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ORIGINAL RESEARCH

Exploring the Impact of Systemic Inflammatory Regulators on Rosacea Risk: A Bidirectional Mendelian Randomization Analysis

Qiao Xue[1], Jian Peng Pan[2], Da Qian[3], Jie Ji[4], Lai Yi Fei[1], Sheng Yao[1], Xing Tan[1], Wen Ge Fan[1]

[1]Department of Dermatology, Changshu No. 1 People's Hospital, Changshu Hospital Affiliated to Soochow University, Changshu, Jiangsu, 215500, People's Republic of China; [2]Department of Hand Surgery, Changshu No. 2 People's Hospital, The Affiliated Changshu Hospital of Nantong University, Changshu, Jiangsu, 215500, People's Republic of China; [3]Department of Burn and Plastic Surgery-Hand Surgery, Changshu No. 1 People's Hospital, Changshu Hospital Affiliated to Soochow University, Changshu, Jiangsu, 215500, People's Republic of China; [4]Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, 210000, People's Republic of China

Correspondence: Qiao Xue, Department of Dermatology, Changshu Hospital Affiliated to Soochow University, Changshu No. 1 People's Hospital, No. 1 Shuyuan Street, Yushan Town, Changshu, Jiangsu, 215500, People's Republic of China, Tel +86-13913657476, Email ahjk157@126.com; Jian Peng Pan, Department of Hand Surgery, The Affiliated Changshu Hospital of Nantong University, Changshu No. 2 People's Hospital, 68 South Haiyu Road, Yushan Town, Changshu, Jiangsu, 215500, People's Republic of China, Tel +86-13814964481, Email 574161036@qq.com

Objective: Rosacea is a common chronic inflammatory disorder primarily affecting the face. While inflammatory factors are known to play a pivotal role in its pathogenesis, their causal relationship with rosacea remains unclear. This study employed a two-sample bidirectional Mendelian randomization (MR) analysis to investigate the causal links between systemic inflammatory regulators and rosacea.

Methods: Data on 41 cytokines and growth factors were analyzed from a genome-wide association study (GWAS) meta-analysis involving 8293 individuals and genetic data from the FinnGen database, comprising 1195 rosacea cases and 211,139 controls. The principal inverse variance weighting (IVW) method was used to assess causal relationships, with sensitivity analyses, including heterogeneity and horizontal pleiotropy assessments, conducted to ensure result robustness.

Results: MR analysis revealed that decreased expression of Stem Cell Factor (SCF), Macrophage Inflammatory Protein-1β (MIP-1β), and Monocyte Chemotactic Protein-1 (MCP-1) was associated with increased rosacea risk (OR = 1.54, 95% CI = 1.05–2.26, p = 0.026). Conversely, elevated expression levels of Stromal Cell-Derived Factor-1α (SDF-1α) and Hepatocyte Growth Factor (HGF) were linked to higher rosacea risk (OR = 1.61, 95% CI = 1.12–2.31, p = 0.009). Reverse MR analyses showed no significant impact of rosacea on systemic inflammatory regulator expression.

Conclusion: This study identified five inflammatory factors—SCF, SDF-1α, MCP-1, HGF, and MIP-1β—as having causal relationships with rosacea pathogenesis. Further research is required to elucidate their mechanistic roles in disease development.

Keywords: rosacea, inflammation, risk, Mendelian randomization, MR, cytokine

Introduction

Rosacea is a clinically significant chronic inflammatory disorder that predominantly affects the cheeks, nose, chin, and forehead. Its characteristic symptoms include transient and persistent erythema, distal vasodilation, papules, and pustules. Additional manifestations may include burning sensations, tingling, dry or flaky skin, and erythematous conjunctivae.[1–3] Rosacea typically presents in individuals aged 30–50 years, with prevalence rates ranging from 1% to 22%, varying by region.[3] These differences are influenced by study design, methodology, demographic factors, geographic location, and cultural perceptions of the disease.

Based on primary and secondary symptoms, the American Academy of Dermatology classifies rosacea into four subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular.[3] Notably, over 50% of patients also exhibit ocular involvement, which may manifest as dryness, irritation, blepharitis, conjunctivitis, keratitis, or, in severe cases,

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vision loss.[4,5] Pathologically, rosacea is characterized by aging elastic fibers, cellular edema, dermal vasodilation, and infiltration of mast cells and lymphocytes.[6]

The pathogenesis of rosacea is attributed to an aberrant immune response, leading to a distinct inflammatory and vascular phenotype.[7] Environmental triggers such as ultraviolet radiation, extreme temperatures, stress, glucocorticoids, sex hormones, and dietary factors (eg, spicy foods) contribute to its onset and progression. These factors influence the production of reactive oxygen species (ROS), matrix metalloproteinases (MMPs), and toll-like receptor (TLR) signaling, which are further modulated by pathogenic microorganisms and antimicrobial neuropeptides.

