Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

Decoding the Causal Effects of Blood-Related Phenotypes in Hypertrophic Scars and Keloids: A Mendelian Randomization Study

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Background: Hypertrophic scars (HS) and keloids are pathological outcomes of aberrant wound healing. Their association with systemic physiological factors remains unclear. Mendelian randomization (MR) uses genetic variants as instrumental variables (IVs) to infer causality, minimizing confounding factors.

Objective: In this study, we aim to investigate the causal effects of blood-related phenotypes, including blood cell counts, blood pressure, lipids, and glucose, on the risk of HS and keloids using a two-sample MR method.

Methods: Genetic instruments for exposures were obtained from publicly available GWAS summary statistics, while outcome data were sourced from the FinnGen database and GWAS Catalog. The IVs were selected based on genome-wide significance ($P < 5 \times 10^{-8}$) and clumped for independence ($r^2 < 0.001$, window = 10,000 kb), with F-statistic > 10 and minor allele frequency > 0.01 applied to minimize weak instrument bias. Causal estimates were primarily derived using the inverse variance weighted method, supplemented by comprehensive sensitivity analyses including heterogeneity, pleiotropy, and reverse causality.

Results: Genetically predicted higher leukocyte (OR: 1.175, 95% CI: 1.049–1.315, P = 0.005) and neutrophil counts (OR: 1.177, 95% CI: 1.040–1.332, P = 0.010) were causally associated with increased keloid risk. Conversely, lower systolic blood pressure (SBP) (OR: 0.709, 95% CI: 0.537–0.938, P = 0.016) and diastolic blood pressure (DBP) (OR: 0.732, 95% CI: 0.565–0.949, P = 0.018) were causally linked to higher HS risk, and lower SBP (OR: 0.760, 95% CI: 0.622–0.928, P = 0.007) was associated with increased keloid risk. No causal relationships were found for other blood cells, lipids, or glucose with either scar type. Sensitivity analyses did not indicate substantial heterogeneity or horizontal pleiotropy, supporting the robustness of the main findings.

Conclusion: Our study suggests the causal effects of blood-related phenotypes in HS and keloids by using an MR method. Our results offer novel etiological insights and a potential perspective for scar-related intervention.

Keywords: hypertrophic scars, keloids, Mendelian randomization, blood phenotypes, causal inference

Introduction

Scars are a common skin condition resulting from abnormal healing during the tissue repair process after skin injury, characterized by excessive proliferation of fibrous connective tissue.[1] Based on pathological features and clinical manifestations, scars are primarily categorized into hypertrophic scars (HS) and keloids. HS are common complications of burns and other soft tissue injuries.[2] HS is typically confined to the boundaries of the original wound and is characterized by symptoms such as itching, pain, mild elevation, and pigmentation abnormalities, leading to suboptimal cosmetic and functional outcomes. In contrast, keloids exhibit aggressive growth that extends beyond the original wound margins and are often accompanied by persistent itching, pain, and even restricted joint mobility.[3] Current treatments for scars primarily include topical medications, intralesional injections, surgical excision, and energy-based therapies such as lasers.[4] These comprehensive therapeutic approaches can alleviate scar symptoms and improve outcomes.[5] The formation of scars is influenced by a variety of factors, including genetic predisposition, immune responses, mechanical trauma, infection, and metabolic status.[6,7] However, the precise

https://doi.org/10.2147/CCID.S593178
Received: 1 January 2026
Accepted: 1 April 2026
Published: 14 April 2026

mechanisms by which these factors contribute to the pathological processes of scar formation remain to be elucidated and require further investigation.

In recent years, physiological and biochemical parameters have been common clinical indicators. Blood-related parameters and blood pressure levels have gradually been recognized as potentially associated with disease formation.[8] Immune cells in the blood, such as white blood cells and neutrophils, play critical roles in the inflammatory response and fibrosis processes, while blood pressure levels may influence scar development by affecting vascular function and tissue repair mechanisms.[9] Additionally, metabolic indicators, such as blood lipid and glucose levels, which reflect metabolic status, may also exert potential effects on scar formation through the regulation of inflammation and oxidative stress. For example, red blood cell distribution width serves as an independent marker of both myocardial scar extent quantified by viability imaging and impaired left ventricular systolic function in patients with ischemic heart disease.[10] Hao et al reported that blood pressure level was a critical factor in keloid recurrence.[11] However, current research investigating the relationship between these physiological indicators and scar-related disorders remains limited, and the causal relationships have yet to be fully established. In particular, the association between blood phenotypes and scar risk is susceptible to distortion by numerous unmeasured or residual confounding factors, such as lifestyle, environmental exposures, socioeconomic status, and comorbidities, and establishing the direction of causality remains challenging.

Mendelian randomization (MR) utilizes statistical approaches derived from economics, enabling investigators to examine how environmental exposures, pharmacological interventions, and other variables impact human biological processes and disease states.[12] MR uses genetic variants as instrumental variables (IVs) to emulate random assignment.[13] The MR approach supports causal inference between modifiable risk factors and disease outcomes in observational data. MR analysis serves as a reliable tool for uncovering the potential causal mechanisms of complex diseases, effectively minimizing the influence of confounding factors and reverse causation. For instance, MR analysis successfully identifies several potential therapeutic targets for keloids, with neurotrimin emerging as a particularly promising candidate.[14] Additionally, Zou et al used MR analysis and thus established a genetically predicted bidirectional causal link, identifying CD66b++ myeloid cell absolute count as a protective factor against keloid formation.[15] Through MR analysis, the direct effects of blood indicators, blood pressure levels, and other physiological characteristics on scars can be more accurately evaluated, thereby providing scientific evidence for further research into their pathological mechanisms.

