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The effects of plasma protein levels on the risk of endometriosis

A Mendelian randomization study

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Abstract

Endometriosis is a prevalent gynecologic disorder that significantly impacts women's health. However, its underlying pathogenesis remains unknown. This study aimed to ascertain causal associations between plasma protein levels and endometriosis using a Mendelian randomization (MR) design. Plasma protein genome-wide association studies (GWAS) data originating from the UK Biobank Pharma Proteomics Project (UKB-PPP) were utilized as exposure variables. Endometriosis GWAS data from the FinnGen study and UKB study served as outcome variables at the discovery and replication stages, respectively. Summary-data-based MR (SMR) and instrument-dependent heterogeneity (HEIDI) tests were conducted to further validate the relationships between proteins and the risk of endometriosis. Genetic variations between the identified plasma proteins and endometriosis were investigated by colocalization analyses. The proteome-wide MR and SMR results revealed that genetically predicted plasma levels of proteins (RSPO3, WASHC3, FSHB, and VEGFB) were positively associated with the risk of endometriosis. Among them, only FSHB and RSPO3 passed the HEIDI tests, and colocalization analyses further supported their causal relationship with endometriosis. Based on large-scale population GWAS data, our research demonstrated causal correlations of FSHB and RSPO3 with the risk of endometriosis. These findings suggest that plasma proteins are involved in the development of endometriosis and may serve as potential biomarkers and therapeutic targets for this complicated disease in the future.

Abbreviations: FSHB = follicle stimulating hormone subunit beta, GWAS = genome-wide association studies, HEIDI = instrument-dependent heterogeneity, MR = mendelian randomization, RSPO3 = roof plate specific spondin 3, SMR = summary-data-based mendelian randomization, UKB-PPP = UK Biobank Pharma Proteomics Project, VEGFB = vascular endothelial growth factor b, WASHC3 = wash complex subunit 3.

Keywords: causal association, endometriosis, Mendelian randomization, plasma protein

1. Introduction

Endometriosis is a common gynecological disorder manifested by endometrial tissues with growth function arising in the endometrium covering the uterine cavity and outside the uterus, which can trigger symptoms like dysmenorrhea, inflammatory response, pelvic pain, dyspareunia, and even infertility, seriously affecting the quality of life of patients.[1] About 10% of women of childbearing age worldwide suffer from this disorder.[2] The etiology and pathogenesis of endometriosis are still undefined, and diversified clinical manifestations often lead to delayed diagnosis.[3] Therefore, early diagnosis of endometriosis is particularly crucial. At present, histopathological examination via a laparoscopic approach is the gold diagnostic standard. However, the limitation of the sampling site may result in the absence of direct pathological evidence in some patients.[4] Furthermore, invasive examinations also have a diagnostic delay, which accelerates disease progression. To this end, developing noninvasive diagnostic approaches, especially identifying specific biomarkers, is of