Although clinical and histological evidence underscores the inflammatory basis of rosacea, the precise molecular and cellular mechanisms remain unclear. Previous studies have explored the roles of chemokines and cellular inflammatory agents in its pathogenesis.[8,9] However, these findings may be confounded by reverse causality or unmeasured variables, making the establishment of definitive causal relationships challenging.

Mendelian randomization is an analytical research technique that infers the causal relationships between exposure and outcomes from uncontrolled data by using information about genetic variation.[10] Stronger support for a causal relationship is provided, typical confounding variables are reduced, and causality is reversed.[11] The test's usefulness and validity are increased by two-sample bidirectional MR studies, which examine the connections between genetic variance data from two separate populations.[12] In the present investigation, we obtained validated genetic variant data of 41 inflammatory cytokines from presented genome-wide correlational research, looked at the correlation between them and the genetic variant data of rosacea, and then further investigated the causal relationship between the two by inverse MR analysis.

Methods

Study Sign

This study adhered to the STROBE-MR guidelines for Mendelian Randomization studies to ensure methodological rigor and transparency (Skrivankova et al, JAMA, 2021). Figure 1 presents an updated flowchart of the bidirectional MR analysis.

This two-sample two-way MR analysis, based on summary statistics from the GWAS and FinnGen databases, was used to investigate the bidirectional relationships between 41 inflammatory cytokines and rosacea. The forward MR

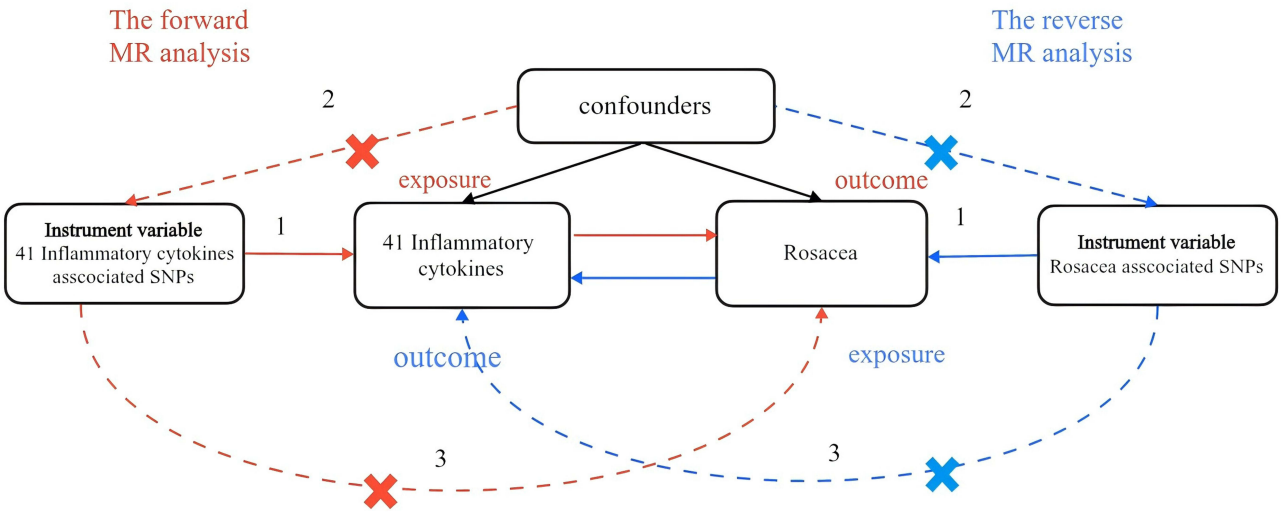

Figure 1 Design of the bidirectional Mendelian Randomization (MR) study examining the relationship between 41 circulating cytokines and rosacea.
Notes: The red analysis investigates the causal effect of 41 circulating cytokines as the exposure on rosacea as the outcome, while the blue analysis examines the reverse association. To serve as a valid instrument, the genetic variant used in the study must meet three criteria: (1) The genetic variant is associated with the exposure. (2) The genetic variant is not associated with any confounders of the exposure-outcome association. (3) The genetic variant does not affect the outcome except through its association with the exposure.
Abbreviations: MR, Mendelian Randomization; SNP, single nucleotide polymorphism.

analysis treats inflammatory cytokines as the exposure and rosacea as the outcome, while the reverse analysis reverses these roles (Figure 1). Ethical approval was not required as the study utilized publicly available aggregate statistics.

Genetic variation serves as an instrumental variable to assess the causal effect of between exposure and outcome. The key criteria for genetic variation to qualify as an instrumental variable in this study are as follows: (1) The genetic variation is strongly associated with the exposure. (2) The genetic variation is independent of any confounders that may influence the exposure-outcome relationship.[13] (3) The genetic variation affects the outcome exclusively through its effect on the exposure (Figure 1).

Date Sources

Data for rosacea genome-wide association study (GWAS) were obtained from the FinnGen database (R9 release), which includes 1195 rosacea cases and 211,139 controls of European descent, collected between 2015 and 2021.[14] Cytokine data were sourced from a pooled analysis of the Finnish Young People's Cardiovascular Risk Study (YFS) and FINRISK studies, encompassing a diverse range of biomarkers. The study cohorts were carefully selected to avoid overlap and ensure unbiased results (Table 1).