As a result, the causal relevance of blood cell traits, blood pressure, lipid profiles, and glucose levels to HS and keloids has not yet been systematically established. Therefore, this study employed a two-sample MR approach to systematically investigate the potential causal relationships of these physiological traits with both keloids and HS. The exposures examined included blood cell traits, blood pressure measures (systolic pressure, diastolic pressure, and pulse pressure), lipid parameters (total cholesterol, LDL-C, HDL-C, and triglycerides), and blood glucose levels. By integrating summary-level data from large-scale genome-wide association studies (GWAS), we performed causal effect estimation and validated the robustness of the findings through multiple sensitivity analyses. Our study provides novel insights into the pathogenesis of scar diseases and offers a theoretical foundation for possible clinical interventions and personalized treatment strategies.

Methods

The Overall Study Framework

This study employs a two-sample MR approach to investigate the causal effects between blood-related phenotypes, and the risk of developing HS and keloids. The MR analysis in our study is mainly based on three fundamental principles: (1) the genetic variants used as IVs must be significantly associated with the exposures; (2) the IVs should influence the outcomes solely through the exposures, without any direct association; (3) the IVs must be independent of potential confounding factors. This study utilizes publicly available, de-identified summary-level data from GWAS. Thus, ethical approval is not applicable.

Exposure Data Resource

The exposure data for this study were obtained from publicly available GWAS summary statistics provided by the IEU OpenGWAS database and the GWAS Catalog, with sample sizes ranging from 40,000 to over 560,000 participants across various blood-related phenotypes. Blood cell phenotypes, blood pressure, blood lipids, and blood glucose were analyzed

as blood-related phenotypes in this study. Blood cell phenotypes included basophil count, eosinophil count, red blood cell count, white blood cell count, lymphocyte count, monocyte count, neutrophil count, and platelet count. Blood pressure-related phenotypes included systolic blood pressure, diastolic blood pressure, and pulse pressure. Blood lipid-related phenotypes included total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Detailed information about these phenotypes is provided in Table 1.

Outcome Data Resource

The GWAS data for HS were obtained from the FinnGen database (R12), consisting of 2068 cases and 465,673 controls. Data for keloids were sourced from the GWAS Catalog, including 4086 cases of European ancestry and 1,278,496 European ancestry controls. The identifier for the keloid dataset is GCST90652488.

Selection of Instrumental Variables (IVs)

The IVs were selected based on a genome-wide significance threshold of P-value < 5e-08. To minimize bias caused by linkage disequilibrium (LD) between single nucleotide polymorphisms (SNPs), only SNPs with LD parameters of $r^2 < 0.001$ and a window size of 10,000 kb were retained. Additionally, SNPs with an F-statistic > 10 were included to reduce weak instrument bias, and variants with a minor allele frequency (MAF) < 0.01 were excluded to avoid potential interference from rare mutations.

MR and Sensitivity Analyses

Two-sample Mendelian Randomization (TSMR) analyses were performed using the TwoSampleMR package (version 0.6.22). This study systematically assessed the causal effect of each exposure phenotype on HS and keloid risk by integrating 5 MR methods, including MR Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted mode. The IVW method was selected as the primary estimator due to its high statistical power and unbiased property under the assumption of no horizontal pleiotropy for all IVs. For causal effect estimation, the IVW method was applied when the number of SNPs (nSNP) was ≥ 2, while the Wald ratio method was used when nSNP = 1. Sensitivity analyses included tests for heterogeneity using Cochrane's Q statistic and horizontal pleiotropy using the MR-Egger intercept test. Reverse causality between exposures and outcomes was assessed using the Steiger filtering method, with steiger_pval < 0.05 indicating the absence of reverse causation.

Table 1 Information on Exposure Phenotypes

Class	Phenotype	Source	ID	Sample Size
Blood cell traits	Basophil cell count	IEU	ieu-b-29	563946
	Eosinophil cell count	IEU	ieu-b-33	563946
	Erythrocyte count	IEU	ieu-a-275	66214
	Leukocyte count	IEU	ieu-b-30	563946
	Lymphocyte cell count	IEU	ieu-b-32	563946
	Monocyte cell count	IEU	ieu-b-31	563946
	Neutrophil cell count	IEU	ieu-b-34	563946
	Platelet count	IEU	ieu-a-1008	66867
Blood pressure	Systolic blood pressure	GWAS Catalog	GCST90301695	349328
	Diastolic blood pressure	GWAS Catalog	GCST90301698	349328
	Pulse pressure	GWAS Catalog	GCST90301701	349328
Blood lipid	Total cholesterol levels	IEU	ebi-a-GCST90025953	437878
	LDL-C levels	IEU	ebi-a-GCST90025954	437068
	HDL-C levels	IEU	ebi-a-GCST90025956	400754
	Triglyceride levels	IEU	ebi-a-GCST90025957	437532
Blood glucose	Blood glucose levels	IEU	ebi-a-GCST90025986	400458

Results

Blood Cell Phenotypes

For HS, the MR analysis results indicated that none of the 8 blood cell phenotypes showed potential causal relationships with HS. The Steiger directionality test showed the absence of reverse causality between these phenotypes and HS (steiger_pval < 0.05). Sensitivity analyses revealed no evidence of heterogeneity or horizontal pleiotropy, with P-values > 0.05 for both tests, suggesting that the data used in the MR analysis were robust and reliable (Tables S1–S5).