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All GWAS datasets included in this study were publicly accessible, and each GWAS utilized in this study was approved by its corresponding Ethical Review Committee. Given that this study involved a reanalysis of publicly available data, no additional ethical approval was necessary. All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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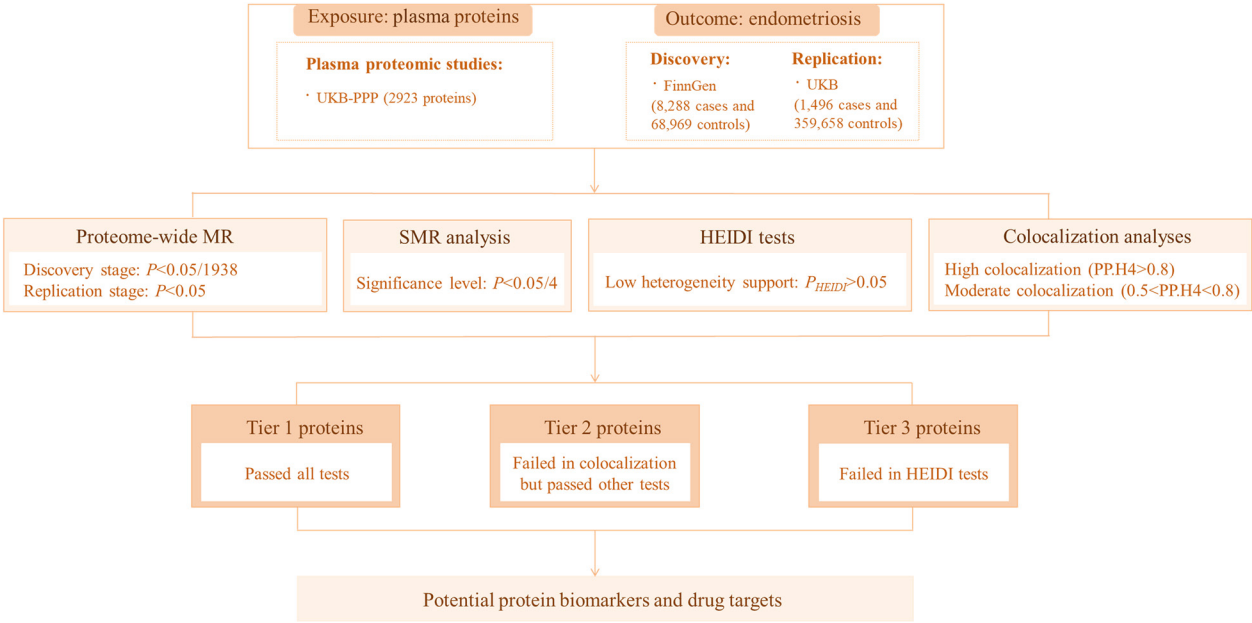

Figure 1. Overview of the study design. UKB-PPP, UK Biobank Pharma Proteomics Project; UKB, UK Biobank; MR, Mendelian randomization; SMR, summary-data-based Mendelian randomization; HEIDI, instrument-dependent heterogeneity; PP.H4, posterior probability of hypothesis 4.

great significance for early intervention and treatment of this disease.

Plasma proteins are important components of plasma that exert a crucial role in multiple biological processes encompassing signal transduction, transportation, growth, repair, infection defense, etc. Their composition and abundance can be differentially regulated during the initiation and progression of diseases. Plasma proteomics analysis delves into the properties and changes of plasma proteins and further seeks potential biomarkers and therapeutic targets for diseases.[5,6] It has been unveiled that the endometriosis stage is positively related to immunoglobulin G (IgG) and immunoglobulin M (IgM) levels, and 6 months of danazol treatment sharply reduced IgG and IgM levels.[7] Further proteomic analyses revealed differences in serum protein expression between endometriosis patients and healthy individuals.[8–10] Another study has also pointed out that plasma levels of coagulation factors ADAMTS13 and vWF are associated with the risk of endometriosis.[11] However, these studies have issues such as small-scale samples or a limited number of investigated proteins, which affect the application of plasma proteins in the etiology and diagnosis of endometriosis.

Mendelian randomization (MR) analysis represents an epidemiological research strategy based on the Mendelian-independent distribution theorem. Single nucleotide polymorphism (SNP), a genetic variation closely related to exposure factors, is selected as an instrumental variable (IV) to determine the relevance of exposures to outcomes. Following the Mendelian inheritance pattern during gamete formation, where parental alleles are randomly allocated to offspring, genetic variation is less susceptible to traditional confounding factors such as the environment or society. Meanwhile, genetic variations are inherited from parents and remain unchanged after birth, which ensures that their association with outcomes is chronologically reasonable. Therefore, MR analysis effectively overcomes the potential confounding and reverse causality in traditional observational investigations.[12] Recently, MR analysis has been extensively applied in etiological research on complex diseases.[13,14]

In this study, we conducted a 2-stage (discovery and replication) proteome-wide MR analysis using data from plasma protein genome-wide association studies (GWAS) and endometriosis GWAS. SNPs were selected as IVs to explore the causal relationship between plasma proteins and the risk of endometriosis.