Selection for Genetic Instruments

To identify instrumental variables (IVs), we first selected all single nucleotide polymorphisms(SNPs) that strongly predicted cytokine levels with high precision ($r^2 < 0.001$, distance = 10,000 kb) at a genome-wide significance threshold ($P < 5 \times 10^{-8}$). At this threshold, only 11 cytokines were associated with more than three SNPs (Table S1). To identify additional potential IVs, we relaxed the significance threshold to $P < 5 \times 10^{-6}$, resulting in 440 SNPs associated with 41 cytokines after applying clumping criteria ($r^2 = 0.001$, distance = 10,000 kb) (Table S2).

To ensure the validity of our results and minimize potential pleiotropic effects, we excluded 74 SNPs that were associated with multiple inflammatory cytokines at $P < 5 \times 10^{-6}$. Additionally, three SNPs (rs23731674, rs10761731, and rs7088799)(T ables S3), which were significantly linked to alcohol consumption and topical corticosteroid use, were removed to account for pleiotropy. After excluding 77 SNPs unavailable in the rosacea dataset, 363 SNPs associated with 41 cytokines were retained as IVs for analysis (Table S2).

The F-statistics for these IVs ranged from 21.28 to 152.52, all exceeding the threshold of 10, indicating minimal risk of weak instrument bias (Table S2). These values align with Mendelian randomization assumptions, reinforcing the robustness of our association findings.

Statistical Analysis

We primarily employed the inverse variance weighting (IVW) method for Mendelian randomization (MR) analysis, which uses the inverse of the variance of instrumental variables as weights to estimate causal relationships.[15] This method provides the most accurate results in the absence of horizontal pleiotropy or heterogeneity. To complement the IVW results, additional MR analysis tools, including Mendelian Randomization-Egger (MR-Egger) regression and the weighted median estimator (WME), were utilized.[15,16] These approaches are particularly effective in addressing multiplicity and heterogeneity, with a focus on assessing the direction and magnitude of causal effects.[16,17]

Sensitivity analyses were conducted to evaluate the impact of potential horizontal pleiotropy and heterogeneity. Heterogeneity was assessed using Cochran's Q-test, with significance set at $P < 0.05$. Horizontal pleiotropy was evaluated using MR-Egger regression, where a P-value < 0.05 indicated the presence of pleiotropy.[18] The Mendelian

Table 1 Details of the Genome-Wide Association Studies and Datasets Used in This Study

Exposure or Outcome	Sample Size	Ancestry	Database	Year
Circulating levels of 41 cytokines and growth factors	8293 participants	European ancestry	European Bioinformatics Institute	2016
Rosacea	1195 cases and 211139 controls	European ancestry	The Finn Gen Biobank	2021

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Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) test was also employed to detect potential pleiotropy and outliers.[19]

To account for multiple comparisons, the Bonferroni correction was applied, setting the significance threshold at $P < 1.22 \times 10^{-3}$ (0.05/41), based on the total number of cytokines analyzed. A P-value between 1.22×10^{-3} and 0.05 was considered indicative of potential causality.[20] All MR analyses were conducted using the "two-sample MR", "MendelianRandomization", and "MRPRESSO" packages in R software (version 4.3.1).[21–23]

Results

Impact of 41 Inflammatory Cytokines on Rosacea

When the genome-wide significance threshold was set at $P < 5 \times 10^{-8}$, only 11 of the 41 systemic inflammatory regulators contained three or more significant genetic variants. For the remaining cytokines, the threshold was relaxed to $P < 5 \times 10^{-6}$ to ensure sufficient SNPs for further MR analysis. All cytokines demonstrated strong instrumental validity, as indicated by F-statistic values exceeding 10 (Figure 2 and Table S2).

Causal analysis using the IVW method did not identify any significant correlations between inflammatory factors and rosacea development after Bonferroni correction ($P < 1.22 \times 10^{-3}$). However, five cytokines were identified as potentially associated with rosacea within a P-value range of 1.22×10^{-3} to 0.05. Among these, genetically determined higher levels of Stromal Cell-Derived Factor-1α (SDF-1α) and Hepatocyte Growth Factor (HGF) were positively correlated with increased risk of rosacea (IVW-OR = 1.54, 95% CI: 1.05–2.26, P = 0.026; IVW-OR = 1.61, 95% CI: 1.12–2.31, P = 0.009). Similar trends were observed using MR-Egger regression (SDF-1α: OR = 2.84, 95% CI: 1.24–6.50, P = 0.04; HGF: OR = 1.15, 95% CI: 0.48–2.75, P = 0.76) and the weighted median method (SDF-1α: OR = 1.38, 95% CI: 0.84–2.28, P = 0.21; HGF: OR = 1.49, 95% CI: 0.92–2.42, P = 0.10).