For keloid, MR analysis revealed a potential causal relationship between leukocyte count and keloids (Figure 1). The results indicated a significant positive association (OR: 1.175, 95% CI: 1.049–1.315, P = 0.005), suggesting that elevated leukocyte count levels may contribute to the exacerbation of keloid formation. Additionally, MR analysis also revealed a significant positive association between neutrophil count and keloids (OR: 1.177, 95% CI: 1.040–1.332, P = 0.010) (Figure 2), indicating that higher neutrophil count levels may promote keloid formation.

Furthermore, there was no evidence of reverse causality between leukocyte count or neutrophil count and keloids (Steiger p < 0.05, Table 2). Sensitivity analyses for leukocyte count, including heterogeneity and horizontal pleiotropy tests, showed P-values greater than 0.05, indicating no evidence of heterogeneity or pleiotropy in the data used for the MR analysis (Tables 3 and 4). Similarly, sensitivity analyses for neutrophil count also revealed no heterogeneity or pleiotropy, with P-values greater than 0.05 (Tables 3, 4 and S6–S10). This data further supported the robustness of our MR analysis results.

Blood Pressure

The MR analysis revealed a potential causal relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP), and HS (Figures 3 and 4). Both SBP (OR: 0.709, 95% CI: 0.537–0.938, P = 0.016) and DBP (OR: 0.732, 95% CI:

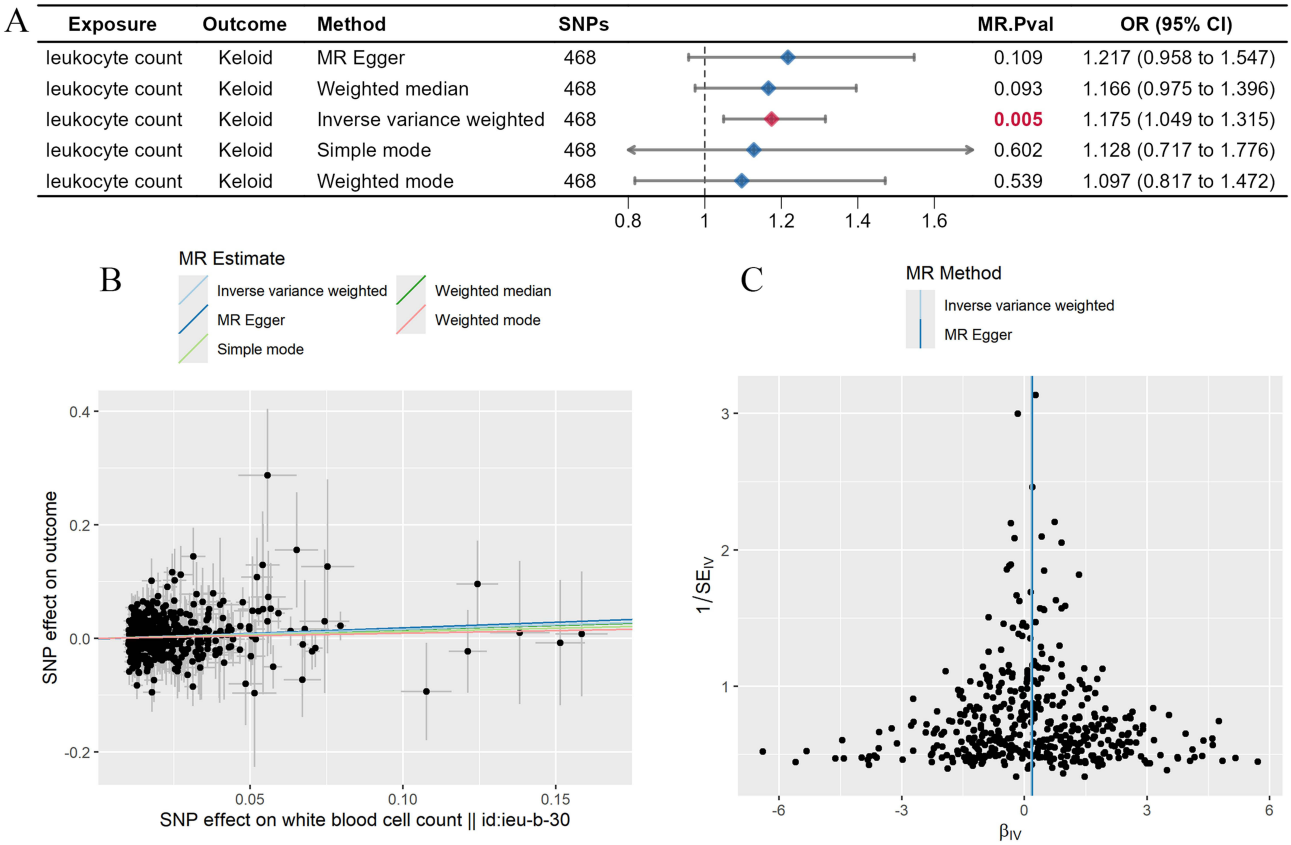

Figure 1 MR analysis for leukocyte count and keloids. (**A**) Forest plot of MR analysis results; (**B**) Linear regression plot of MR analysis results; (**C**) Scatter plot of heterogeneity test.