2. Methods

2.1. Study design

The research design is depicted in Fig. 1. Comprehensive protein quantitative trait loci (pQTLs) data were acquired from the UK Biobank Pharma Proteomics Project (UKB-PPP)[15] for a 2-stage (discovery and replication) proteome-wide MR analysis. Additionally, the causality between protein biomarkers and endometriosis was validated by means of summary-data-based MR (SMR), instrument-dependent heterogeneity (HEIDI) tests, and colocalization analyses. All datasets contained in this article are publicly available, so this research was exempt from medical ethics.

2.2. Data sources

The plasma protein GWAS data adopted in this article were sourced from UKB-PPP (https://www.synapse.org/#!Synapse:syn51364943/files/), which involved plasma proteomic analysis of 54,219 participants, exhibited pQTLs mapping of 2923 proteins, and identified 14,287 dominating genetic associations, of which 81% have not been previously reported.[15]

The endometriosis GWAS data adopted in this research consisted of 2 parts: the discovery phase and the replication phase. The data in the discovery phase originated from the FinnGen study (https://www.finngen.fi/en),[16] in which the definition of endometriosis followed N80 in the International Classification of Diseases, 10th edition (ICD-10), 617 in ICD-9, as well as 6253 in ICD-8. These GWAS data contained 8288 cases and 68,969 controls. Data during the replication phase were from the UKB study (https://www.ukbiobank.ac.uk/),[17] where the definition of endometriosis conformed to N80 in ICD-10. This GWAS dataset involved 1496 cases and 359,698 controls. The participants in both GWAS datasets were Europeans and non-overlapping. All GWAS summary data were preprocessed in the original studies, and no additional missing data handling was required in the present analysis.

2.3. Proteome-wide MR analysis

IVs were screened using the following criteria: (1) SNPs highly related to exposure factors (plasma proteins) were selected ($P < 5 \times 10^{-8}$); (2) to eliminate IVs with a linkage disequilibrium (LD) bias, independent SNPs were selected with $r^2 < 0.001$, clumping distance = 10000 kb as criteria; (3) *F* statistic, a function reflecting the magnitude and accuracy of genetic effects on traits, was used to evaluate the strength of each SNP, and SNPs showing F statistic > 10 were selected. *F* statistic was calculated using the formula: $F = R^2 \times (N\text{--}2)/(1-R^2)$, wherein R^2 refers to the fraction of trait variance explained by the SNP, and N signifies the sample size of GWAS for the SNP with that trait. R^2 was calculated as follows: $R^2 = 2 \times EAF \times (1\text{-}EAF) \times \beta^2$.

Based on the IVs selected above, MR analysis was implemented with the assistance of the "TwoSampleMR" packages in *R* (version 4.2.3).[5] Meanwhile, Wald ratio (NSNP = 1) or inverse variance weighted method (IVW, NSNP ≥ 2) was chosen as the primary method, and simple mode, weighted mode, weighted median, and MR Egger were adopted as auxiliary methods to investigate the causation between plasma protein composition and the risk of endometriosis. The horizontal pleiotropy was detected with the MR Egger intercept test, and $P > .05$ denoted no horizontal pleiotropy.[18] Bonferroni correction was applied for multiple comparisons, $P < 2.58 \times 10^{-5}$ (0.05/1937) suggested significance. According to the endometriosis GWAS summary data from UKB, the identified proteins were then subjected to replication MR analysis, with $P < .05$ at the level of significance.

