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ARTICLE

The Association between Rheumatic Diseases and the Risk of Polycystic Ovary Syndrome: A Two-Sample Mendelian Randomization Analysis

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Abstract

Aims/Background The association between rheumatic immune diseases and polycystic ovary syndrome (PCOS) remains elusive. The purpose of this study was to investigate the causal relationship between rheumatic immune diseases and the risk of PCOS through a two-sample Mendelian randomization (MR) analysis.

Methods In the assessment of exposure variables, we chose systemic lupus erythematosus (SLE), polymyositis (PM), and rheumatoid arthritis (RA) as representative rheumatic immune diseases, while PCOS was designated as the outcome of interest. All data utilized in this investigation were obtained from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) database. A two-sample MR analysis was conducted using summary statistics for both the exposure and outcome variables, which were gathered from the genome-wide association study (GWAS) datasets. Single nucleotide polymorphisms (SNPs) significantly associated with rheumatic diseases were selected as instrumental variables (IVs) to estimate the causal effects on PCOS. The final results were analyzed using five MR analysis methods, namely MR-Egger, inverse variance weighted (IVW), weighted median (WM), simple mode, and weighted mode. Causal estimation of MR was primarily obtained using the IVW method. Sensitivity analyses were also conducted to evaluate pleiotropy and heterogeneity.

Results In this two-sample MR analysis, a total of 1,000,246 participants were included. Among them, there were 647 cases of SLE, 44 cases of PM, 5539 cases of RA, and 797 cases of PCOS. The IVW approach indicated a causal relationship between RA and an increased risk of PCOS (odds ratio [OR] = 1.069, 95% confidence interval [CI] = 1.007–1.134, $p = 0.041$). The MR-Egger intercept and Cochran's Q test ($p > 0.005$) further verified the stability of the MR results. However, no significant correlation was observed between the other two rheumatic immune diseases (PM and SLE) and the risk of developing PCOS (both $p > 0.05$).

Conclusion This study suggests a potential causal association between RA and PCOS, while SLE and PM do not exhibit a causal association with PCOS, enhancing our comprehension of the etiological factors of PCOS and shedding light on prevention strategies for the disease. Additional research is required to elucidate the underlying biological mechanisms by which RA contributes to the progression of PCOS.

Key words: polycystic ovary syndrome; rheumatoid arthritis; systemic lupus erythematosus; polymyositis; mendelian randomization; causality

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Introduction

Polycystic ovary syndrome (PCOS), a metabolic syndrome characterized by endocrine disruption, is prevalent among females of childbearing age and is a sig-

nificant contributor to female infertility. The global prevalence of PCOS ranges from 6% to 15% of the population and is distinguished by ovulatory disorders, hyperandrogenemia, and polycystic changes in the ovaries (PCOM) (Liu et al, 2024c). The presence of hormonal imbalances in PCOS patients may trigger a persistent state of inflammation (Xiang et al, 2023), which in turn advances the development of autoimmune disorders (Hu et al, 2020; Xiao et al, 2023). Meanwhile, women with PCOS who suffer from autoimmune diseases have impaired immune tolerance (Moulton, 2018), which leads to persistent mild inflammation in the body (Alpízar-Rodríguez et al, 2017; Liu et al, 2024a), further impacting oocyte production, development and the ovulation process (Li et al, 2024a; Muscogiuri et al, 2016). Given the significant influence of PCOS on individual metabolism and female reproductive function, screening for rheumatic diseases in women of reproductive age is important for early identification and standardized management of PCOS.

The relationship between PCOS and rheumatic diseases, including systemic lupus erythematosus (SLE), polymyositis (PM), and rheumatoid arthritis (RA), is barely clarified. Epidemiological studies suggest that patients with PCOS are significantly more likely to develop RA, systemic sclerosis (SS) and undifferentiated connective tissue disease (UCTD). It also suggests that its potential pathogenicity is related to autoimmune, sub-inflammatory cascades (Liu et al, 2024b). Additionally, genetic investigations have also proposed a strong correlation between PCOS and autoimmune disorders. The aberrantly expressed DNA methylation signaling pathways in PCOS patients were also found to be involved in autoimmune response pathways (Li et al, 2017; Miranda et al, 2024). Genome-wide association study (GWAS) (Glintborg and Andersen, 2017; Sun et al, 2016) proposes that there may be shared genetic polymorphisms between PCOS and certain autoimmune diseases, indicating a potential genetic susceptibility. Nevertheless, the causal relationship between rheumatologic diseases and PCOS remains uncertain. This uncertainty primarily stems from the heterogeneous nature of PCOS and the presence of confounding factors such as obesity, hyperandrogenemia, insulin resistance, and inflammation (Zhao et al, 2024). In previous studies, the presence of numerous confounding factors and substantial heterogeneity made it difficult to draw a causal inference. Furthermore, the majority of current studies are retrospective in design and are thus unable to elucidate the temporal relationship of disease occurrence.

To address this issue, the utilization of Mendelian randomization (MR) analysis, which employs genetic variation as an instrumental variable (IV), can help evaluate the causal association between various exposure and outcome variables. Single nucleotide polymorphisms (SNPs) are inherited by offspring from parents through random assignments, which are not affected by confounding variables such as environmental upbringing, socioeconomic status, and behavioral characteristics. This process resembles the random allocation observed in a randomized controlled trial. Reverse causality can be effectively avoided due to the fact that SNPs are passed on to offspring at birth and unquestionably precede the phenomenon or phenotype of the observed variables. Thus, MR analysis is perceived to have the potency to overcome confounding effects and allow confirmation of the temporal relationship between exposure and outcome variables (Nguyen and Mitchell, 2024). The

genotypes represented by SNPs in MR studies by MR are ethnographic category concepts, which excludes the influence of factors such as insufficient sample size, and can better represent the whole and obtain more reliable conclusions.

This study employed a two-sample MR analysis to evaluate the causal relationship between rheumatic diseases, such as RA, SLE and PM, and PCOS.

Methods

An overview of the MR analysis for this study is shown in Fig. 1.

