cells), stages of T cell maturation, monocytes, myeloid cells, TBNK (T cells, B cells, natural killer cells), and Treg (regulatory T cells) have been of particular interest due to their potential roles in modulating inflammatory signals,

immune surveillance, and tissue remodeling processes [2, 7, 8, 12, 14, 15].

Numerous studies have provided evidence for alterations in immune cell populations and their functional activities in women with EM. For instance, aberrant B cell responses, including altered antibody production and autoantibody profiles, have been observed in both peripheral blood and peritoneal fluid of EM patients [7, 14, 16]. Disturbances in T cell subsets, such as an imbalance between Th1 and Th2 cells, have also been reported, suggesting a potential role for T cell-mediated immune dysregulation in EM development [2]. Additionally, the involvement of monocytes, myeloid cells, and regulatory T cells in the establishment and maintenance of endometriotic lesions has been proposed [11, 12, 15].

To elucidate the association between immune cell populations and EM, this study aims to employ a Mendelian randomization (MR) analysis approach. Leveraging data from a comprehensive panel of 731 immunophenotypes sourced from a genome-wide association study (GWAS) database, we will explore the potential correlation of these immune cell types on the risk and pathophysiology of EM. By utilizing genetic variants as instrumental variables, MR enables us to overcome confounding biases and provide insights into the relationships between immune cell biology and EM.

Understanding the intricate interactions between immune cell populations and the development of EM holds great promise for the identification of novel therapeutic targets and the development of personalized treatment strategies. This research endeavor may contribute to improved management and care for women affected by EM, ultimately alleviating the burden imposed by this complex and prevalent disease.

Methods

Study design

We used a two-sample MR analysis to assess association between 731 immune cell features and EM. According to Bownden et al. [17], the two-sample MR analysis satisfied the following three assumptions: (1) The instrumental variables (IVs) chosen from the datasets were associated with the exposure; (2) The IVs were not associated with any unobserved confounders of the exposure; and (3) The IVs were associated with the outcomes solely through the exposure and not through any other pathways. The study's exposure and outcome samples consisted of human individuals, and it involved a secondary analysis of previously published data that had already received ethical approval and informed consent. Consequently, obtaining additional ethical approval or informed consent was unnecessary. The study design and workflow are presented in Fig. 1.