2.4. SMR analysis and HEIDI tests

SMR analysis serves as a supplementary approach to further validate the causal association between plasma proteins and endometriosis.[19] The HEIDI tests were designed to distinguish between pleiotropy and linkage,[20] and a value of P_HEIDI > 0.05 indicated that the relation between proteins and endometriosis was not triggered by LD. SMR and HEIDI tests were conducted through the SMR software (SMR v1.3.1).

2.5. Colocalization analyses

To explore whether there is a common genetic variation between plasma proteins and endometriosis, the "coloc" package was adopted for Bayesian colocalization analyses.[21] Colocalization analyses had 5 assumptions: H0 indicated that SNPs were irrelevant to both plasma proteins and endometriosis; H1 signified that SNPs were only linked to plasma proteins; H2 suggested that SNPs were only associated with endometriosis; H3 denoted that SNPs correlated with both plasma proteins and endometriosis, but there existed different causal variants; H4 signified that SNPs were related to plasma proteins and endometriosis, and a shared causal variant existed.[22] Bayesian colocalization analyses can calculate the posterior probability (PP) of each hypothesis based on the prior probability. We used the default parameter: the prior probability of SNPs only related to plasma proteins (p1) was set as 1×10^{-4}; the prior probability of SNPs only linked to endometriosis (p2) was set as 1×10^{-4}; the prior probability of SNPs correlated with both plasma proteins and endometriosis (p12) was set as 1×10^{-5}. Strong colocalization evidence for the SNP was defined with the PP of hypothesis 4 (PP.H4) > 0.8; moderate colocalization evidence for this SNP was considered if 0.5 < PP.H4 < 0.8.[23]

3. Results

3.1. Relations between plasma proteins and endometriosis shown by proteome-wide MR analysis

In this research, the plasma protein GWAS dataset was sourced from UKB-PPP, and SNPs significantly related to endometriosis were retained ($P < 5 \times 10^{-8}$). After removing LD and evaluating the strength of IVs, 1937 eligible IVs were obtained (Supplementary Table S1). Herein, F statistics were all higher than 10, so these SNPs were regarded as strong IVs (Supplementary Table S6).

Endometriosis GWAS data for the discovery cohort were acquired from FinnGen, and proteome-wide MR analysis were subsequently conducted to explore the relations between plasma proteins and endometriosis. The Wald ratio or IVW method was utilized as the primary research approach for proteome-wide MR analysis (Supplementary Table 1 shows the MR analysis results of all IVs in the discovery phase). As presented in Table 1, after Bonferroni correction, causal associations were noted between 4 plasma proteins (RSPO3, WASHC3, FSHB, and VEGFB) and the risk of endometriosis ($P < 2.58 \times 10^{-5}$). Also, beta values of these 4 plasma proteins were all higher than 0, indicating positive causal correlations of RSPO3, WASHC3, FSHB, and VEGFB with the risk of endometriosis.

3.2. Causation between plasma proteins and endometriosis validated by SMR analysis and HEIDI tests

To further validate the causality between plasma proteins and endometriosis, the aforementioned 4 plasma proteins were subjected to SMR analysis (Supplementary Table. S2). RSPO3, WASHC3, FSHB, and VEGFB all exhibited statistical significance ($P < 1.25 \times 10^{-2}$, 0.05/4) in SMR analysis (Table 1), further substantiating that these 4 plasma proteins had positive causal effects on the risk of endometriosis.

To address the potential issue of pleiotropy between plasma proteins and endometriosis, HEIDI tests on 4 plasma proteins were individually carried out (Supplementary Table S2). The results revealed that 2 plasma proteins, RSPO3 and FSHB, passed the HEIDI tests ($P_{HEIDI} > 0.05$), indicating that the relation between plasma proteins and endometriosis was not driven by LD. However, the other 2 plasma proteins, WASHC3 and VEGFB, failed the HEIDI tests ($P_{HEIDI} < 0.05$), suggesting that the relation might be driven by pleiotropy (Table 1). Therefore, WASHC3 and VEGFB were excluded in the subsequent analysis.