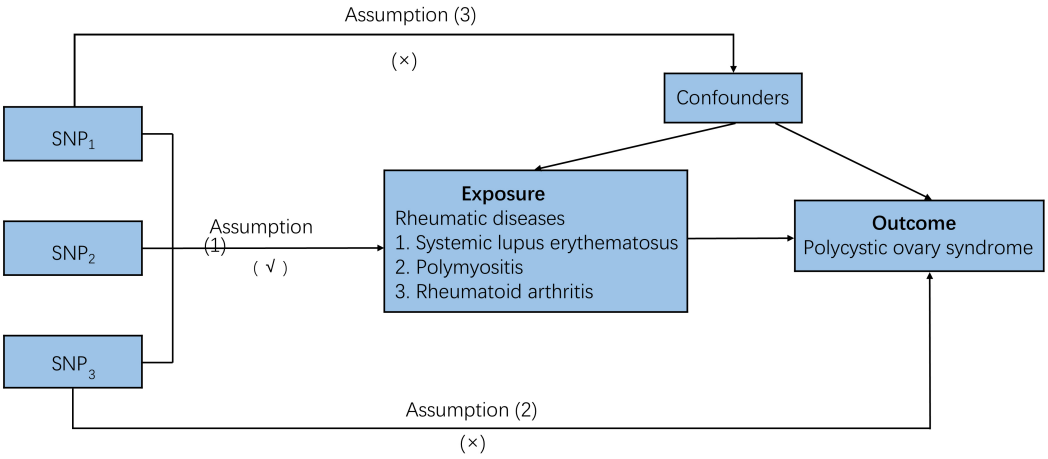

Fig. 1. An overview of MR analysis of rheumatic immune diseases and PCOS. SNP, single nucleotide polymorphism; MR, Mendelian randomization; PCOS, polycystic ovary syndrome.

Sample Source for MR Analysis

All data were obtained from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) database (https://gwas.mrcieu.ac.uk/) (Table 1). According to Sakaue et al (2021), we obtained the genetic variation data of SLE from the publicly available GWAS data (ebi-a-GCST90018917) of IEU Open GWAS project (https://gwas.mrcieu.ac.uk/), which comprises a total of 482,911 samples with 24,198,877 SNPs, and gathered the genetic variation data of PM obtained from the GWAS database (ebi-a-GCST90018891), which comprises 350,272 samples with 19,086,071 SNPs. According to Stahl et al (2010), the genetic variation data of RA were obtained from the GWAS database (ieu-a-834), which encompasses 25,708 samples with 2,556,272 SNPs. Genetic data for PCOS were obtained from the GWAS database (ebi-a-GCST90044902) (Tyrmi et al, 2022), which comprises a total of 141,355 samples with 22,981,890 SNPs. All samples were exclusively of European descent, thereby addressing the concerns about ethnic heterogeneity in the sample data. Given that this MR analysis relied solely on previously published and publicly accessible GWAS data, no research ethical clearance or clinical trial registration was deemed necessary.

Table 1. Sources of rheumatic diseases and PCOS data, and further details.

Phenotypes		ID	PMID	First author (Year)	Sample size	SNPs	N_{cases}	$N_{controls}$	Population
Exposure variables	SLE	ebi-a-GCST90018917	34594039	Sakaue et al (2021)	482,911	24,198,877	647	482,264	European
	Polymyositis	ebi-a-GCST90018891	34594039	Sakaue et al (2021)	350,272	19,086,071	44	350,228	European
	Rheumatoid arthritis	ieu-a-834	20453842	Stahl et al (2010)	25,708	2,556,272	5539	20,169	European
	PCOS	ebi-a-GCST90044902	34791234	Tyrmi et al (2022)	141,355	22,981,890	797	140,558	European

SLE, systemic lupus erythematosus; PCOS, polycystic ovary syndrome; SNPs, single nucleotide polymorphisms.

MR Analysis

To conduct MR analysis, we employed a method that involved identifying independent SNPs associated with rheumatic immune diseases by considering linkage disequilibrium (LD) and retaining SNPs with genome-wide significance. A threshold of 0.001 was set for the LD parameter (r2), and a genetic distance of 10,000 KB was utilized. We selected genome-wide SNPs with the smallest *p*-value ($p < 5 \times 10^{-6}$) to ensure the inclusion of significant SNPs and to ensure the independence of instrumental variables while excluding the influence of LD on the results. It is important to note that three essential prerequisites must be fulfilled to guarantee validity and credibility of the MR analysis results (Carter and Anderson, 2024): (1) a strong association between IVs and the exposure variable under investigation; (2) the influence of IVs on the occurrence of the outcome solely through their impact on the exposure variable; and (3) IVs are not influenced by other confounding factors that may impact the relationship between exposure variable and outcome variable. To identify IVs, we compared the SNPs obtained from our screening process with SNPs from PCOS data.

This study employed the inverse variance weighted (IVW) method to conduct an initial screening for the causal effect between three rheumatic diseases and PCOS. We employed Cochran's Q-tests and Rucker's Q-tests, utilizing the IVW analysis and the MR-Egger analysis, respectively, to evaluate the presence of heterogeneity among IVs. A $p < 0.05$ suggests that the observed heterogeneity does not compromise the results of the random-effects IVW analysis, thereby affirming the stability and reliability of the findings. Additionally, the MR-Egger intercept and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) tests were conducted to assess horizontal pleiotropy. A $p < 0.05$ in these tests indicates the presence of pleiotropic effects among the selected IVs. Sensitivity analyses were conducted using the "leave-one-out" approach, whereby each SNP was successively eliminated to calculate the combined effect of the remaining SNPs. This process allowed for the observation of the influence of each SNP on the results and the overall stability of the findings.

Statistical Analysis

Significance for all descriptive analyses was assessed using two-sided tests ($p < 0.05$). The Two Sample MR RC program package was employed for the MR analyses, and all data analyses were performed using R.4.3.0 (http://www.R-project.org).

Results

Individual SNP (IVs) for Rheumatic Diseases

This experiment utilized three rheumatic immune diseases (namely RA, SLE, and PM) as exposure variables, with PCOS serving as the outcome variable. SNPs were employed as IVs, and the flow of the two-sample MR analysis is depicted in Fig. 1. The MR analysis incorporated IV-SNPs, consisting of 5 SNPs associated

with PM, 6 SNPs associated with SLE, and 22 SNPs associated with RA. Detailed information regarding these SNPs can be found in **Supplementary Table 1**.

