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ORIGINAL RESEARCH

Immune Cells Phenotypes and Causal Relationship with Acne Vulgaris: Insights from Mendelian Randomization

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Object: We adopted a 2-sample bidirectional Mendelian randomization study to figure out whether circulating immune cells profiles causally impact acne vulgaris liability.

Methods: Applying large-scale genome-wide association studies (GWAS) pooled data. We obtained the summary-level data for acne vulgaris (N=212,438) from the FinnGen Biobank. Using publicly available genetic data, we investigated the causal link between 731 immune cell profiles and DN risk. Included were four different types of immune systems: morphological parameters (MP), absolute cell (AC), relative cell (RC), and median fluorescence intensities (MFI). The results' robustness, heterogeneity, and horizontal pleiotropy were confirmed through extensive sensitivity analysis.

Results: Our study identified causal associations between eight immune cells as potential mediators and acne vulgaris. Surprisingly, CD28 on CD39+ CD4+ T cell, CD39+ secreting CD4+ regulatory T cell and secreting CD4+ regulatory T cell were identified as the protective immunophenotype (OR=0.902, 0.944, 0.967, 95% CI 0.847–0.961, 0.906–0.983, 0.944–0.991). Moreover, CD24+ CD27 +AC, CD24 on IgD+ CD38br mediated 5.723% and 6.844% of the decreased risk for acne vulgaris. Furthermore, FSC-A monocytes were found to mediate the increased risk of acne vulgaris, contributing 7.384% to this mediation. CD20-CD38-AC cells were identified to be associated with the 17.04% increased risk of acne vulgaris.

Keywords: acne vulgaris, causality, genetic variants, immune cells, Mendelian randomization

Introduction

Acne, a chronic infectious disease affecting the sebaceous glands, exhibits its highest prevalence during adolescence.[1] Although the specific pathogenesis remains unclear, current research suggests that it primarily involves four aspects: 1) localized inflammation in affected skin; 2) aberrant follicular keratinization leading to comedone formation; 3) excessive secretion and compositional changes in sebum due to hormonal dependence or other factors; and 4) abnormal colonization of Propionibacterium acnes.[2,3] Among these factors, the atypical infiltration of activated immune cells exacerbates the crucial influencing factor - the degree of local skin inflammatory reaction.[4] Previous studies have demonstrated that the immune system plays a pivotal role throughout all stages by regulating not only abnormal immune cell infiltration but also promoting recovery through T cell regulation for controlling skin barrier function.[5,6] Therefore, elucidating the interaction between the immune system and this prevalent dermatological issue will provide vital insights for discovering novel management strategies and preventive measures.

Immune cells are categorized into innate immune cells, such as monocytes, macrophages, and dendritic cells, and adaptive immune cells mainly composed of B lymphocytes and T lymphocytes that carry out specific immune responses. Current studies have demonstrated that in the lesion area, innate immune cells primarily activate toll-like receptors through auxiliary receptors CD14 expressed by monocytes and macrophages to activate downstream nuclear transcription factor B (NF-KB), thereby positively regulating mRNA expression of pro-inflammatory factors.[7,8] Adaptive immune

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cells are activated by innate immunity to induce skin cell secretion of CXC8 for recruiting T lymphocytes around the hair follicle sebaceous gland unit to play an immunoregulatory role.[9] However, current studies only focus on certain types of immune cells while research on other immune cell phenotypes remains unknown, which limits our understanding regarding their involvement in acne development. Due to uncontrollable factors like economy and environment, large-scale observational analysis may lead to potential confounding factors or unmeasured reverse causality relationships; therefore exploring causal effects between various immune cell phenotypes and acne poses significant challenges.

Mendelian randomization (MR) is an experimental approach that employs genetic variation, specifically single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to infer causality.[10] By leveraging the principles of Mendelian independent assortment and random allocation, this method can effectively minimize confounding bias in observational studies.[11] In this study, we utilized MR to investigate the causal relationship between acne and 731 immune cell phenotypes.

Methods

Research Design

In this experiment, a two-way Mendelian randomization was conducted on acne and 731 immune cell phenotypes, adhering to the three fundamental principles of Mendelian randomization: 1) ensuring a robust correlation between instrumental variables and exposure factors to mitigate weak instrumental variable bias; 2) establishing no association between instrumental variables and confounding factors; 3) confirming that instrumental variables solely influence exposure intervention outcomes without any direct impact on the final results. The stability of the findings was validated through a series of sensitivity analyses. An overview of the study is depicted in Figure 1.