Table 1

Summary results from MR, SMR, and colocalization for discover proteome-wide MR-identified proteins.

Protein	Protein full name	$MR_{discovery}$		$SMR_{discovery}$			Colocalization
		Beta	*P*	Beta	*P*	P_{HEIDI}	
RSPO3	Roof plate specific spondin 3	0.4615	6.68E-10	0.4705	2.89E-09	0.1403	0.74
WASHC3	WASH complex subunit 3	0.6919	1.74E-07	0.6919	2.43E-06	0.0079	-
FSHB	Follicle stimulating hormone beta polypeptide	1.2928	3.47E-07	1.3623	3.99E-25	0.2851	0.99
VEGFB	Vascular endothelial growth factor B	0.3921	1.06E-05	0.3654	2.54E-03	0.0062	-

MR = Mendelian randomization, SMR = summary-data-based Mendelian randomization.

3.3. Colocalization evidence

To confirm whether there is a shared genetic variation between plasma proteins and the risk of endometriosis, RSPO3 and FSHB, which passed SMR analysis and HEIDI tests, were subjected to colocalization analyses (Supplementary Table S3). The results displayed significant colocalization evidence for the relation between FSHB and endometriosis (PP.H4 > 0.8) (Fig. 2), while RSPO3 showed moderate colocalization evidence (0.5 < PP.H4 < 0.8) (Fig. 3).

Integrating the aforementioned results, these plasma proteins were classified into 3 levels: FSHB passed all tests and was classified as tier 1; RSPO3 passed MR analysis, SMR analysis, and HEIDI tests, but the results of colocalization analyses showed a PP.H4 value of 0.74, which failed to meet strict standards, so RSPO3 could be classified as tier 2; WASHC3 and VEGFB passed MR and SMR analyses but failed the HEIDI tests, so they could be classified as tier 3.

3.4. Replication cohort

During the replication phase, the endometriosis GWAS data were provided by UKB, which contained 1496 cases and 359,698 controls. MR analysis was performed on RSPO3 and FSHB identified during the discovery phase in the replication cohort using the Wald ratio or IVW method (Supplementary Table S4). The results corroborated significant positive causal correlations ($P < .05$, beta > 0) of RSPO3 and FSHB with the risk of endometriosis (Table 2). Additionally, RSPO3 and FSHB results were further demonstrated to be reliable through the SMR analysis ($P < .05$) and HEIDI tests ($P_{HEIDI} > 0.05$) (Table 2, Supplementary Table S5).

4. Discussion

In this research, we investigated the causality between 1937 plasma proteins and the risk of endometriosis. In the discovery cohort, a proteome-wide MR approach was applied to analyze GWAS data, the results of which exhibited positive causation between plasma proteins (RSPO3, WASHC3, FSHB, and VEGFB) and the risk of endometriosis. In short, genetically predicted higher plasma levels of the aforementioned proteins were suggested to increase the risk of endometriosis. Subsequently, these 4 plasma proteins were subjected to SMR analysis, HEIDI tests, and Bayesian colocalization analyses, which further validated the reliability of the results in the replication cohort. Ultimately, the results identified FSHB with the strongest evidence (tier 1), RSPO3 with relatively strong evidence (tier 2), as well as WASHC3 and VEGFB with moderate evidence (tier 3). These findings offer new insights into the etiology of endometriosis, along with promising targets for identifying biomarkers of this disease and developing therapeutic drugs.