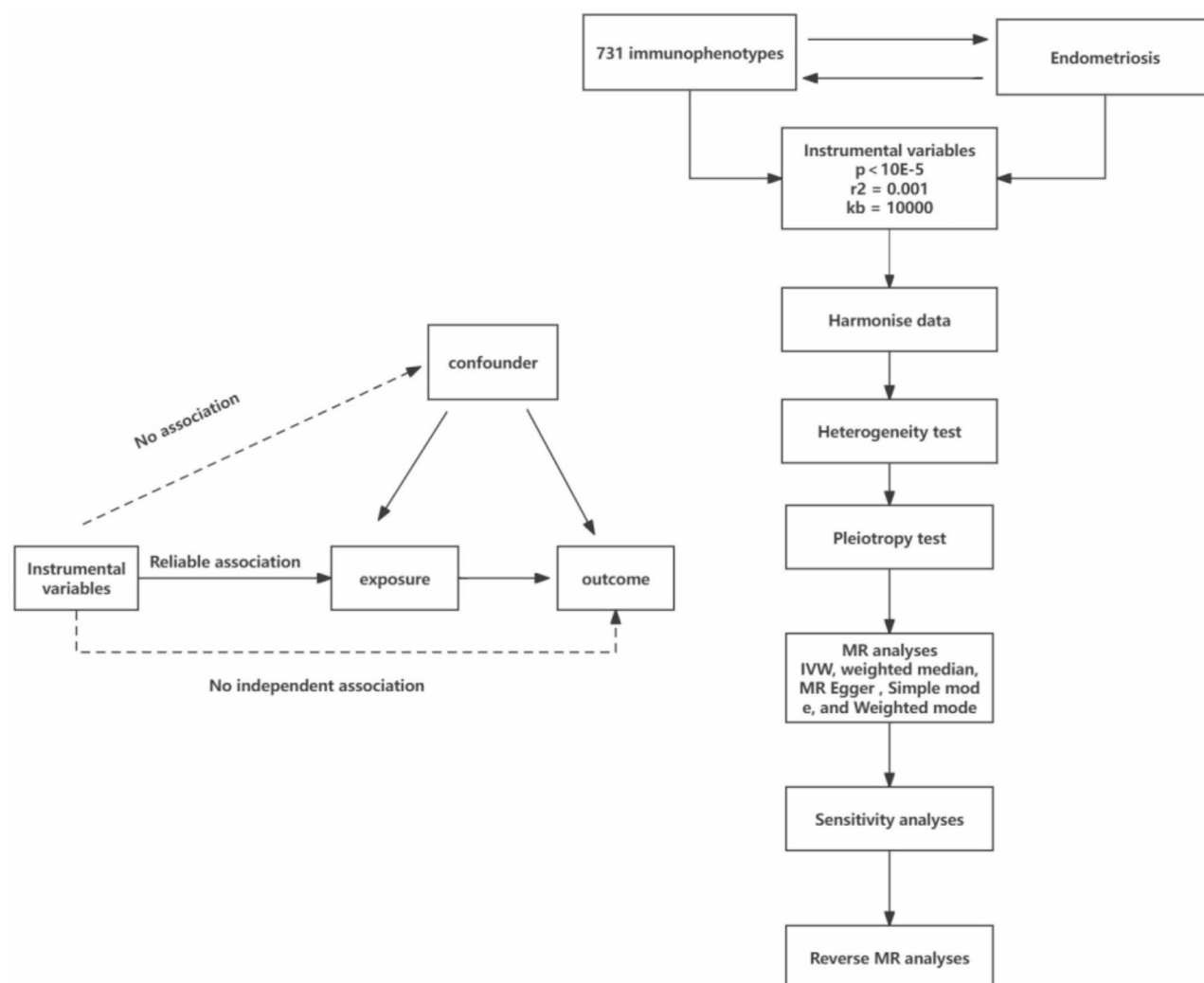


Fig. 1 The study design and workflow of the present MR study

Data sources

The summary statistics for each immunophenotype can be publicly accessed from the GWAS catalog (accession numbers from GCST90001391 to GCST90002121) [18]. A total of 731 blood-derived immunophenotypes were included, encompassing absolute cell (AC) counts ($n=118$), median fluorescence intensity (MFI) reflecting surface antigen levels ($n=389$), morphological parameters [MP] ($n=32$), and relative cell (RC) counts ($n=192$). Specifically, MFI, AC, and RC features include B cells, CDCs, stages of T cell maturation, monocytes, myeloid cells, TBNK (T cells, B cells, natural killer cells), and Treg panel, while MP features include CDC and TBNK panel. The original GWAS for immunophenotypes was conducted using data from 3,757 European individuals with no overlapping cohorts. Summary statistics for EM GWAS in the FinnGen cohort can be accessed through the R package TwoSampleMR (v 0.5.6), utilizing the IEU OpenGWAS database (<https://gwas.mrcieu.ac.uk/>) with

the recorded GWAS ID “finn-b-N14_ENDOMETRIOSIS”. In FinnGen, EM is defined as N80 in ICD-10, 617 in ICD-9, and 6253 in ICD-8. The GWAS summary statistics for EM in FinnGen include 8,288 cases and 68,969 controls.

Instrumental variables selection

We employ instrumental variables to investigate the association between immune cells and EM. Based on recent research, the significance level for each immunophenotype’s instrumental variable is set at 1×10^{-5} [18, 19]. We utilize clumping based on linkage disequilibrium (LD) to remove strong LD ($r^2=0.001$, window size=10000 kb). The clumping step is performed using the European reference panel from the 1000 Genomes Project, which is used to estimate LD between SNPs.