https://doi.org/10.2147/CCID.S593178

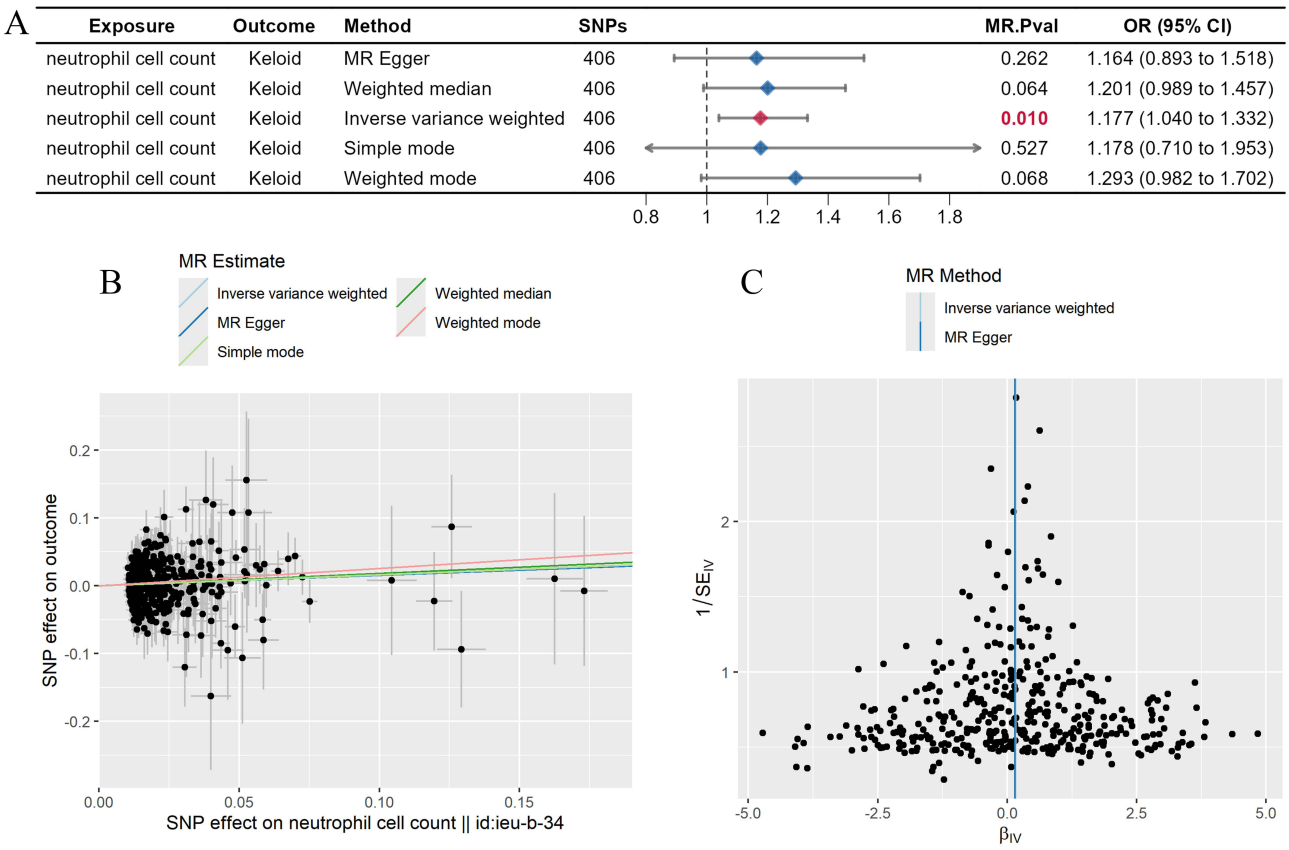

Figure 2 MR analysis for neutrophil count and keloids. (**A**) Forest plot of MR analysis results; (**B**) Linear regression plot of MR analysis results; (**C**) Scatter plot of heterogeneity test.

0.565–0.949, P = 0.018) showed a significant negative association with HS (OR < 1), suggesting that lower levels of SBP and DBP might increase the risk of developing HS. In contrast, no causal relationship was observed between pulse pressure and HS.

Table 2 Steiger Test Results for Leukocyte Count and Neutrophil Count with Keloids

Exposure	Outcome	snp_r2.exposure	snp_r2.outcome	steiger_pval
Leukocyte count	Keloid	0.0938	0.0004	0
Neutrophil cell count	Keloid	0.0820	0.0004	0

Table 3 Heterogeneity Test Results for Leukocyte Count and Neutrophil Count with Keloids

Exposure	Outcome	Heterogeneity Test (IVW)			Heterogeneity Test (MR-Egger)		
		Cochrane's Q	Q_df	Q_pval	Cochrane's Q	Q_df	Q_pval
Leukocyte count	Keloid	508.403	467	0.090	508.284	466	0.086
Neutrophil cell count	Keloid	452.643	405	0.051	452.634	404	0.047

Table 4 Pleiotropy Test Results for Leukocyte Count and Neutrophil Count with Keloids

Exposure	Outcome	egger_intercept	se	pval
Leukocyte count	Keloid	−0.001	0.003	0.741
Neutrophil cell count	Keloid	0.000	0.003	0.927