Additionally, an inverse association was observed between rosacea risk and genetically determined higher levels of circulating Stem Cell Factor (SCF) (IVW-OR = 0.68, 95% CI: 0.49–0.94, P = 0.018), a result supported by similar patterns from MR-Egger regression (OR = 0.58, 95% CI: 0.26–1.30, P = 0.22) and the weighted median method (OR = 0.75, 95% CI: 0.59–0.96, P = 0.12). Comparable inverse associations were also identified for Macrophage Inflammatory Protein-1β (MIP-1β)(IVW-OR = 0.88, 95% CI: 0.78–0.99, P = 0.03) and Monocyte Chemotactic Protein-1 (MCP-1) (IVW-OR = 0.75, 95% CI: 0.59–0.96, P = 0.02) (Table 2, Figure 2 and Table S4).

Sensitivity analyses using MR-Egger regression confirmed the absence of horizontal pleiotropy for all instrumental variables (P > 0.05, Tables 2 and S5). Cochran's Q-test revealed no heterogeneity (P > 0.05, Tables 2 and S5), and MR-PRESSO identified no pleiotropy or outliers among the instrumental variables (P > 0.05, Tables 2 and S5). Consistent causal estimates were observed in terms of both magnitude and direction. Specifically, SCF, MIP-1β, and MCP-1 exhibited a protective effect against rosacea, whereas SDF-1α and HGF showed a risk-enhancing effect. These findings highlight the complex and diverse roles of inflammatory cytokines in modulating rosacea risk. Scatter plots illustrating the identified relationships in the MR analysis across various tests are presented in Figure 3, while leave-one-out sensitivity analyses demonstrated that no single SNP exerted a disproportionate influence on the overall results (Figure 4). Additional analyses, including funnel plots and forest plots, are provided in the supplementary materials as Figures S1 and S2, respectively. These supplementary analyses further validate the findings and demonstrate the robustness and consistency of the causal inferences.

Influence of Rosacea on 41 Inflammatory Cytokines

Using the same methods, we investigated the reverse causal relationship between rosacea and the expression of 41 inflammatory cytokines. No significant associations were identified between rosacea and any of the cytokines analyzed. Detailed results, including MR analyses, heterogeneity assessments, and sensitivity evaluations, are provided in the Supplementary Material (Tables S6–S8).

Discussion

Rosacea is a persistent inflammatory skin condition that significantly impacts a patient's appearance. It affects approximately 10% of the global population.[24] While its pathophysiology remains unclear, several triggers have been identified,