Statistical analysis

To assess the association between 731 immune phenotypes and EM, we primarily used the “Mendelian Randomization” package (version 0.4.3) for inverse variance-weighted (IVW), weighted median, MR Egger, Simple mode, and Weighted mode [17, 20–25]. These methods were carefully selected to address potential biases and ensure the validity of our findings. Specifically, MR-Egger regression was used to correct for directional pleiotropy, while the Weighted Median, Simple Mode, and Weighted Mode methods were utilized to account for heterogeneity in the correlation effect estimates. Additionally, MR-PRESSO was employed to identify and correct for any potential outliers that might have significantly affected the results. The “leave-one-out” sensitivity analysis was applied for exploring whether there was a single SNP which created bias to influence the overall association effect. The scatter plots demonstrated that the results were not influenced by outliers, while the funnel plots exhibited robustness of the correlation and no heterogeneity. Overall, these complementary approaches provided robust and reliable estimates of the relationship between immune cell features and EM.

Results

Exploration of the association effect of immunophenotypes on EM

To investigate the relationship between EM and immunophenotypes, a two-sample MR analysis was conducted, with the IVW method being utilized as the primary

analysis approach. We identified statistically significant differences in 22 immune phenotypes ($p < 0.05$), with 3 in the B cell panel, 1 in the cDC panel, 6 in the TBNK panel, 5 in the Treg panel, 2 in the Myeloid cell panel, 2 in the Monocyte panel, and 3 in the Maturation stages of T cell panel (Fig. 2). The MR results demonstrate that the immune cells associated with an increased risk of EM include: CD24+CD27+ %lymphocyte, CD33br HLA DR+CD14- %CD33br HLA DR+, CM CD8br AC, HLA DR+NK %NK, Granulocyte AC, CD19 on IgD+CD38br, CD28 on CD39+activated Treg, CD45 on NK, CD127 on T cell, CD25 on CD28+CD4+, CX3CR1 on monocyte, CD45 on lymphocyte. Furthermore, the MR results reveal that the immune cells associated with a protective effect against EM include: CD11c+HLA DR++ monocyte %monocyte, CD25hi CD45RA+CD4 not Treg AC, Naive DN (CD4-CD8-) %DN, DN (CD4-CD8-) %leukocyte, HLA DR+T cell AC, CD25 on IgD- CD38br, CD25 on CD39+CD4+, CCR2 on CD14+CD16+ monocyte, CD8 on TD CD8br, HLA DR on HLA DR+CD8br. The robustness of the observed associations was confirmed through the results obtained from the other four methods and sensitivity analysis (Supplementary Table). Additionally, scatter plots and funnel plots demonstrated the consistency and reliability of the findings (Supplementary Figure).