MR Estimates for Multi-Polymorphism Scores

The initial screening conducted using the IVW method indicated a noteworthy association between RA and the likelihood of developing PCOS, suggesting a potential causal relationship (OR = 1.069; 95% CI 1.007–1.134, $p = 0.041$). However, no significant correlation was observed between PM/SLE and PCOS (PM: OR = 0.992; 95% CI 0.968–1.017, $p = 0.517$; SLE: OR = 0.956; 95% CI 0.796–1.146, $p = 0.65$) (Fig. 2, **Supplementary Table 2**). Meanwhile, similar risk predictions were obtained in MR-Egger regression and weighted median (WM). MR-Egger regression analysis suggested a significant causal association between RA and PCOS (OR = 1.042; 95% CI 1.001–1.085, $p = 0.046$). PM was not causally associated with PCOS (OR = 0.989; 95% CI 0.942–1.038, $p = 0.683$). SLE was negatively associated with PCOS (OR = 0.946; 95% CI 0.889–1.007, $p = 0.081$), although this relationship was not statistically significant. The weighted median method also demonstrated that PM (OR = 1.000; 95% CI 0.968–1.032, $p = 0.976$) and SLE (OR = 0.949; 95% CI 0.876–1.029, $p = 0.206$) were not causally associated with PCOS. Although the correlation between RA and PCOS assessed by the WM method did not reach statistical significance (OR = 1.047; 95% CI 0.993–1.103, $p = 0.088$), the overall trend was consistent. In summary, the results obtained from the three MR analysis methods showed consistent direction and magnitude, demonstrating the robustness of the causal relationships involved. The causal relationship between RA and PCOS was dissected in greater details, with their findings presented in the next section.

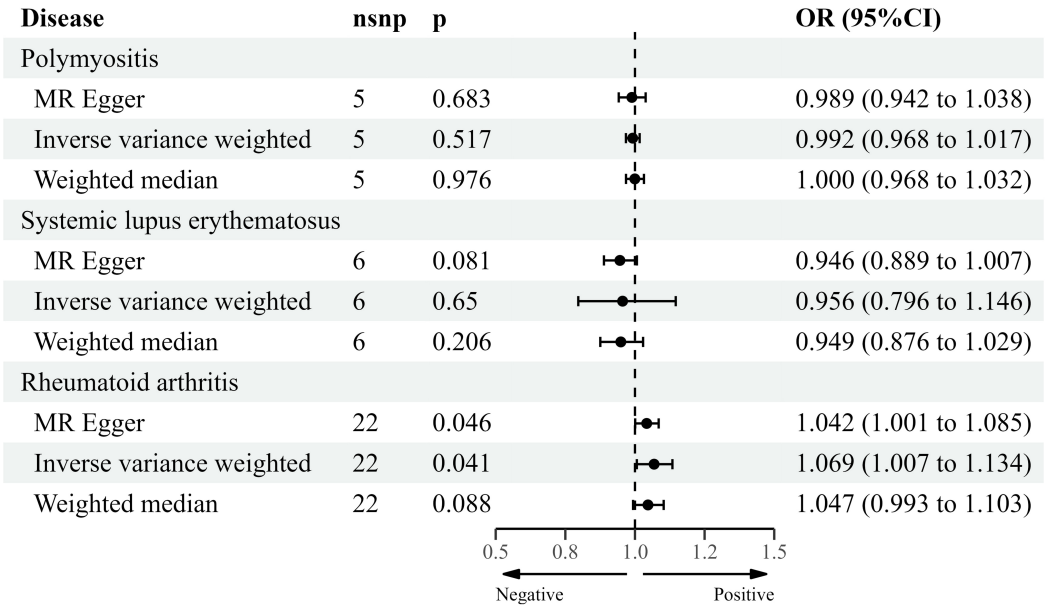

Fig. 2. MR analysis the effect of rheumatic immune diseases composition on PCOS. MR, Mendelian randomization; PCOS, polycystic ovary syndrome; nsnp, number of single nucleotide polymorphisms; CI, confidence Interval; OR, odds ratio.

Causal Relationship between RA and PCOS

MR analyses involving the five methods are detailed in Fig. 3, suggesting that most of the effects of RA on PCOS were found to be positively correlated. The findings depicted in Fig. 4 demonstrate that the MR-Egger and IVW methods consistently align in terms of the causal effects, indicating the stability of the results. In this study, the selection of SNPs was based on a genome-wide significance threshold of $p < 5 \times 10^{-6}$, which adheres to the "correlation hypothesis" (Carter and Anderson, 2024). A total of 22 SNPs were utilized as IVs, with an MR-Egger intercept of –0.011 ($p = 0.46$) (**Supplementary Table 3)**, which is close to 0, and a Cochran's Q test effect value of 20 ($p = 0.874$) (**Supplementary Table 4**), indicating that there were no pleiotropic effects or horizontal heterogeneity in the MR analyses (Fig. 4). In this study, the utilization of a solitary SNP as an instrumental variable yielded causal effects that exhibited a symmetrical distribution. This suggests that the utilization of 22 SNPs as IVs in the analysis was less susceptible to potential bias, thereby ensuring the reliability and stability of the obtained results (Fig. 5). Consequently, the "assumption of independence" was satisfied. The results of the "leave-one-out" analysis revealed that the outcomes of the remaining 21 SNP analyses closely mirrored those of the 22 SNP analyses included in the IVs. Furthermore, no SNP loci within the IVs were identified as having a significant impact on the results, as depicted in Fig. 6, thereby satisfying the "exclusion restriction hypothesis". Consequently, all sensitivity analyses provided support for the robustness of the results. Additionally, no significant correlation was observed between the other two rheumatic diseases and the risk of PCOS ($p > 0.05$).

Discussion

The present study employed GWAS data from a European population to explore the potential causal association between rheumatic diseases and PCOS. In our analysis, the genetically predicted risk of RA was associated with an increased risk of PCOS, while no significant associations were observed for SLE and PM. However, given the intricate nature of rheumatic diseases and PCOS, further investigations are warranted to validate our findings.