Data Source

Summary statistics for immune cell data were obtained from a meta-analysis of genome-wide association studies (GWAS) (ID: GCST90001391-GCST90002121), encompassing 3,757 participants from the Sardinian cohort.[12] A total of 731 immune cell phenotypes were identified, including absolute cell (AC) counts (n=118), median fluorescence

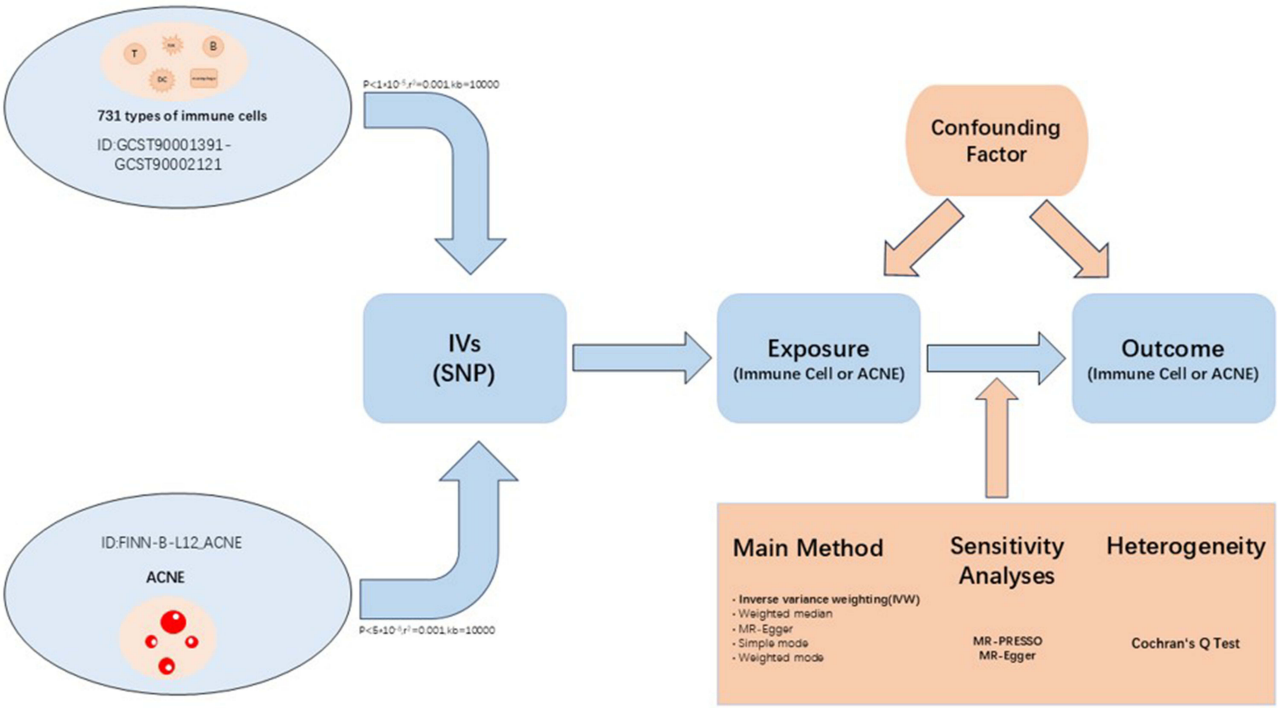

Figure 1 The overview of the study.

intensity (MFI) values (n=389), morphological parameters (MP) (n=32), and relative cell (RC) counts (n=192). Acne data was sourced from the FinnGen database (ID: finn-b-L12_ACNE), comprising information from 212,438 individuals in 2021 and analyzed across more than 16 million SNPs. According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings adopted by the National Science and Technology Ethics Committee of the People's Republic of China, ethical review can be exempted because the data used in this study do not cause any harm to human beings, do not involve any sensitive personal information or commercial interests, and the databases selected are open and legal.

Instrumental Variable Selection

The exposed data will be preliminarily filtered, including only SNPs with a significance level of p<1×10-5 for the 731 immune cell data and p<5×10-8 for acne data. Additionally, to ensure the validity and independence of the SNPs, we eliminate linkage disequilibrium using a threshold of r2=0.001 and kb=10000. Finally, to mitigate weak instrumental variable (IV) bias, we calculate the F-value for all IVs and consider those with an F-value greater than 10 as strong instrumental variables.[13]

Statistical Analysis

In this experiment, Mendelian randomization (MR) was employed to analyze the causal relationship between acne and immune cell activity. Initially, F-statistic calculation was conducted on the selected instrumental variables (IVs), where F=(Beta/Se)2. Only single nucleotide polymorphisms (SNPs) with an F value exceeding 10 were retained to ensure robustness of the instrumental variables and mitigate potential weak instrument bias.

The primary analysis method employed in the follow-up is the inverse variance weighted (IVW) random effects model. Additionally, we utilize supplementary analyses including the weighted median method, MR-Egger method, Simple mode method, and Weighted mode method. In cases where discrepancies arise among these five methods, IVW is selected as the benchmark approach. To ensure result stability and reliability, Cochran's Q statistic is calculated to quantify and assess potential heterogeneity. The level of horizontal pleiotropy is estimated through MR-Egger intercept test.[14] Furthermore, a leave-one-out analysis is conducted to examine sensitivity and evaluate whether this association is influenced by a single SNP. Furthermore, we also employed MR-PRESSO (Mendelian Randomization Pleiotropy Residual Sum and Outlier) to examine and rectify potential outliers.