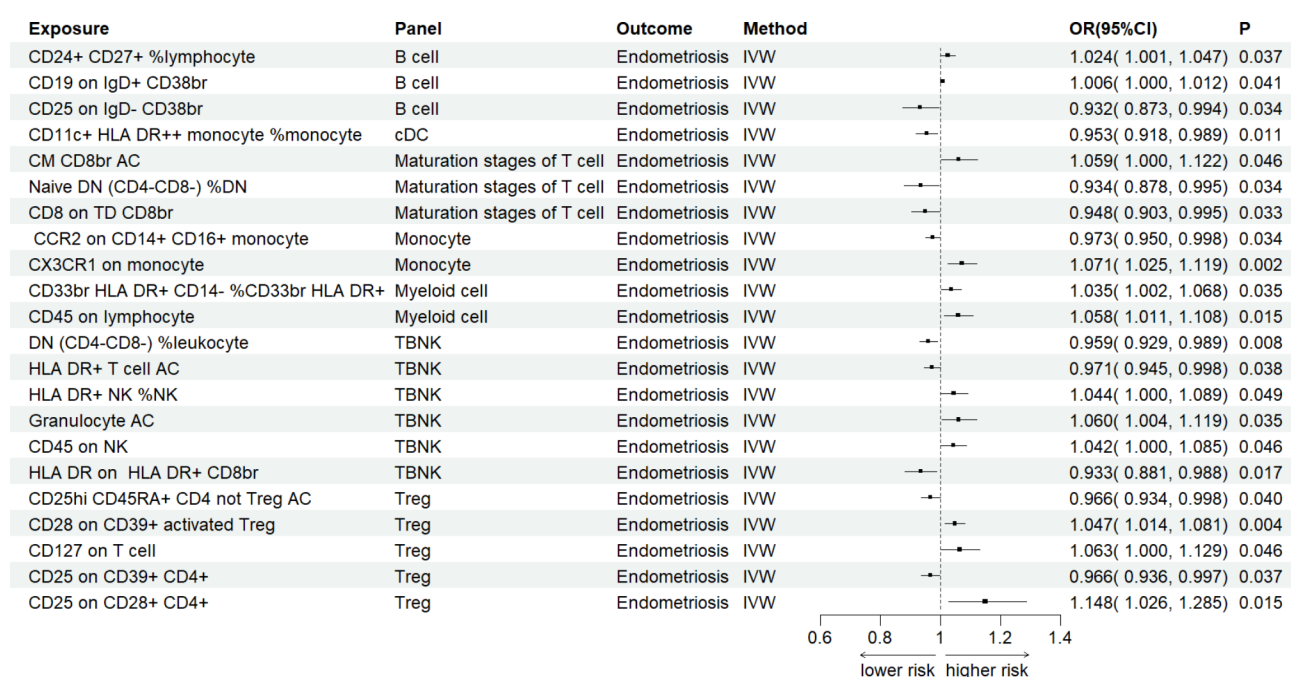


Fig. 2 Forest plots of MR estimates of genetic association between immune traits and EM. IVW, inverse variance weighting; CI, confidence interval; OR, odds ratio; MR, Mendelian randomization

Exploration of the association of EM onset on immunophenotypes

Based on the MR analysis, we have obtained the following results. Firstly, we observed the impact of EM, as an exposure factor, on various immunophenotypes. We identified statistically significant differences in 11 immune phenotypes($p<0.05$), with 1 in the cDC panel, 4 in the TBNK panel, 1 in the Treg panel, 1 in the Myeloid cell panel, 1 in the Monocyte panel, and 3 in the Maturation stages of T cell panel(Fig. 3). EM is associated with an increase in CD11c+monocyte %monocyte, and a decrease in CD33br HLA DR+CD14dim %CD33br HLA DR+, CD4+CD8dim AC, CD4+CD8dim %lymphocyte, CD4+CD8dim %leukocyte, CD3 on TD CD8br, HVEM on naive CD8br, HVEM on CM CD8br, CD25 on CD39+CD4+, PDL-1 on CD14+CD16+monocyte, and CD8 on NKT. We confirmed the strength of the associations we found by using four additional methods and conducting a sensitivity analysis (Supplementary Table). We also used scatter plots and funnel plots to show that the results were consistent and reliable (Supplementary Figure), which further supports the validity of our findings.

Discussion

Utilizing extensive publicly accessible genetic data, we conducted an investigation into the associative links between 731 immune cell traits and EM. To the best of our knowledge, this study represents the first bidirectional MR analysis examining the correlational relationship between numerous immunophenotypes and EM. Our findings revealed significant relational effects of 22 immunophenotypes on EM, while also establishing that EM exerts relational effects on 11 immunophenotypes. These findings provide valuable insights into the potential immunological mechanisms underlying the development and progression of EM.

Our findings revealed several risk factors and a protective factor associated with EM, as identified in B lymphocytes. This study demonstrates that the increased percentages of immune cells CD24+CD27+ %lymphocyte, and CD19 on IgD+CD38br are associated with an elevated risk of developing EM. The characterization of human B cell populations depends on the presence of specific surface markers, primarily including CD20, CD19, CD24, CD38, and CD27 [26]. CD19, CD24, and CD27 are capable of producing IL-10, and numerous studies have indicated a significant increase in IL-10 levels in ectopic lesions, peripheral blood, and peritoneal fluid of patients with EM [26–28]. This study demonstrates that CD25 on IgD- CD38br cells is a protective factor in EM, which contradicts previous research findings [29, 30]. CD25 is the α chain of the IL-2 receptor and plays a key role in the responsiveness to IL-2, triggering the activation of T lymphocytes and further production of IL-2. IL-2 is known to be instrumental in the immune response, particularly in cellular response, and it appears to effectively address immunological defects associated with EM in vitro [29]. When administered intraperitoneally, both rat IL-2 and human IL-2 exhibit a similar effect in reducing experimental EM, indicating a non-species-specific effect [30].