Currently, the relationship between rheumatic diseases and PCOS remains perplexing, and the underlying mechanisms of their pathogenesis remain unclear. PCOS patients exhibit low progesterone levels due to anovulation or infrequent ovulation, which consequently leads to immune system overstimulation, excessive estrogen production, and the generation of various autoantibodies (Torstensson et al, 2024). Hormonal imbalance in patients with PCOS has the potential to induce chronic inflammatory states and facilitate the development of autoimmune diseases (Xiao et al, 2023). Sex hormones play a significant role in immunomodulation. For instance, estrogens inhibit T and B cell lymphopoiesis, enhance B cell differentiation and immunoglobulin (Ig) production (Ascani et al, 2023), and regulate cytokine synthesis. Estrogens diffuse through the cell membrane and bind to the estrogen receptor to form heterodimers, translocate into the nucleus and bind to the promoters of target genes to regulate gene expression. Estrogen affects post-translational modification

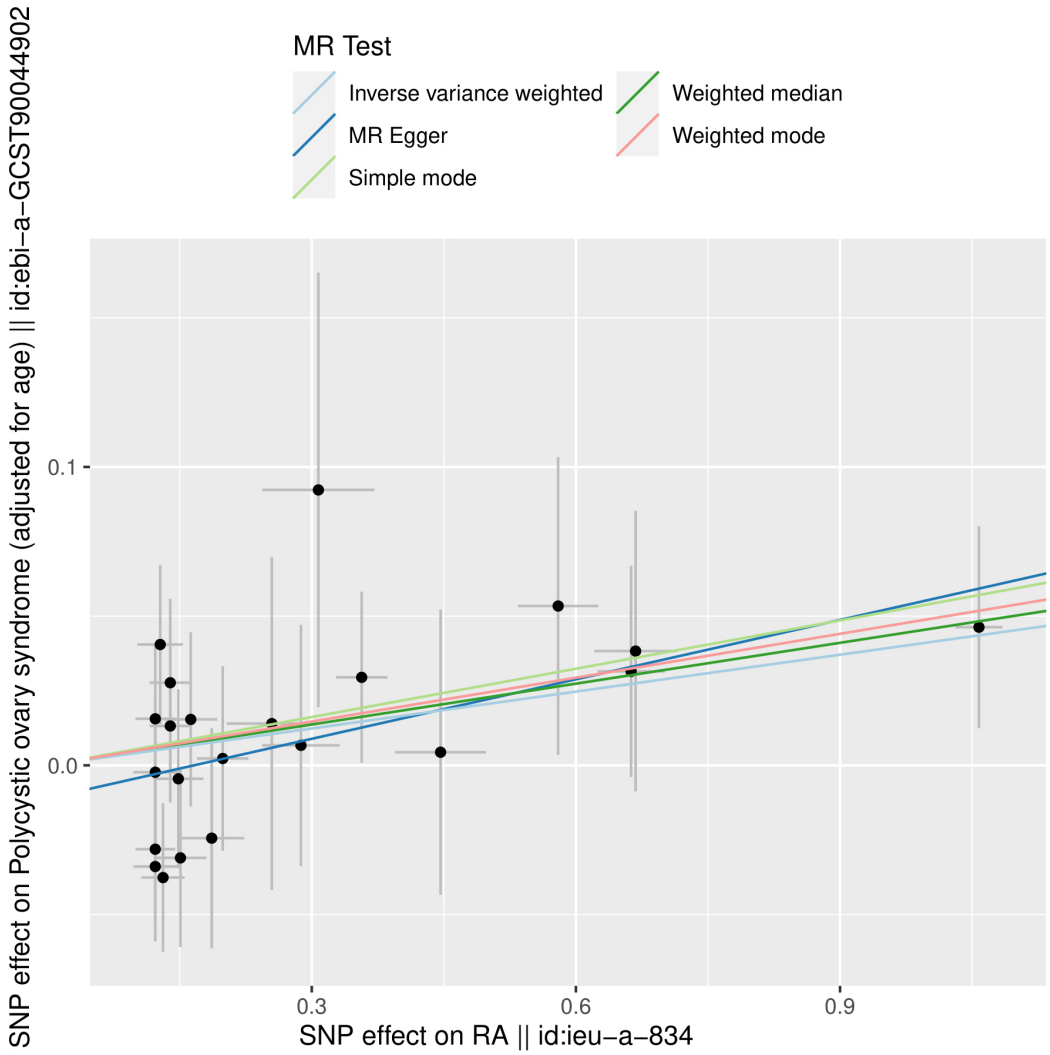

Fig. 3. Scatter plot of significant MR association between RA and PCOS. SNP, single nucleotide polymorphism; MR, Mendelian randomization; RA, rheumatoid arthritis; PCOS, polycystic ovary syndrome.

and degradation of proteins through activation of the ubiquitin-proteasome pathway (UPP) and participates in downstream signaling cascades. Estrogen has an impact on autoimmune diseases by regulating microRNA expression to control genes for innate and adaptive immune responses. Separately, progesterone affects Cluster of Differentiation 4 receptors (CD4) T helper cell (Th) differentiation and cytokine production by increasing interleukin (IL)-4, enhancing regulatory T cell (Treg) differentiation, and decreasing interferon gamma (IFN-γ), Th17 responses, T cell proliferation, and T cell-dependent antibody responses (Luan et al, 2022). In CD8 T cells, progesterone reduces IFN-γ and cytotoxicity (Shamsi et al, 2022). Effects on B cells include reduced class switch recombination and reduced T cell-dependent antibody production. Low testosterone levels are associated with higher B cell and antibody responses. Testosterone can nonselectively cause peripheral T cell death, promote Treg expansion, and inhibit inflammatory responses in peripheral lymphoid cells (Shabbir et al, 2023). Hyperandrogenaemia may alter inflammation by affecting macrophage numbers and phenotype (Banerjee et al, 2023).