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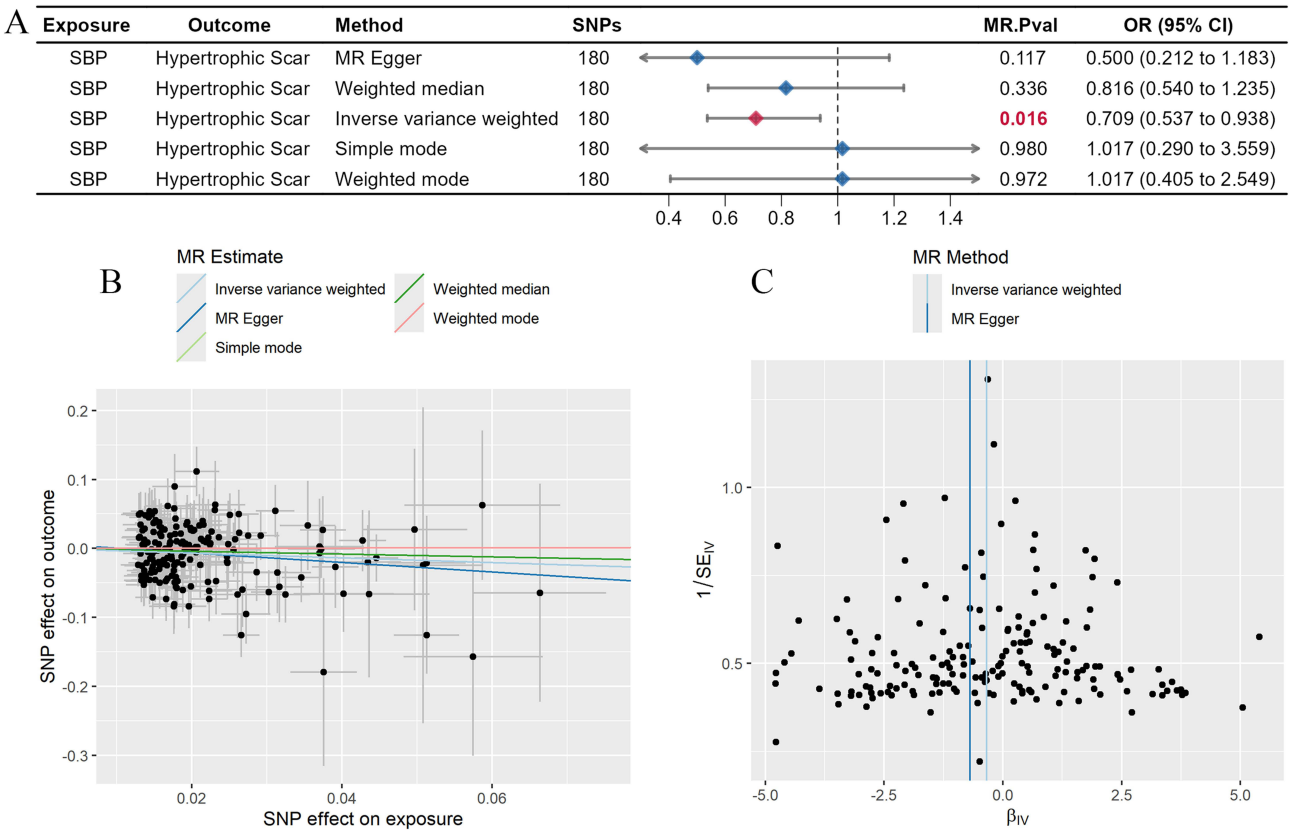

Figure 3 MR analysis for SBP and hypertrophic scars. (**A**) Forest plot of MR analysis results; (**B**) Linear regression plot of MR analysis results; (**C**) Scatter plot of heterogeneity test.

The Steiger directionality test indicated no evidence of reverse causality between SBP, DBP, and HS (steiger_pval < 0.05, Table 5). Sensitivity analyses, including heterogeneity and pleiotropy tests, demonstrated P-values greater than 0.05, confirming the absence of heterogeneity and horizontal pleiotropy in the data used for the MR analysis (Tables 6 and 7).

Additionally, the MR analysis identified a potential causal relationship between SBP and keloids (Figure 5). SBP was found to have a significant negative association with keloids (OR: 0.760, 95% CI: 0.622–0.928, P = 0.007), indicating that lower SBP levels may increase the risk of developing keloids. In contrast, no causal relationship was observed between DBP, pulse pressure, and keloids.

The Steiger directionality test showed no evidence of reverse causality between SBP and keloids (steiger_pval < 0.05, Table 5). Sensitivity analyses, including heterogeneity and pleiotropy tests, yielded P-values greater than 0.05, suggesting no heterogeneity or horizontal pleiotropy in the data used for the MR analysis. These findings supported the robustness of our MR analysis results (Tables 6 and 7).

Blood Lipids and Blood Glucose

The MR analysis revealed no causal relationships between the 4 blood lipid-related phenotypes, blood glucose levels, and HS or keloids. The Steiger directionality test showed the absence of reverse causality between these phenotypes and HS or keloids (steiger_pval < 0.05). Sensitivity analyses, including heterogeneity and pleiotropy tests, demonstrated P-values greater than 0.05, indicating no evidence of heterogeneity or horizontal pleiotropy in the data used for the MR analysis (Tables S11–S20).