Dendritic cells (DCs) are immune cells that play a crucial role in antigen presentation during immune responses [31]. They possess the ability to induce both immune rejection and immune tolerance, and are involved in the regulation of T cell differentiation and the secretion of immunomodulatory molecules [32–34]. Previous studies have shown a close association between dendritic cells and the occurrence and development of EM [35–39]. This study reveals a significant correlation between CD11c+monocyte %monocyte, CD11c+HLA DR++monocyte %monocyte, and EM; however, the specific underlying mechanisms still require further investigation.

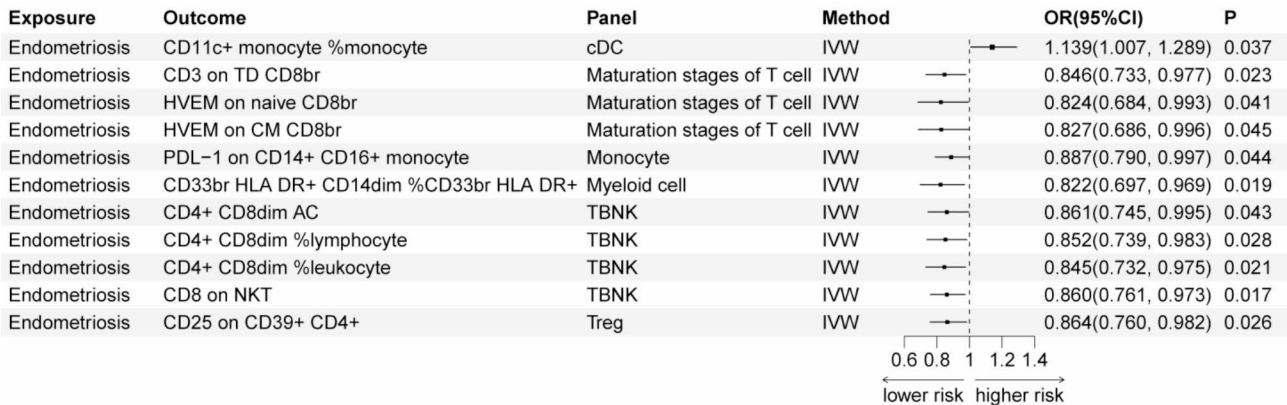


Fig. 3 Forest plots of MR estimates of genetic association between EM and immune traits. IVW, inverse variance weighting; CI, confidence interval; OR, odds ratio; MR, Mendelian randomization

T lymphocytes arise from hematopoietic progenitor cells in the bone marrow and subsequently undergo migration to the thymus. Following their differentiation and maturation within the thymus, T lymphocytes disperse to immune organs and tissues throughout the body, where they exert immune functions via circulation through lymphatic vessels, bloodstream, and tissue fluid [40]. T lymphocytes account for 1–2% of the total endometrial cell population, and their distribution varies throughout the menstrual cycle [41–43]. During the proliferative phase, they constitute 40–60% of the total leukocyte count in normal endometrial cells, while their proportion decreases to less than 10% during the secretory phase [44]. Based on different cell surface markers and functions, mature T lymphocytes can be classified into distinct subsets, including CD8-expressing cells (cytotoxic T lymphocytes), CD4-expressing cells (helper T lymphocytes), and cells that do not express CD8 or CD4. The CD4+ cell population includes helper T lymphocytes 1, 2 (Th1, Th2), Th17, as well as regulatory T lymphocytes (Treg) [45, 46]. Previous studies have shown a close relationship between T lymphocytes and related cytokines in the development and progression of EM, with possible imbalances in the Th1/Th2 or Th17/Treg immune responses [44, 47–50]. This study demonstrates that three maturation stages of T cell immunophenotypes and five Treg cell immunophenotypes have significant associative effects on EM. Additionally, EM was found to have associative effects on one Treg cell immunophenotype and three maturation stages of T cell immunophenotypes. However, it should be noted that further research is required to fully comprehend the specific mechanisms involved.