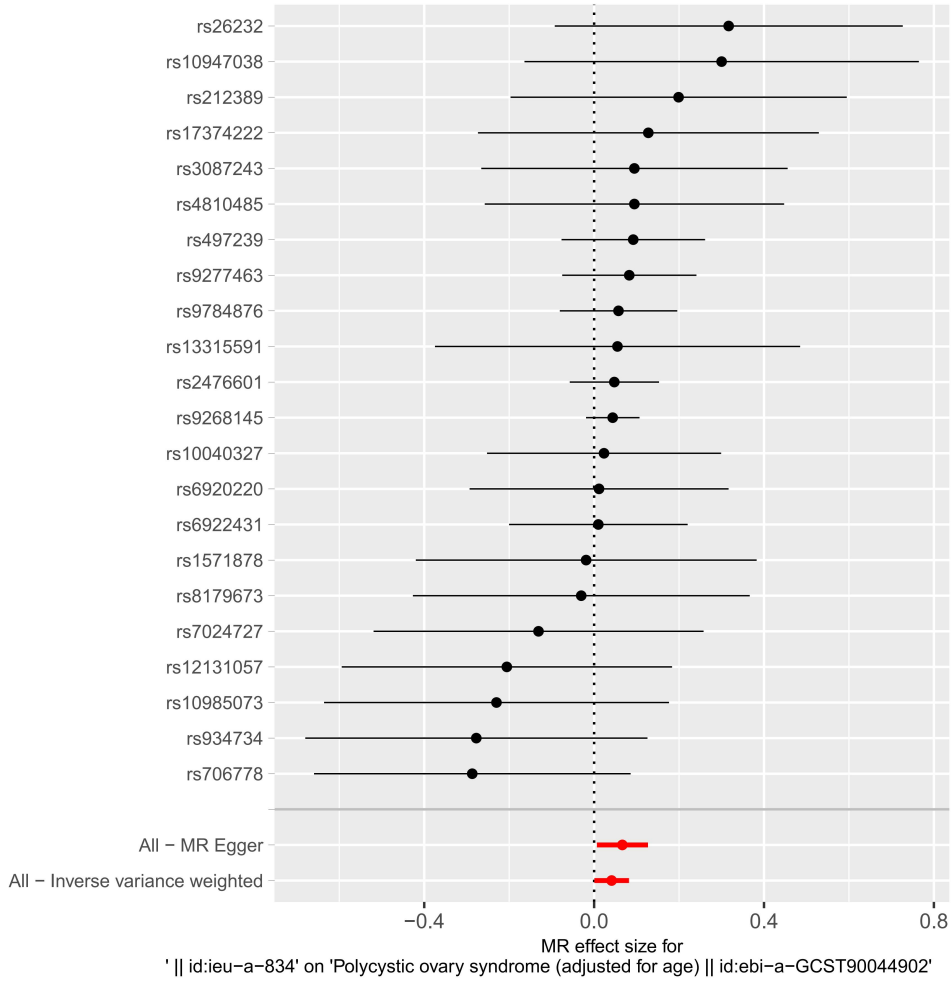

Fig. 4. Forest plot of significant MR association between RA and PCOS. MR, Mendelian randomization; RA, rheumatoid arthritis; PCOS, polycystic ovary syndrome.

Specifically, the excessive levels of estrogen in PCOS patients contribute to the upregulation of IL-4 expression by Th2 cells, IL-1 expression by monocytes, IL-6 expression by T cells, and gamma-interferon expression by Th1 cells (Singh et al, 2011). These immune responses further exacerbate autoimmune reactions, leading to the breakdown of immune tolerance and the production of autoantibodies. Low progesterone levels, which are frequently observed in individuals with PCOS, have been found to be correlated with heightened levels of the inflammatory factors IL-6 and tumor necrosis factor (TNF)-α8 (Aru et al, 2023). The immune system of the hyperandrogenic PCOS patients can be impacted due to the synthesis modulation of cytokines, such as IL-6 (Torstensson et al, 2024). On the other hand, most PCOS patients exhibit overweight or obesity, and adipose tissue can also produce TNF-α8 and IL-6, synergizing hormonal imbalances and driving autoimmune disease (Li et al, 2024b).

Two clinical studies (Mobeen et al, 2016; Petrikova et al, 2015) have reported abnormally elevated levels of autoimmune biomarkers (such as antinuclear antibodies (ANAs), anti-dsDNA antibodies, and anti-histone) in patients with PCOS, indicating a heightened risk of autoimmune disease in this population. However, it

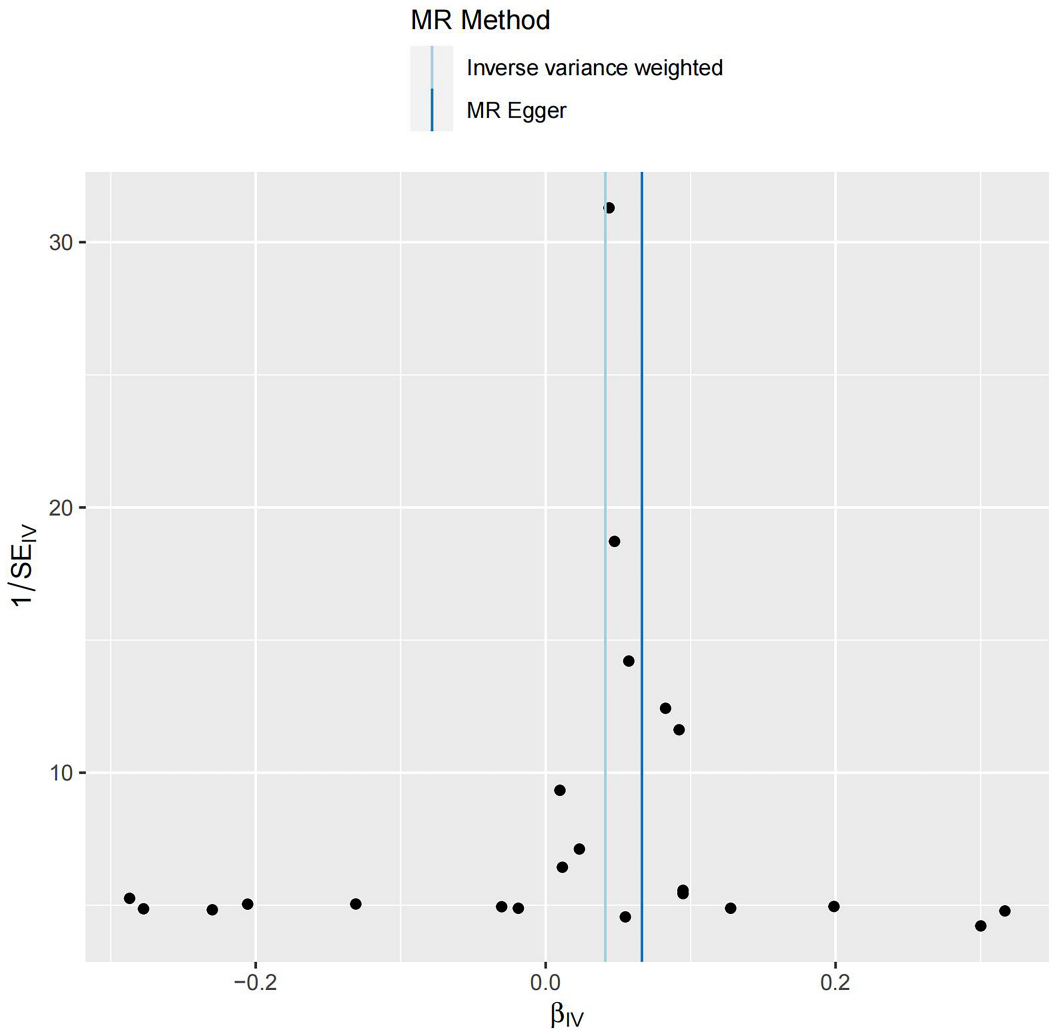

Fig. 5. Funnel plot of significant MR association between RA and PCOS. MR, Mendelian randomization; RA, rheumatoid arthritis; PCOS, polycystic ovary syndrome; SE, standard error.