FSHB, which is encoded by the FSHB gene, as a hormone-specific β subunit, forms FSH together with the glycoprotein hormone α subunit, ensuring that FSH can specifically bind to its receptors, thereby effectively facilitating estrogen synthesis and follicle development.[24–26] FSHB expression and genetic variation may indirectly regulate estrogen levels and follicle development by directly affecting the formation and biological activity of FSH, consequently posing a potential impact on the risk of endometriosis. Our research findings demonstrated that the elevated plasma FSHB level was a risk factor for endometriosis. FSHB SNPs (rs11031006 and rs10835638) have been verified to be correlated with FSH levels and the risk of endometriosis. For instance, the G allele of SNP (rs11031006) is remarkably linked to higher FSH levels.[27] The data from the ENCODE project suggest that this SNP variant may affect feedback inhibition of hormones by altering the sequence of 11 protein binding motifs encompassing estrogen receptor α.[28] A study involving 316 females (166 endometriosis patients and 150 controls) showed a genetic association between SNP (rs11031006) and endometriosis.[29] Furthermore, disagreements exist in the positive regulatory impact of the T allele of FSHB-211G > T (rs10835638) on female FSH levels,[30–32] and its role in endometriosis also remains controversial. Among them, a GWAS study conducted using UKB reported that the T allele of rs10835638, which reduces FSH levels, was significantly associated with prolonged menstrual cycles and delayed menopausal age, posing a protective effect on endometriosis.[33] Another case-control study in Brazil unveiled that the frequency of the GT genotype of rs10835638 was higher in patients with minimal/mild endometriosis than in the controls, suggesting a relationship between the T allele and the onset of minimal/mild endometriosis.[34] The differences in results of different studies may be linked to

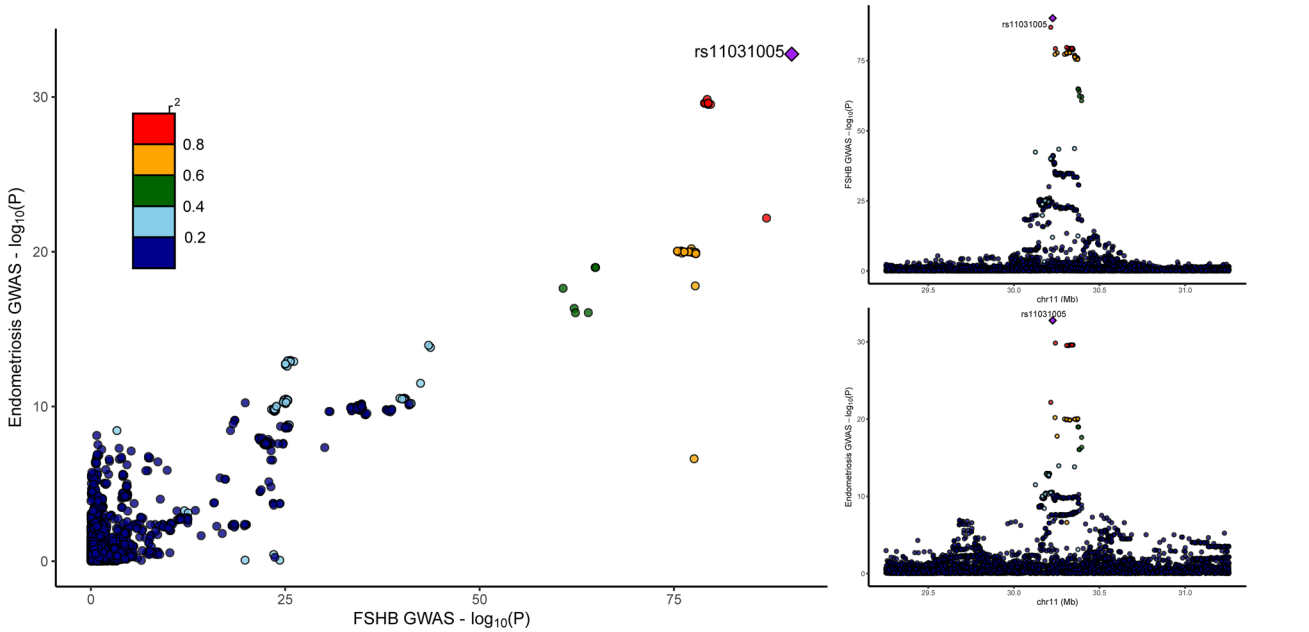

Figure 2. Colocalization of FSHB with endometriosis. FSHB, follicle stimulating hormone beta polypeptide.