It is widely recognized that lymphocytes, in addition to T lymphocytes (T cells), encompass B lymphocytes (B cells) and natural killer (NK) cells. B cells play a crucial role in the humoral immune response by generating antibodies against foreign antigens. Within the normal eutopic endometrium, B cells constitute approximately 1–2% of the total leukocyte population and exhibit no dependence on the menstrual cycle [51]. NK cells, comprising approximately 5–15% of peripheral blood lymphocytes, are vital components of the innate immune system [52, 53]. Within the human endometrium, uterine natural killer (uNK) cells represent the major leukocyte population, constituting 30–40% of total leukocytes in the proliferative phase and up to 70% in the secretory phase [44, 53].

Previous research has indicated that B lymphocytes and NK cells are involved in the pathogenesis and progression of EM [52–59]. The role of NK cells in the development of EM was initially documented by Oosterlynck et al., who reported a decreased cytotoxic activity of NK cells against ectopic endometrial cells [60]. This

phenomenon was particularly evident in NK cells present in the peritoneal fluid, but it was also observed in NK cells circulating in the peripheral blood [10, 61]. However, the mechanism underlying the inhibition of NK cell function in EM has not been fully elucidated. Similarly, there is considerable controversy surrounding the role of B cells in EM. Although numerous studies have demonstrated that B cells within ectopic EM lesions, as well as in peritoneal fluid and serum, generate autoantibodies or antibodies specifically targeting endometrial epitopes [62, 63], there is a lack of consensus regarding the concentration of B cells and their roles in this disorder.

Studies have reported varying results regarding the number of B cells in peritoneal fluid and circulation in EM patients compared to control subjects, with some reporting an increase [57, 64–73], others a decrease [74, 75], and still others finding no significant differences [76–81]. The findings of this study provide compelling evidence that six TBNK cell immunophenotypes play a substantial relational role in the development and progression of EM. Furthermore, the study reveals that EM also exerts associative effects on four additional TBNK cell immunophenotypes.

Macrophages (M ϕ) play a crucial role as part of the mononuclear phagocyte system (MPS). M ϕ are crucial cells in both innate and humoral immunity, as they have the ability to recognize and phagocytose pathogens, act as antigen-presenting cells (APC) to activate T cells, and contribute to tissue regeneration. These functions are essential for their role in the endometrium [11, 82]. Macrophages (M ϕ) can be classified into two categories based on their activation state and surface markers: ‘classically activated’ M ϕ (M ϕ 1) and ‘alternatively activated’ M ϕ (M ϕ 2). M ϕ 1 are responsible for secreting pro-inflammatory factors, while M ϕ 2 play a role in angiogenesis, anti-inflammatory processes, and coordinating tissue repair [82, 83]. There has been a notable rise in the quantity of macrophages observed in the eutopic endometrium of women with EM [84, 85]. As M ϕ 2 predominate in ectopic EM lesions, the resulting anti-inflammatory environment fosters lesion formation, activates T cell-mediated responses, and promotes angiogenesis [86]. Other factors that contribute to the formation of endometriotic lesions include the reduced phagocytic function of peritoneal macrophages in women with EM, as well as the production of vascular endothelial growth factor (VEGF) by these macrophages, which plays a critical role in angiogenesis [86–88]. Moreover, the production of inflammatory mediators by macrophages promotes the implantation and proliferation of endometrial cells, contributing to the development of endometrial lesions [89]. In women diagnosed with EM, the prevalence of the pro-inflammatory phenotype of endometrial M ϕ 1 and secretion of pro-inflammatory cytokines create an unfavorable

milieu for successful implantation and progression of pregnancy [90]. Additionally, the presence of Mø2 within the peritoneal cavity and lesions in women with EM may potentially contribute to the sensation of pain by facilitating the growth of nerve fibers [91, 92]. This study provides evidence for the significant associative effects of two specific monocyte cell immunophenotypes on the development of EM. Additionally, reciprocal MR analysis revealed that EM exerts an associative influence on one particular monocyte cell immunophenotype.