is important to note that PCOS patients commonly exhibit characteristics such as obesity, insulin resistance, and hyperandrogenism, which also play significant roles in influencing autoimmunity. The two clinical observational studies incorporated limited sample sizes and lacked comprehensive subgroup analysis, thus providing a less accurate assessment of the correlation between PCOS and RA. A prospective cohort study involving older women indicates that a persistent PCOS history is a significant factor contributing to a heightened risk of RA, although the magnitude of this risk remains relatively low in absolute terms (Sharmeen et al, 2021). The association between PCOS and RA in older women suggests that disturbances in endocrine immunoreactivity in PCOS patients may advance the development of RA, or may have a protective effect that delays the onset of RA into old age (Vine et al, 2024). It has been widely acknowledged that sex hormone levels influence susceptibility to RA, with women being at a heightened risk compared to men, particularly during their reproductive ages (Di Matteo et al, 2023). Additionally, the symptoms of RA tend to ameliorate during pregnancy and exacerbate following childbirth (Schenone et al, 2024). Low levels of serum cortisol and testosterone have been

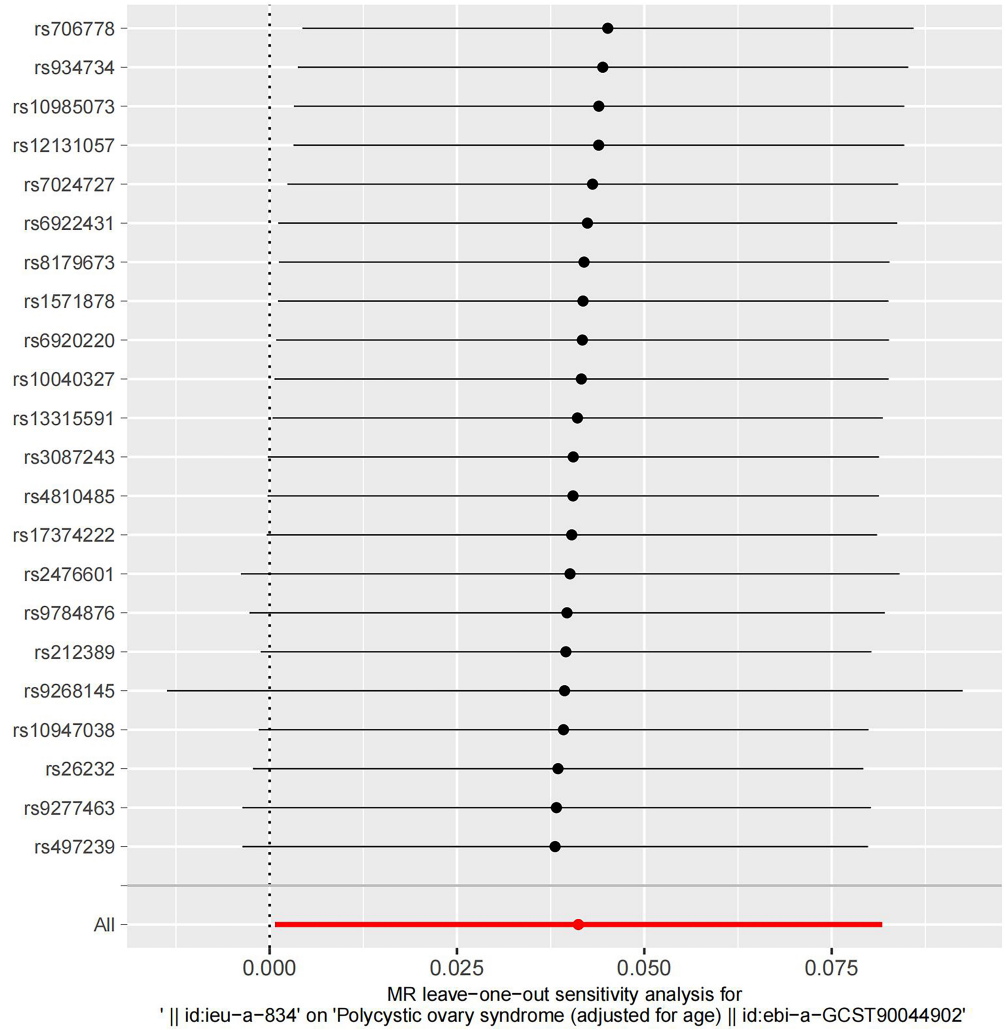

Fig. 6. Leave-one-out of significant MR association between RA and PCOS. MR, Mendelian randomization; RA, rheumatoid arthritis; PCOS, polycystic ovary syndrome.

identified as separate risk factors for RA in postmenopausal women (Salliot et al, 2022). It has been observed that many patients with PCOS display hypertrophy in their ovaries or adrenal glands, indicating a potential common mechanism between PCOS and RA (Mehta, 1998). The relative deficiencies in glucocorticoids and androgens may raise the susceptibility to developing RA or accelerating its progression at an early age. Interestingly, this hormone deficiency pattern contrasts with that observed in PCOS, suggesting a potential protective effect of PCOS in young women, delaying the onset of RA until later in life. Additional research is required to validate the pathogenicity of PCOS and RA due to the singularity of the study population. Similarly, a retrospective single-center study (Sharmeen et al, 2021) revealed a higher prevalence of autoimmune disease, specifically RA, among individuals with PCOS. The prevalence of RA in PCOS patients was determined to be 2.25%, surpassing the rates observed in both the general population of the United States and non-PCOS patients (Sharmeen et al, 2021). This result suggests an interesting association between PCOS and RA, potentially related to endocrine immune disruption and sub-inflammatory cascade responses. For an epidemiological study,

the small-size sample employed in this study limits its capability to further determine the significance of rheumatic disease development in patients with PCOS, and thus, a multicenter prospective study is warranted for further analysis.