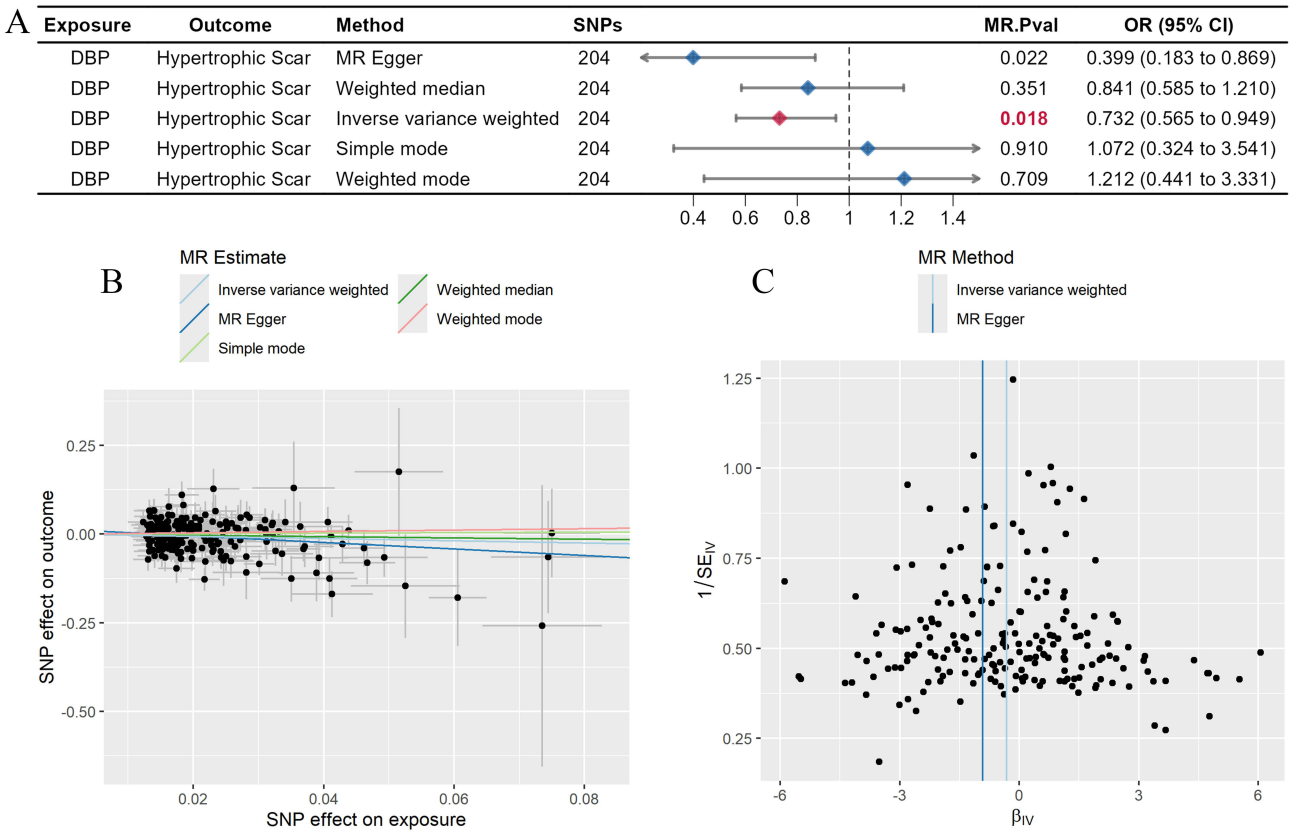

Figure 4 MR analysis for DBP and hypertrophic scars. (**A**) Forest plot of MR analysis results; (**B**) Linear regression plot of MR analysis results; (**C**) Scatter plot of heterogeneity test.

Discussion

Keloids and HS represent pathological outcomes of aberrant wound healing, characterized by distinct clinical features and substantial therapeutic challenges.[16] Their underlying pathological mechanisms remain incompletely understood. In the following section, we discuss the primary results of our MR analysis.

First, we employed MR analysis to investigate potential causal relationships between hematological traits and the development of keloids and HS. Our results demonstrated a significant positive association between elevated leukocyte

Table 5 Steiger Test Results for SBP and DBP with Hypertrophic Scars and Keloids

Exposure	Outcome	snp_r2.exposure	snp_r2.outcome	steiger_pval
SBP	Hypertrophic Scar	0.0299	0.0005	0
DBP	Hypertrophic Scar	0.0376	0.0005	0
SBP	Keloid	0.0317	0.0002	0

Table 6 Heterogeneity Test Results for SBP and DBP with Hypertrophic Scars and Keloids

Exposure	Outcome	Heterogeneity Test (IVW)			Heterogeneity Test (MR-Egger)		
		Cochrane's Q	Q_df	Q_pval	Cochrane's Q	Q_df	Q_pval
SBP	Hypertrophic Scar	197.860	179	0.159	197.078	178	0.156
DBP	Hypertrophic Scar	229.892	203	0.095	226.949	202	0.110
SBP	Keloid	207.274	194	0.244	207.135	193	0.231

https://doi.org/10.2147/CCID.S593178

Table 7 Pleiotropy Test Results for SBP and DBP with Hypertrophic Scars and Keloids

Exposure	Outcome	egger_intercept	se	pval
SBP	Hypertrophic Scar	0.007	0.009	0.402
DBP	Hypertrophic Scar	0.013	0.008	0.107
SBP	Keloid	−0.002	0.006	0.719

and neutrophil counts and keloid formation, whereas no causal links were observed for other blood cell traits with either keloids or HS. These findings suggest a potential role of the immune system in keloid pathogenesis, particularly implicating leukocyte and neutrophil activation in inflammatory responses and fibrotic processes.

Notably, existing MR literature contains no direct reports regarding the specific involvement of circulating leukocytes and neutrophils in keloid etiology. Research attention has predominantly focused on local immune cells and stromal components within scar tissue. For instance, immune cells and fibroblasts are critical cell types in keloids. RNA Sequencing reveals a predominant Th2-skewed immune signature with concurrent JAK/STAT activation in both lesional and non-lesional keloid tissue.[17] Shim et al used single-cell and spatial transcriptomic profiling of keloid tissue and revealed fibrovascular niche interactions, with disease-associated fibroblasts enriched in deep regions exhibiting spatial co-localization with mesenchymal-activated endothelial cells characterized by dysregulated TGF-β/SMAD signaling.[18] Endothelial–mesenchymal transition mediated by aberrant TGF-β signaling may drive keloid pathogenesis through fibrovascular communication. We therefore hypothesize that circulating cells may play mechanistically distinct roles compared to resident cells within scar tissue. Circulating immune cells may primarily function as inflammatory initiators during early disease pathogenesis, while resident cells, including fibroblasts and endothelial cells, likely sustain disease progression and fibrotic phenotypes through complex cellular