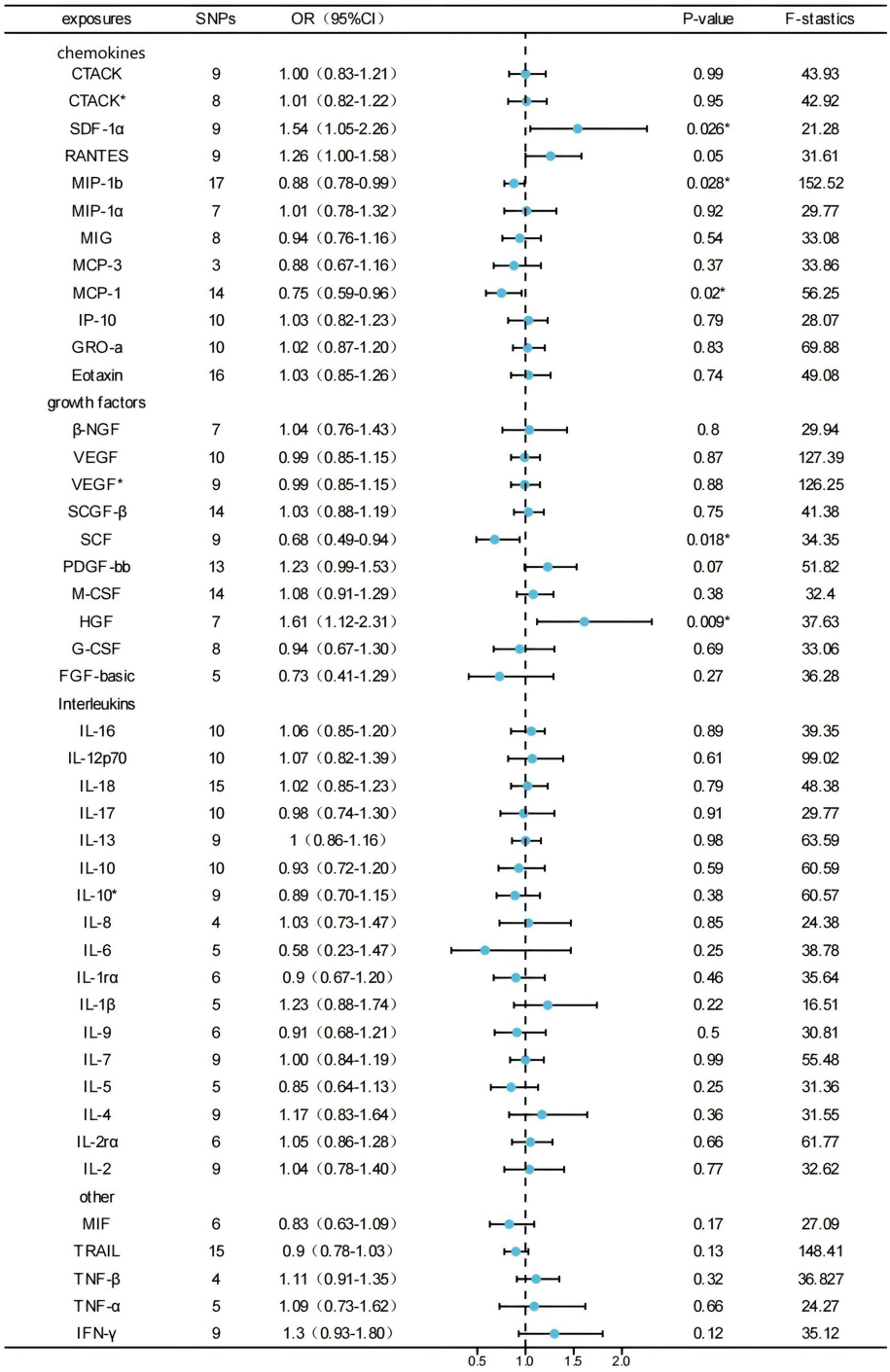

Figure 2 Forest plot of the forward Mendelian Randomization analysis of the relationship between inflammatory cytokines and rosacea risk.

Notes: 95% confidence interval (CI) represent the change in the SD of inflammatory cytokines per log odds increase in rosacea. After correcting for multiple comparisons, a p-value < 0.0012 (after adjusting for 41 comparisons, with a significance threshold of 0.05/41) was considered significant; when 0.0012 < p-value < 0.05, it indicates potential associations. (*P<0.05) The F-statistic is used to assess the strength of genetic associations with instrumental variables.

Abbreviations: CTACK, Cutaneous T Cell-Attracting Chemokine; SDF-1α, Stromal Cell-Derived Factor 1 Alpha; IP-10, Interferon Gamma-Induced Protein 10; RANTES, Regulated upon Activation, Normal T Cell Expressed and Secreted; MIP-1β, Macrophage Inflammatory Protein 1 Beta; MIP-1α, Macrophage Inflammatory Protein 1 Alpha; MIG, Monokine Induced by Gamma Interferon; MCP-3, Monocyte Chemoattractant Protein 3; MCP-1, Monocyte Chemoattractant Protein 1; GRO-α, Growth-Regulated Oncogene Alpha; Eotaxin, Eosinophil Chemotactic Protein; β-NGF, Beta Nerve Growth Factor; VEGF, Vascular Endothelial Growth Factor; SCGF-β, Stem Cell Growth Factor Beta; SCF, Stem Cell Factor; PDGF-bb, Platelet-Derived Growth Factor BB; M-CSF, Macrophage Colony-Stimulating Factor; HGF, Hepatocyte Growth Factor; G-CSF, Granulocyte Colony-Stimulating Factor; FGF-basic, Fibroblast Growth Factor Basic; IL-16, Interleukin 16; IL-12p70, Interleukin 12 p70 Subunit; IL-18, Interleukin 18; IL-17, Interleukin 17; IL-13, Interleukin 13; IL-10, Interleukin 10; IL-8, Interleukin 8; IL-6, Interleukin 6; IL-1rα, Interleukin 1 Receptor Antagonist; IL-1β, Interleukin 1 Beta; P-value, Probability Value; OR, Odds Ratio; SNP, single nucleotide polymorphism.

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Table 2 Three MR Models' Estimation of the Causal Relationships Between Circulating Cytokines and Rosacea and Tests for Heterogeneity and Horizontal Pleiotropy

Cytokines	nSNP	Beta	OR (95% CI)	*P-value*	$P_{Heterogeneity}$	$P_{Pleiotropy}$	$P_{Global\ test}$
SCDF-1α							
IVW	10	0.43	1.54 (1.05–2.26)	0.03*	0.67	0.15	0.70
MR Egger	10	1.04	2.84 (1.24–6.50)	0.04	0.87		
Weighted median	10	0.32	1.38 (0.84–2.28)	0.21			
HGF							
IVW	9	0.48	1.61 (1.12–2.31)	0.01*	0.39	0.44	0.27
MR Egger	9	0.14	1.15 (0.48–2.75)	0.76	0.36		
Weighted median	9	0.40	1.49 (0.92–2.42)	0.10			
MIP-1β							
IVW	20	−0.13	0.88 (0.78–0.99)	0.03*	0.84	0.93	0.61
MR Egger	20	−0.12	0.88 (0.74–1.05)	0.19	0.79		
Weighted median	20	−0.05	0.96 (0.81–1.13)	0.59			
MCP-1							
IVW	15	−0.28	0.75 (0.59–0.96)	0.02*	0.21	0.80	0.08
MR Egger	15	−0.21	0.81 (0.45–1.46)	0.50	0.16		
Weighted median	15	−0.22	0.81 (0.59–1.10)	0.17			
SCF							
IVW	11	−0.39	0.68 (0.49–0.94)	0.02*	0.41	0.69	0.37
MR Egger	11	−0.55	0.58 (0.26–1.30)	0.22	0.33		
Weighted median	11	−0.35	0.71 (0.46–1.09)	0.12			