RA, an autoimmune disease characterized by progressive accumulation in various tissues and organs, features a multifaceted pathogenic mechanism influenced by genetic, environmental, infectious, and immunologic factors (Gravallese and Firestein, 2023). However, there are still no studies on whether an RA history is a contributor to the disease progression of PCOS. Theoretically, ovarian tissue is the primary target of autoimmune disease attacks, which adversely affect ovarian function through the concerted effects of a variety of antibodies and cytokines involved in autoimmune responses. In autoimmunity, self-reactive cells, such as B and T lymphocytes, are induced and produce antibodies, leading to a breakdown of the mechanisms responsible for self-tolerance, inducing inflammation in ovarian tissue and triggering the pathogenesis of PCOS (Kicińska et al, 2023). The findings of clinical studies indicate that female patients diagnosed with RA experience prolonged pregnancy and an earlier onset of menopause, suggesting the detrimental impact of RA on female fertility (Brouwer et al, 2020). A clinical cross-sectional study indicates a higher prevalence of RA in patients with unexplained female infertility compared to the general population, suggesting the potential detrimental effects of RA on ovarian function (Brouwer et al, 2017). This damage may be attributable to the direct effects of cumulative inflammatory damage to the ovaries. According to a meta-analysis, RA individuals exhibit notably diminished levels of anti-müllerian hormone and an elevated susceptibility to ovarian failure, which stand in stark contrast to those with PCOS (Zhang et al, 2022). Previous studies have suggested that relative glucocorticoid and androgen deficiencies may increase susceptibility to RA development, or precipitate early-onset age of this rheumatic disease. This hormone deficiency presents a contrasting pattern to the prevalent trend observed in patients with PCOS, who commonly exhibit strong adrenocortical activity, frequently accompanied by hyperandrogenemia and insulin resistance (Stener-Victorin et al, 2024). Meanwhile, a separate study posits that the administration of nonsteroidal anti-inflammatory drugs for RA treatment may impede ovulation in women and diminish rates of conception (Fattah et al, 2020). These findings contradict our prior deductions. Therefore, for the first time, we use MR analysis to elaborate on a causal association between RA and PCOS using SNPs as IVs. The role of hormonal disruption in PCOS in RA still needs to be validated in larger multicenter cohort studies. If a causal correlation between RA and PCOS were to be established in future studies, we suggest clinically utilizing steroid drugs, low-dose aspirin, and low-molecular heparin in women diagnosed with PCOS during ovulation induction to help enhance their pregnancy outcomes. In addition, appropriate supplementation with relevant cytokines such as gamma-linolenic acid (GLA) can help with ameliorating the inflammation associated with PCOS adiposity and maintain a healthy ovarian microenvironment (Prabhu et al, 2021). It has been postulated that improving the underlying immune status can strengthen PCOS treatment (Hu et al, 2020).

In summary, PCOS is a systemic, multifactorial autoimmune disease affecting multiple organs and systems, characterized by inflammation and hormone dysregulation, and is regulated by the neuro-immune-endocrine axis (Wang et al, 2023). To date, there are a number of hypotheses that may shed light on the potential mechanisms of cooccurrence of RA and PCOS. On the one hand, PCOS individuals experience a state of low-grade chronic inflammation as a result of abnormal secretion of cytokines, dysfunction of immune cells, and hormonal imbalances. The similar cytokine disturbances for TNFα, IL-1, and IL-6 have been observed in the RA and PCOS populations (Fig. 7). From the therapeutic perspective, the potential beneficial effect of biological anti-rheumatic drugs (e.g., IL-6 blockers) on improving both RA and PCOS also attest to the shared pathogenic mechanisms between the two disorders (Borthakur et al, 2020). On the other hand, the disordered immune microenvironment in patients with autoimmune diseases is also a high-risk factor for PCOS. Overall, PCOS and autoimmune diseases share an overlapping set of high-risk factors, including obesity, hyperandrogenism, and insulin resistance, which contribute to the set-up of a vicious cycle wherein the accumulation of inflammatory cells and associated cytokines in PCOS results in the establishment of a chronic low-grade inflammatory microenvironment and subsequent systemic organ dysfunction. Presently, the management of PCOS patients primarily revolves around lifestyle interventions, modifications to the menstrual cycle, promotion of fertility, and long-term health management (Hoeger et al, 2021). Our study provides evidence of a plausible causal link between RA and PCOS, suggesting an immunopathogenic mechanism and potential therapeutic implications for PCOS. Prior investigations consisting of mostly cross-sectional and case-control studies did not delve into analyzing the temporal elements of disease onset and were subjected to numerous confounding factors and biases. Consequently, these studies failed to establish a definitive causal relationship between RA and PCOS. A two-sample MR study can effectively circumvent the above shortcomings, which may explain the inconsistency of our findings with those of the previous observational studies. An additional factor contributing to the incongruous findings could be the disparity in age distribution within the study cohort. The majority of contemporary observational investigations on PCOS have predominantly concentrated on young females. However, RA can manifest throughout a woman's lifespan, with significantly increased risks during the perimenopausal phase. In order to obtain more reliable results, future large-scale prospective studies of women with RA grouped by age are needed. Additional investigations are warranted to explore novel immune-targeted treatments. In the meantime, it is advisable to regularly monitor RA-related antibodies (including rheumatoid factors [RFs] and anti-citrullinated protein antibodies [ACPAs]) in PCOS patients to facilitate early detection and timely intervention for RA, which could contribute to the effective management and treatment of PCOS, ultimately reducing long-term complications and enhancing clinical pregnancy outcomes. Whether prophylactic use of non-steroidal anti-inflammatory drugs, prednisone, and other anti-rheumatic drugs are effective in deterring PCOS progression needs to be further validated.