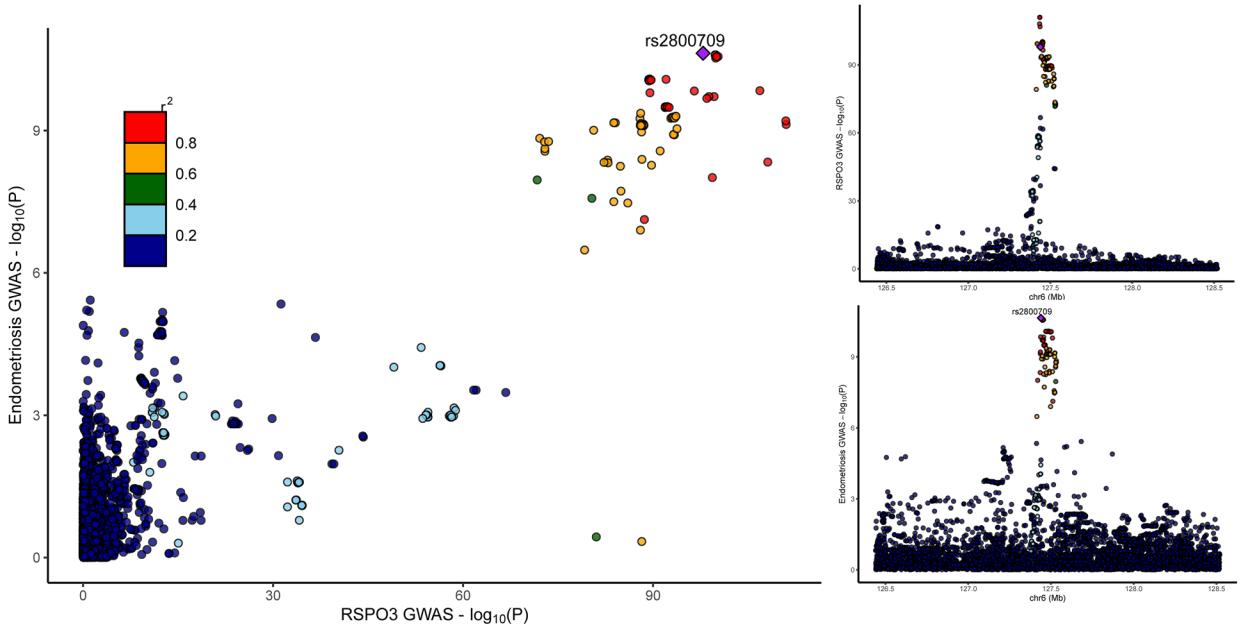

Figure 3. Colocalization of RSPO3 with endometriosis. RSPO3, roof plate specific spondin3.

Table 2

Summary results from MR and SMR for replication proteome-wide MR-identified proteins.

		$MR_{replication}$		$SMR_{replication}$		
Protein	**Protein full name**	**Beta**	***P***	**Beta**	***P***	P_{HEIDI}
RSPO3	Roof plate specific spondin 3	0.0033	4.59E-04	0.0031	1.27E-03	0.5568
FSHB	Follicle stimulating hormone beta polypeptide	0.0033	2.24E-02	0.0029	4.98E-02	0.9533

MR = Mendelian randomization, SMR = summary-data-based Mendelian randomization.

genetic background and study design. Thus, the specific mechanism of the FSHB gene variation in the risk of endometriosis deserves to be elucidated through more in-depth studies.