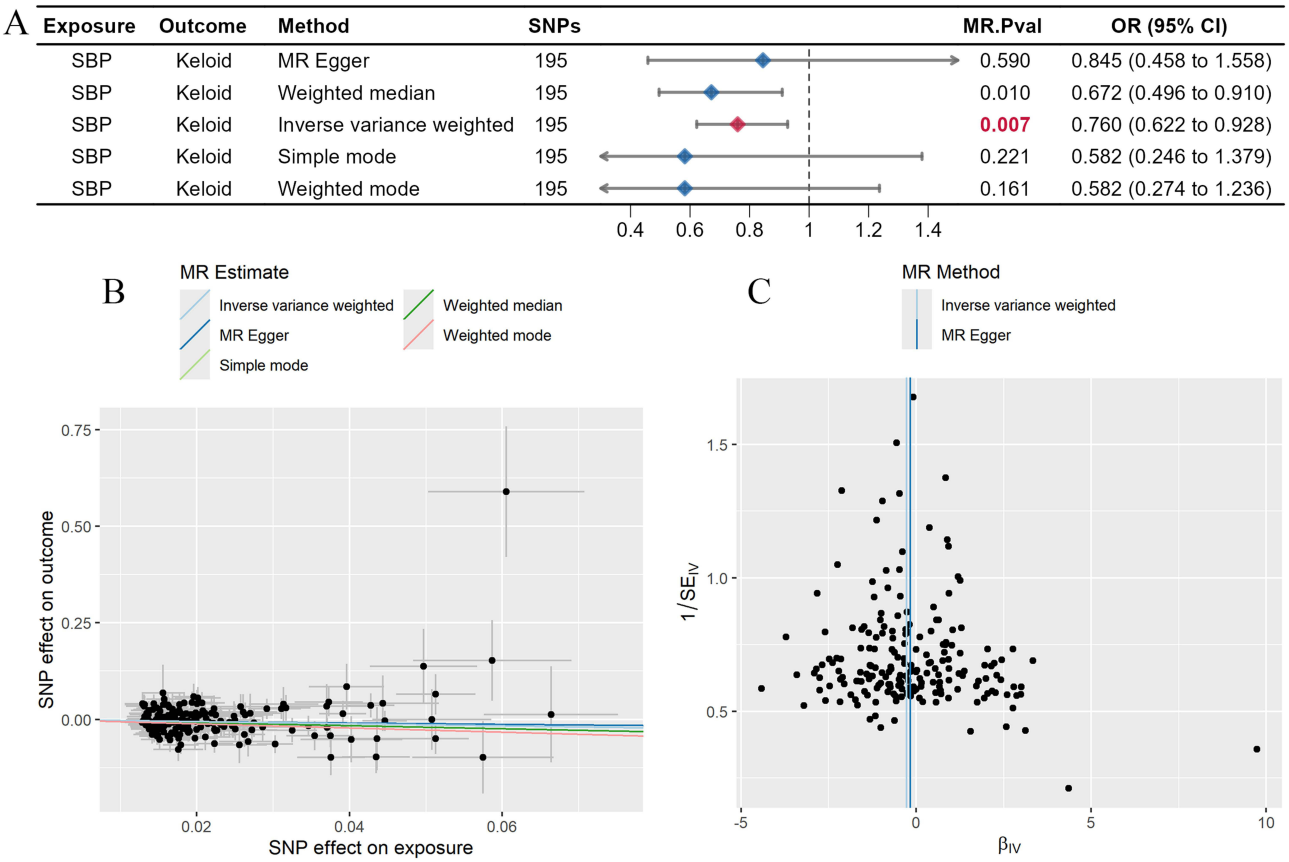

Figure 5 MR analysis for SBP and keloids. (**A**) Forest plot of MR analysis results; (**B**) Linear regression plot of MR analysis results; (**C**) Scatter plot of heterogeneity test.

communication networks. These two cellular compartments appear to exert temporally and spatially distinct, yet synergistic, effects throughout keloid development and progression.

Second, our study also examined the relationship between blood pressure phenotypes and scar pathologies. The results demonstrated that decreased SBP and DBP were significantly associated with an increased risk of HS, while reduced SBP was also linked to higher keloid risk. This suggests that blood pressure levels may influence scar formation by modulating vascular function and tissue repair processes. Notably, pulse pressure showed no significant association with either scar disorder. This might show potential differences in the pathophysiological roles of distinct blood pressure parameters. Notably, in a bidirectional MR study, genetic evidence supported a causal protective effect of elevated blood pressure against pathological scar development, with higher systolic/diastolic pressure and hypertension significantly associated with reduced risks of both keloids and HS.[19] However, this appears inconsistent with clinical observations indicating that severe keloids often coexist with hypertension, and hypertensive patients demonstrate higher risks of pathological scarring following invasive procedures.[20] Furthermore, an epidemiological study in Japanese populations suggested that essential hypertension may exacerbate keloid formation, proposing the skin as a potential target organ in hypertension.[21] Given these contradictory findings, the relationship between blood pressure and scar pathologies remains incompletely understood. The apparent differences could be attributable to methodological differences between genetic studies and clinical observations, or possibly reflect distinct pathophysiological mechanisms operating at different disease stages. Further investigations with standardized designs and larger cohorts are warranted to clarify these relationships.