In addition, we found no causal relationship between SLE, PM and PCOS. Indeed, sex hormones have complex role and exert different effects in different autoimmune diseases (Moulton, 2018). Typically, estrogens have immune-activating effects, whereas progesterone and androgens have immunosuppressive effects and counteract pathways affected by estrogens. However, the role of estrogen in cellular homeostasis is complex and depends on cell type, hormone concentration, and physiological/pathological context. In various autoimmune diseases, estrogen may exhibit contrasting roles. For instance, during pregnancy, autoimmune conditions such as RA, multiple sclerosis, and thyroiditis tend to improve as the maternal immune response transitions from a Th1 to a Th2 phenotype to prevent fetal rejection. Conversely, this Th2 shift exacerbates conditions like SLE by promoting autoantibody production. Although no significant differences in estrogen levels have been observed in patients with SLE, there is evidence of increased estrogen metabolism and greater variability in estrogen receptor expression. A clinical study has demonstrated that ovarian reserve function, as indicated by serum levels of anti-müllerian hormone and sonographic antral follicle count (AFC), is significantly diminished in women with SLE and PM. This reduction may be attributed to the administration of immunosuppressive agents, such as cyclophosphamide (de Souza et al, 2015). Currently, there are no documented associations between SLE/PM and PCOS. Consequently, further large-scale clinical studies are warranted to explore this potential relationship. Taken together, our research reveals a substantial causal association between genetically predicted RA and an increased vulnerability to PCOS among individuals of European ancestry. The utilization of exposure and outcome data from exclusively European populations in this study can mitigate bias resulting from population stratification in the derived conclusions. However, this approach also restricts the generalizability of the findings to other ethnicities and geographic regions. Thus, our next step will focus on external validation in non-European populations to expand the study population and strengthen the validity and credibility of the findings.

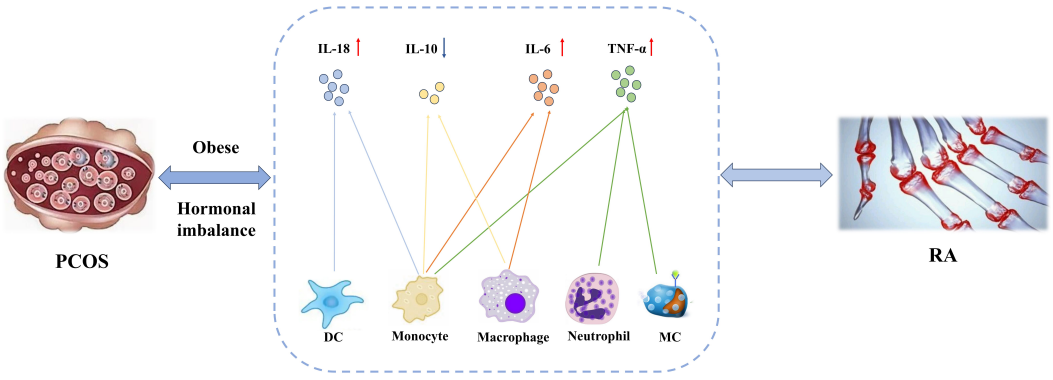

Fig. 7. Identical cytokine dysregulation profiles shared by both PCOS and RA. PCOS, polycystic ovary syndrome; RA, rheumatoid arthritis; MC, mast cell; DC, dendritic cell; TNF, tumor necrosis factor; IL, interleukin.

Strengths

Notably, our study possesses several strengths compared to conventional observational investigations: (1) It employs a two-sample MR design incorporating extensive GWAS data, thereby mitigating the potential for reverse causality and confounding factors, while enhancing the robustness and reliability of the study's conclusions. (2) The inclusion of exclusively European populations in our analysis effectively minimizes bias stemming from demographic stratification. (3) The sensitivity analyses performed in this study utilizing the "leave-one-out" technique demonstrated the independence of IVs from other potential confounding factors that could impact the relationship between the exposure variable and the outcome variable. Consequently, the obtained results can be considered reliable. (4) To the best of our knowledge, there has been no prior epidemiological investigation into the prevalence of PCOS among patients with RA. Therefore, the findings of this study provide valuable insights into future epidemiological studies in this area.

Limitations

Nevertheless, caution should be exercised in interpreting our findings due to several limitations. Firstly, the IVs utilized in our study were derived from the largest European PCOS-GWAS, which incorporates various diagnostic criteria, thereby augmenting the clinical heterogeneity of the included patients. Secondly, the sample size of PM patients in our study was relatively modest, comprising only 44 individuals. Furthermore, it is crucial to recognize that the applicability of our findings to various ethnic or geographic regions may be limited due to the exclusive utilization of exposure and outcome data from European populations. Fourth, the limited representation of PCOS cases in the database could potentially lead to diminished statistical power in establishing genuine causality. Therefore, it is imperative to conduct future validation studies using GWAS data obtained from a more diverse range of ethnic sources and larger datasets. Despite the absence of significant pleiotropy or confounders identified through the MR-PRESSO examination and the MR-Egger intercept assessment, it is crucial to acknowledge that the potential existence of these factors cannot be entirely dismissed.

Our study implies that individuals with RA may be more prone to developing PCOS, which may subsequently lead to impaired fertility. This study enhances our clinical comprehension of the health condition of individuals with concurrent rheumatic diseases and PCOS, and offers recommendations for the diagnosis and differential diagnosis of PCOS in RA.

Conclusion

A potential causal link between RA and PCOS exists, whereas no causal association of SLE and PM with PCOS has been established. Nevertheless, given the intricate nature of rheumatic diseases and PCOS, additional research is imperative to validate our findings. Also, since the precise nature of the association between rheumatoid diseases and PCOS remains incompletely elucidated, more investigations need to be conducted to examine the underlying pathogenic mechanisms and

associated signaling pathways. Regular monitoring of antibodies associated with RA in patients with PCOS can facilitate early detection and timely intervention of RA, contributing to effective management and treatment of PCOS, ultimately reducing long-term complications and improving clinical pregnancy outcomes. From the therapeutic point of view, affected women can be given appropriate cytokine supplementation (e.g., GLA) and anti-rheumatic drugs (e.g., IL-6 inhibitors) to help relieve inflammation and promote a healthy ovarian microenvironment.

Key Points

- Polycystic ovary syndrome (PCOS) is recognized as a systemic autoimmune disorder triggered by hormonal imbalances.
- This is the first Mendelian randomization analysis examining the causal relationship between rheumatic diseases and PCOS.
- There is a potential causal relationship between rheumatoid arthritis and PCOS, whereas no such causal relationship has been established between systemic lupus erythematosus or polymyositis and PCOS.

Availability of Data and Materials

The data utilized in this study were sourced exclusively from the MRC-IEU database (https://gwas.mrcieu.ac.uk/) (Table 1). The datasets generated and analyzed during the course of this study can be obtained from the corresponding author upon reasonable request.

Author Contributions

QZ designed and performed the research. JW analyzed the data and drafted the manuscript. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0478.

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