Notes: nSNP, number of the SNP used as the IVs for the MR analyses; 95% CI, 95% confidence interval; $P_{Heterogeneity}$, p-value of the heterogeneity test; $P_{Pleiotropy}$, p-value of the intercept of the MR Egger; $P_{Global\ test}$, p-value of the MR-PRESSO global test. *P<0.05.
Abbreviations: IVW, Inverse Variance Weighting; SNP, Single Nucleotide Polymorphism; OR, Odds Ratio; MR Egger, MR Egger Regression.

including ultraviolet (UV) radiation, inflammatory stimulation by skin-resident microbes, temperature fluctuations, hot food, and stress.[25] Furthermore, growing evidence suggests a link between rosacea and genetic susceptibility. Dysregulation of both innate and adaptive immune cells, along with neuroinflammation, has been implicated in the altered skin and ocular immune status observed in rosacea patients.[26] Although this study focuses on inflammatory cytokines, the role of neuro inflammation in rosacea remains critical. Toll-like receptor 2 (TLR-2) activation and nuclear factor kappa B (NF-κB) signaling pathways have been implicated, emphasizing the need for future research into neuro inflammatory markers.

Research on the role of growth factors in rosacea is limited. In this study, we identified potential associations between the genetic regulation of HGF andSCF and rosacea pathogenesis. HGF exerts various biological effects on multiple cell types through the Mesenchymal to Epithelial Transition(MET) receptor, a transmembrane tyrosine kinase expressed on Langerhans cells (LCs). HGF influences mitosis, morphogenesis, and cell motility.[27] Dendritic cells (DCs) have been shown to regulate HGF production during immune responses and inflammation. Inflammatory cytokines such as interleukin-1α (IL-1α), Interleukin-1β(IL-1β), tumor necrosis factor-α (TNF-α), and Interleukin-6(IL-6) stimulate HGF production during infection or tissue injury.[28,29] Conversely, anti-inflammatory substances such as glucocorticoids,1,25-dihydroxyvitamin D3, and transforming growth factor beta (TGF-β) inhibit HGF formation, indicating its role as a pro-inflammatory mediator.[30,31] HGF further enhances the expression of pro-inflammatory cytokines, including Interleukin-4 (IL-4), IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and MIP-1β.[32] Consistent with its pro-inflammatory function, our findings suggest that elevated genetic levels of HGF increase rosacea risk. However, the role of the HGF/MET signaling pathway in cutaneous immunomodulation requires further investigation. It is hypothesized that this pathway induces mast cell activation and degranulation, releasing pro-inflammatory mediators such as matrix metalloproteinases (MMPs), TNF-α, and interleukins, which contribute to inflammation in both skin and ocular tissues.[33,34]