Moreover, the observed associations of increased circulating leukocyte and neutrophil counts with elevated scar risk may not be independent of each other, but rather may reflect an underlying integrated physiological mechanism. Systemic blood pressure is closely related to peripheral vascular resistance and microcirculatory hydrostatic pressure. By altering the local hemodynamic milieu of the microcirculation, blood pressure may influence immune cell recruitment, tissue perfusion, and metabolic waste clearance during wound healing. In addition, neutrophil function may affect local lesions through systemic circulation. For example, the loss of PAD4-dependent NETosis attenuated hypertension, aortic inflammation, and endothelial dysfunction, whereas hypertension-related mechanical stretch promoted neutrophil extracellular traps (NETs) formation, with a more pronounced effect in the presence of endothelial cells.[22] TRPV4-mediated NETosis may contribute to the development of hypertension by inducing endothelial dysfunction. Moreover, higher blood pressure was associated with increased NETs in untreated hypertensive patients.[23] Taken together, these findings imply that increased blood pressure may facilitate leukocyte recruitment, tissue infiltration, and activation through changes in perfusion pressure and microcirculatory hemodynamics, while leukocyte-mediated inflammation may further participate in hypertension-related vascular damage.[24,25] Moreover, an abnormal hemodynamic environment may intensify local inflammatory responses and promote their persistence. Conversely, lower blood pressure may reduce local oxygen and nutrient supply, thereby establishing a microenvironment that favors fibrotic repair over regenerative wound healing.[26] On this basis, we hypothesize that blood-based indices and blood pressure-associated features are involved in the development of pathological scars. This concept warrants further validation through studies combining hemodynamic assessment, intravital imaging, and cellular as well as molecular investigations.

Regarding the relationship between blood lipid/glucose levels and scar disorders, our study did not reveal significant causal associations. This may indicate that although metabolic factors play roles in certain chronic diseases or inflammatory responses, they are not primary drivers in the pathogenesis of keloids or HS. However, an MR report by Li et al suggested causal effects of specific plasma lipid components on keloid risk, identifying sterol esters and glycerophospholipids as risk factors, while a specific triglyceride exhibited a protective effect.[27] Zhao et al revealed a dual role of remnant lipoproteins in keloid pathogenesis, with triglyceride-rich lipoprotein particles promoting disease susceptibility, while cholesterol-rich components conferred protection.[28] Although our findings differ from these reports, they are not necessarily contradictory. We propose that these differences stem from variations in the specific exposures examined, such as our focus on conventional lipid profiles (Total cholesterol, LDL-C, HDL-C, and Triglycerides) rather than specific lipid subspecies, as well as differences in the study cohorts and analytical methods.

Concerning blood glucose, no other MR studies have reported an association with scar formation. Nevertheless, we note a fundamental study indicating that hypoxic conditions induce metabolic reprogramming in keloid fibroblasts, characterized by enhanced glycolysis and mitochondrial dysfunction, suggesting hypoxia-driven glucose metabolism as a potential

therapeutic target.[29] It is important to distinguish cellular glucose metabolism, a key factor in scar progression, from systemic blood glucose levels. Collectively, these findings expand our understanding of factors associated with scarring. Interventions targeting metabolic regulation may hold potential value for the prevention and treatment of scar-related disorders.

Next, the robustness of scar-related causal inferences was confirmed through systematic sensitivity analyses. Heterogeneity tests indicated no significant heterogeneity for all significantly associated exposure phenotypes across keloid and HS subtypes, demonstrating consistent effects of the genetic instruments. MR-Egger regression further ruled out horizontal pleiotropy, and Steiger directionality tests supported unidirectional causal pathways from exposures to outcomes. These findings strengthen the causal roles of leukocyte subsets and blood pressure in scar pathogenesis.

Our study indicates that leukocyte count, neutrophil count, and blood pressure are likely involved in scar-related pathology, offering complementary insight into disease pathogenesis. It is important to focus on validating the roles of leukocytes and neutrophils through in vitro and animal models, particularly regarding inflammatory cytokine release and fibrotic regulation. Moreover, the link between blood pressure and scarring should be examined in greater depth, particularly in relation to angiogenesis and oxidative stress. Integrating multi-omics data could help elucidate key molecular mechanisms and accelerate the identification of candidate therapeutic targets. Clinically, targeting immune regulation may lead to novel anti-inflammatory therapies.[30] Additionally, gene–environment interactions involving mechanical stress and infection represent a critical area for developing optimized interventions.

Conclusion

Through MR analysis, this study showed that elevated leukocyte and neutrophil counts were significantly and positively associated with the formation of keloids, whereas other blood cell traits showed no significant causal relationship with scar disorders. Additionally, lower SBP and DBP levels were causally linked to an increased risk of HS, and reduced SBP was also associated with a higher risk of keloids. However, no significant causal associations were observed between blood lipid or glucose levels and the development of either keloids or HS. These findings provide important insights into the etiology of scar-related disorders and novel possibilities for developing potential therapeutic strategies.

Data Sharing Statement

All datasets used in this study were obtained from publicly available GWAS summary statistics databases, as described in the Methods section. Further questions can be directed to the corresponding author Fang Zhou.

Ethics Approval and Consent to Participate

This study utilized publicly available data from open-access databases (GWAS) and did not collect or generate new human data. According to Article 32, Items 1 and 2 of China's "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" (effective February 18, 2023), our study using publicly available data does not require additional ethical approval or informed consent.

(i) Research that utilizes legally obtained public data or data generated from observation of public behaviors without interference;
(ii) Research that utilizes anonymized information or data.

Therefore, this study is exempt from Institutional Review Board review.

Consent for Publication

All authors have provided their consent for publication.

Funding

This work was supported by None.

Disclosure

The authors reported no conflicts of interest. Fang Zhou is the first author.

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