Different types of myeloid cells can be identified based on the expression of PDL-1, CD33, HLA-DR, CD14, CD45, and CD16 [93–101]. Studies have indicated that myeloid cells play a significant role in the occurrence and development of EM [99, 102–108]. This study presents compelling evidence supporting the substantial correlational impact of three distinct immunophenotypes of monocyte cells on the progression of EM. Moreover, reciprocal MR analysis uncovered that EM exhibits a causative influence on a specific immunophenotype of monocyte cells. Nevertheless, it is important to acknowledge that additional investigations are necessary to gain a comprehensive understanding of the precise underlying mechanisms involved in this process.

It is important to note that our study utilized MR, which provides evidence for associative relationships between exposures and outcomes. However, further functional studies are needed to elucidate the precise mechanisms by which these immune cells contribute to EM pathogenesis. Additionally, the results from our sensitivity analyses and alternative MR methods supported the robustness of the observed associations, enhancing the reliability of our findings.

It is essential to recognize the limitations present in our research. First and foremost, the study utilized publicly accessible genetic data, which may be limited in terms of sample size, diversity of populations, and representation of genetic variants associated with immune cells and EM. Secondly, our application of MR presupposes that genetic variants are independent from confounding variables, which could introduce bias into our interpretations of the associations. Even though we meticulously selected genetic instruments that have a strong correlation with the exposure, the issue of residual pleiotropy persists and could compromise the accuracy of our findings. While MR provides evidence supporting associations, the complex interactions between immune cells and EM involve biological mechanisms that are not fully captured by the genetic instruments used in this study. Thirdly, Our study primarily focused on genetic associations and did not account for potential confounding factors. Future research incorporating comprehensive clinical and lifestyle data—such as BMI, age, treatment history, and menopausal status—will be necessary to

overcome this limitation. Furthermore, our research findings are derived from populations of European ancestry, which restricts the applicability of results to other ethnic demographics. Lastly, the relatively modest sample size may also hinder the broader applicability of our conclusions. To substantiate our results and clarify the underlying mechanisms, further validation through replication in independent cohorts, as well as functional studies, is imperative.

In conclusion, our study highlights the potential correlational role of specific immune cell phenotypes in the development and onset of EM. These findings contribute to our understanding of the immunological mechanisms underlying this complex disease. Future research focusing on these immune cell populations may provide novel targets for therapeutic interventions and personalized treatment strategies for EM patients.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12905-024-03493-2>.

Supplementary Material 1: Supplementary Figure: Results of sensitivity analysis and visualization of the association between immune cells and endometriosis

Supplementary Material 2: Supplementary Table: A summary of 731 immune cell types and MR analysis results on the association between immune cells and endometriosis

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Author contributions

L.P. and Z.Z. contributed to the methodology and design. S.M. and Y. Cao. was involved in material preparation and data collection. L.P. and Y. Chen performed analyses. L.P., Y. Chen, and Z.Z. contributed to writing-original draft, writing-review and editing. Y.M. provided funding acquisition, resources, and study conceptualization. All authors have read and agreed to the published version of the manuscript.

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Data availability

All the data included in this manuscript were previously deposited in public repositories and they were accessible and free to download. The GWAS summary statistics for each immune trait are publicly available from the GWAS Catalog (accession numbers from GCST90001391 to GCST90002121) (<https://www.ebi.ac.uk/gwas/>). The GWAS summary statistics for endometriosis are available on the IEU GWAS database (<https://gwas.mrcieu.ac.uk/>) for FinnGen.

Declarations

Competing interests

The authors declare no competing interests.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

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