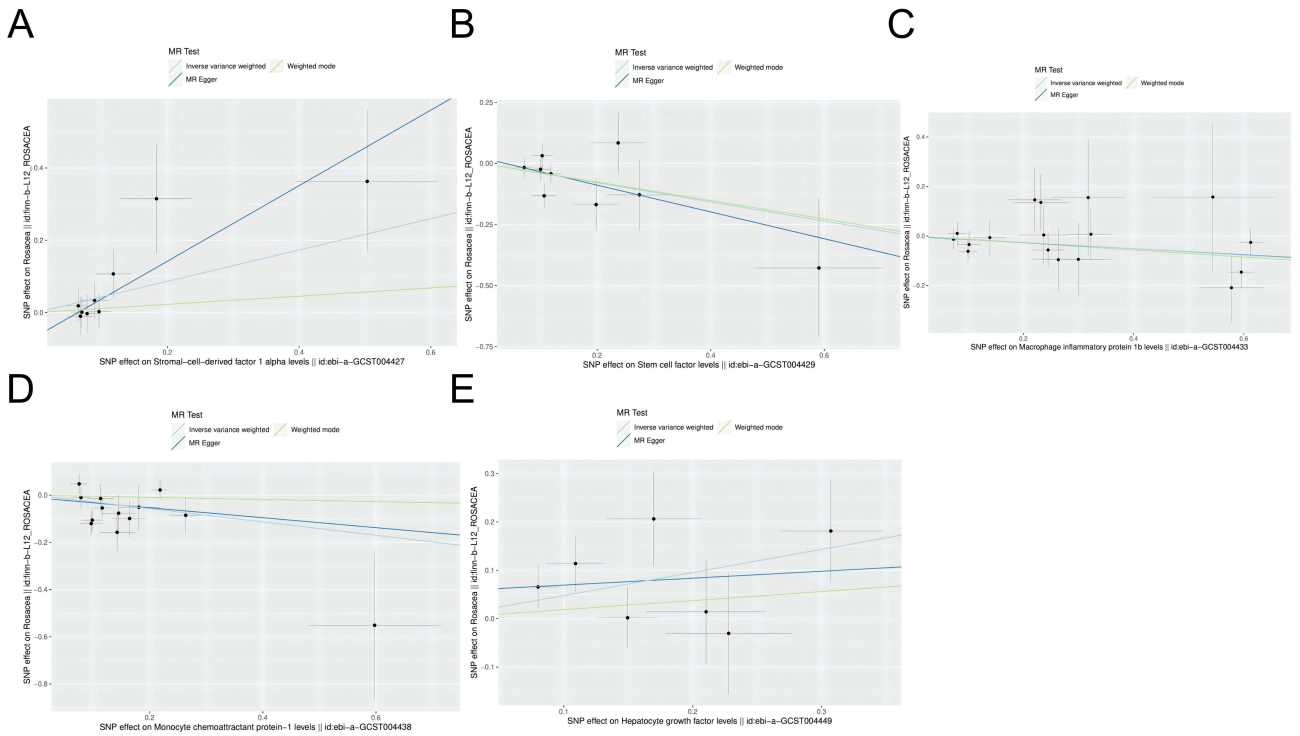

Figure 3 Scatter plot of Mendelian Randomization (MR) analysis of rosacea and inflammatory cytokines.
Notes: Black dots represent the association between individual instrumental variables (IV) and rosacea risk, as well as the association between individual IVs and cytokines. The 95% confidence intervals (CI) of the odds ratio (OR) for each IV are represented by the vertical and horizontal lines. The slope of the line represents the estimated causal effect using the MR method. (**A**) Stromal Cell-Derived Factor 1 Alpha(SDF-1α); (**B**) Stem Cell Factor (SCF); (**C**) Macrophage Inflammatory Protein 1 Beta(MIP-1β); (**D**) Monocyte Chemoattractant Protein 1(MCP-1); (**E**) Hepatocyte Growth Factor(HGF).