RSPO3 is a plasma protein with tier 2 evidence, and its genetically elevated plasma protein levels are related to an augmented risk of endometriosis. As a member of the RSPO family, RSPO3 is a secreted protein with 1 thrombospondin module 1 (TSP1) domain and 2 furin-like cysteine-rich domains,[35] which enable a significant role in activating the WNT/β-catenin signaling pathway as well as promoting angiogenesis and embryogenesis.[35,36] It has been illustrated that the WNT signal modulator RSPO3 is abundantly expressed in the angiogenic area.[36] RSPO3 gene knockout experiments uncovered severe vascular defects in the placenta of RSPO3-deficient embryos.[37] Correspondingly, in an RSPO3 deficiency mouse model, microvessel density is significantly reduced owing to endothelial cell apoptosis and vascular pruning.[38] These findings emphasize the crucial role of RSPO3 in angiogenesis. Angiogenesis is critical for the pathogenesis of endometriosis, and the formation and maintenance of ectopic endometrial tissues rely on the oxygen and nutrient supply from angiogenesis.[39,40] Angiogenesis-relevant biomarkers and antiangiogenic therapy are also of great significance for the early diagnosis and treatment of endometriosis.[41] Nonetheless, there are currently no research reports on the relation between RSPO3 and endometriosis. This study first unveils a positive causal association between plasma protein RSPO3 and the risk of endometriosis, offering new research directions for investigating the potential roles of RSPO3 in endometriosis.

The 2 proteins with tier 3 evidence (VEGFB and WASHC3) are positively linked to the risk of endometriosis. VEGFB, belonging to the VEGF family, has highly homologous sequences and a similar receptor binding pattern to VEGFA, and it was initially considered a kind of angiogenic factor.[42] However, VEGFB has no significant activity under normal conditions, and its pro-angiogenic ability is still controversial.[43,44] As a matter of fact, VEGFB is more linked to a crucial role in vascular survival and protection against apoptosis.[45,46] By detecting endometrial biopsy specimens from healthy females, it was found that VEGFB was expressed within and around endometrial blood vessels.[47,48] Moreover, our research results illustrate that an increase in the genetically predicted VEGFB levels correlates with an elevated risk of endometriosis. Based on these findings, we speculate that VEGFB might participate in the pathological process of endometriosis by affecting the survival and stability of endometrial blood vessels. The specific function of VEGFB in the pathogenesis of endometriosis remains to be clarified in the future. As a component of the WASH complex, WASHC3 functions as a nucleation-promoting factor on the surface of endosomes and promotes actin polymerization through the recruitment and activation of the Arp2/3 complex, exerting a crucial role in the fission of tubules during the endosomal sorting process.[49,50] Up to now, there have been few studies on WASHC3, and there is no direct evidence for its correlation with endometriosis. Thus, the exact biological role of WASHC3 and its significance in endometriosis still require in-depth investigations.

In this research, we utilized GWAS data and systematically discussed the relations between plasma protein biomarkers and the risk of endometriosis through the 2-stage proteome-wide MR analysis. Large sample size and broad proteome coverage are

the advantages of this method, which can effectively decreases bias triggered by confounding factors and reverse causal relationships. This research involved multiple databases, further strengthening the stability of the results. However, there are still several limitations. First, our analysis of endometriosis cases is restricted to the European population, which reduces racial bias but also limits the generalizability of experimental results across racial groups. Second, this research only assessed the role of plasma proteins in endometriosis, and if combined with protein detection in other tissues, it may offer more insights into the pathogenesis of endometriosis.

5. Conclusion

Taken together, our research identified multiple plasma proteins positively correlated with the risk of endometriosis, encompassing RSPO3, WASHC3, FSHB, and VEGFB. The colocalization evidence supported the causation between plasma proteins (FSHB and RSPO3) and endometriosis. These findings are of great significance for the screening of biomarkers for endometriosis and the development of therapeutic drugs, but more fundamental and clinical experiments are still required for further validation.

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