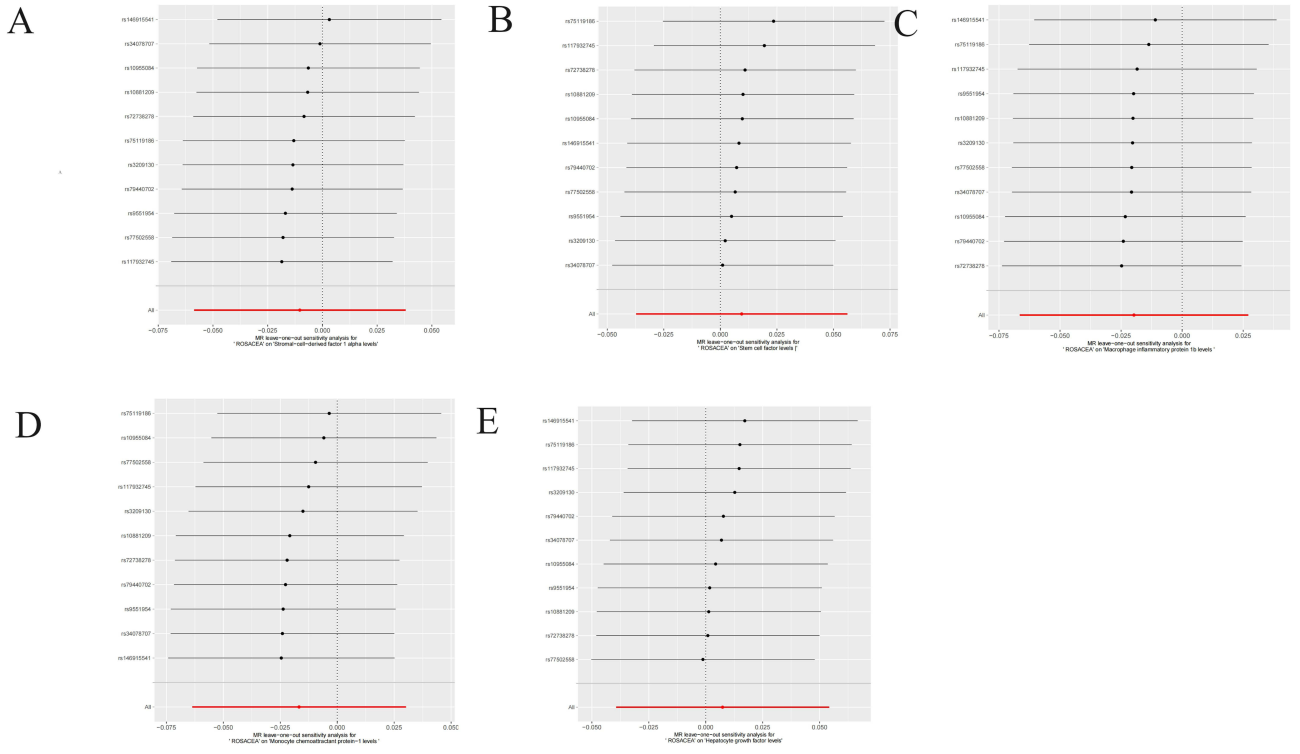

Figure 4 The leave-one-out plots of 41 cytokines that are causally related to rosacea.
Notes: Red lines represented estimations from the inverse variance weighted test. (**A**) Stromal Cell-Derived Factor 1 Alpha(SDF-1α); (**B**) Stem Cell Factor (SCF); (**C**) Macrophage Inflammatory Protein 1 Beta(MIP-1β); (**D**) Monocyte Chemoattractant Protein 1(MCP-1); (**E**) Hepatocyte Growth Factor(HGF).

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In contrast, SCF appears to have a protective effect. SCF, a cytokine produced by hematopoietic stem cells (HSCs), promotes cell division and differentiation by binding to its receptor c-KIT.[35] SCF supports skin repair by recruiting cells from nearby epidermis, hair follicles, and sebaceous glands. Additionally, SCF inhibits pseudoallergic mast cell degranulation, reducing mast cell activity.[36] Our findings reveal a genetic association between SCF and a reduced risk of rosacea, although further experimental validation is needed.

Chemokines and their receptors also play crucial roles in rosacea pathophysiology.[8] A previous study found positive correlations between serum levels of chemokine (C-C motif) ligand 5 (CCL5), C-X-C motif chemokine ligand 8 (CXCL8), and C-X-C motif chemokine ligand 9 (CXCL9) with rosacea severity.[8] A genome-wide association study (GWAS) in a European population identified rs763035, located between the BRN2 and HLA-DRA loci, as a significant genetic risk factor for rosacea.[37] Similarly, polymorphisms in the tachykinin receptor 3 (TACR3) gene (rs3733631) have been linked to genetic predisposition to rosacea.[38]

Our study established a causal genetic link between three chemokines—MIP-1β, MCP-1, and SDF-1α—and rosacea risk. Elevated levels of SDF-1α were positively associated with rosacea, while increased MIP-1β and MCP-1 levels were linked to a reduced risk. SDF-1α has been shown to participate in multiple inflammatory pathways, including TLR-2 and NF-κB signaling.[39,40] Elevated transcript levels of the SDF-1α gene have been reported in rosacea-like mouse models and are enriched in chemokine signaling pathways.[41]

Conversely, MIP-1β and MCP-1 play anti-inflammatory roles. MIP-1β (CCL4) and CCL5 are ligands for the C-C chemokine receptor 5 (CCR5), although CCL4 has a weaker binding affinity and does not significantly activate CCR5.[42] Our findings suggest that increased genetic levels of MIP-1β may reduce rosacea risk through negative regulation of inflammatory pathways. Similarly, MCP-1 (CCL2) facilitates monocyte migration to inflamed tissues, aiding in immune regulation. MCP-1 polymorphisms have been reported to protect against inflammatory bowel disease (IBD) in European populations.[43–45] In vitro studies suggest that MCP-1 promotes monocyte clustering and bacterial clearance, potentially regulating facial bacterial load in rosacea.[46]

Overall, our results highlight the protective role of MCP-1 and MIP-1β, as well as the pro-inflammatory role of SDF-1α in rosacea pathogenesis. Further clinical studies are needed to confirm these findings and elucidate the mechanisms underlying these associations.

Limitations

A key limitation of this study is its reliance on the FinnGen database, which primarily includes European populations. This introduces potential population-specific biases and may limit the generalizability of the findings to other ethnic groups. Expanding the analysis to include multi-ethnic cohorts is essential to confirm the validity and applicability of these results across diverse populations. Future research should prioritize incorporating datasets from underrepresented populations to enhance the robustness and universality of these conclusions.

Conclusion

This study identified genetic causal associations between five cytokines—SCF, SDF-1α, MCP-1, HGF, and MIP-1β—and rosacea, marking the first MR analysis to clarify the role of inflammatory cytokines in rosacea risk. Unlike observational studies, this MR approach minimized confounding and reversed causation, providing robust evidence of causality.

The data for this study were derived from publicly available GWAS datasets and the FinnGen database, both of which are well-established resources with extensive prior validation. This strengthens the reliability and generalizability of our findings. Furthermore, this investigation demonstrates the efficiency of MR analysis as a cost-effective alternative to traditional randomized controlled trials (RCTs), achieving credible results with relatively modest time and financial investment.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Changshu No.1 People's Hospital (2022, No.21). All data analyzed in this study were sourced from publicly available

databases. Ethical approval was obtained for each cohort, and written informed consent was provided by all participants prior to their participation in the study.

Consent for Publication

Consent for publication was obtained from every individual whose data are included in this manuscript.

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Disclosure

The authors declare that the work is original, has not been submitted elsewhere, and has not been previously published. Furthermore, none of the authors have any financial disclosures or conflicts of interest to declare.

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