To accurately assess the "direct" impact of various phenotypes on outcomes, we performed a secondary analysis using multivariable Mendelian randomization (MVMR) by grouping similar immune cells from positive results,[15,16] considering the potential interference of duplicate SNPs between different phenotypes. Only results with P<0.01 were included for analysis due to the extensive screening range.

Result

Description of Instrumental Variables

By applying a significance threshold (P<1×10-5) to filter the entire genome, conducting LD testing for removing linkage disequilibrium, and performing harmonization and F-value calculation, we carefully selected SNPs. To ensure strong correlation with the corresponding immune cell phenotypes, only SNPs with F-statistic values greater than 10 were retained. Supplementary Table S1 provides comprehensive information on these selected SNPs along with their associated statistics.

Positive MR Analysis Results

As depicted in Figure 2, among them, the levels of CD24+ CD27+ AC (OR=0.94, 95% CI: 0.91–0.98, P=0.0046), CD24+ CD27+% lymphocyte (OR=0.95, 95% CI: 0.92–0.99, P=0.0091), Secreting Treg AC (OR=0.97, 95% CI: 0.94–0.99, P=0.008), CD39+ secreting Treg %CD4 Treg (OR=094, 95% CI: 095−098, P=0051), CD24 on IgD + CD38br (OR=093, 95% CI: 088−098, P=0074) and CD28 on CD39 +CD4+(OR=090, 95% CI: 085−096, P=0014) were negatively associated with acne presentation, while the levels of CD20-CD38-AC (OR=1.17, 95% CI: 1.04−1.32,

panel	methods	nsnp	pval	OR(95%CI)
CD24+ CD27+ AC	MR Egger	25	0.009853603	0.93(0.89 to 0.98)
	Weighted median	25	0.017786746	0.93(0.88 to 0.99)
	Inverse variance weighted	25	0.004606542	0.94(0.91 to 0.98)
	Simple mode	25	0.471131579	0.93(0.76 to 1.13)
	Weighted mode	25	0.026610517	0.93(0.88 to 0.99)
CD20− CD38− AC	MR Egger	14	0.047205240	1.28(1.03 to 1.60)
	Weighted median	14	0.102143440	1.15(0.97 to 1.36)
	Inverse variance weighted	14	0.008838458	1.17(1.04 to 1.32)
	Simple mode	14	0.184146951	1.20(0.93 to 1.54)
	Weighted mode	14	0.109725431	1.21(0.97 to 1.50)
CD24+ CD27+ %lymphocyte	MR Egger	22	0.019560536	0.95(0.91 to 0.99)
	Weighted median	22	0.033693851	0.94(0.88 to 1.00)
	Inverse variance weighted	22	0.009148365	0.95(0.92 to 0.99)
	Simple mode	22	0.474595005	0.95(0.84 to 1.08)
	Weighted mode	22	0.020376765	0.95(0.90 to 0.99)
Secreting Treg AC	MR Egger	22	0.046914883	0.97(0.94 to 1.00)
	Weighted median	22	0.051904867	0.96(0.93 to 1.00)
	Inverse variance weighted	22	0.008037047	0.97(0.94 to 0.99)
	Simple mode	22	0.449434075	0.98(0.94 to 1.03)
	Weighted mode	22	0.028661982	0.96(0.94 to 0.99)
CD39+ secreting Treg %CD4 Treg	MR Egger	21	0.036514076	0.94(0.89 to 0.99)
	Weighted median	21	0.010165551	0.93(0.88 to 0.98)
	Inverse variance weighted	21	0.005092500	0.94(0.91 to 0.98)
	Simple mode	21	0.860399536	1.01(0.92 to 1.11)
	Weighted mode	21	0.014905994	0.94(0.89 to 0.98)
CD24 on IgD+ CD38br	MR Egger	25	0.003382946	0.89(0.83 to 0.95)
	Weighted median	25	0.007559050	0.91(0.84 to 0.97)
	Inverse variance weighted	25	0.007374119	0.93(0.88 to 0.98)
	Simple mode	25	0.251473062	0.92(0.79 to 1.06)
	Weighted mode	25	0.007993639	0.91(0.86 to 0.97)
CD28 on CD39+ CD4+	MR Egger	15	0.009050809	0.85(0.77 to 0.94)
	Weighted median	15	0.010943862	0.90(0.83 to 0.98)
	Inverse variance weighted	15	0.001439685	0.90(0.85 to 0.96)
	Simple mode	15	0.083420950	0.91(0.82 to 1.00)
	Weighted mode	15	0.015272941	0.90(0.83 to 0.97)
FSC−A on monocyte	MR Egger	19	0.102273756	1.06(0.99 to 1.12)
	Weighted median	19	0.070196276	1.06(1.00 to 1.13)
	Inverse variance weighted	19	0.005798050	1.07(1.02 to 1.13)
	Simple mode	19	0.058816639	1.26(1.01 to 1.59)
	Weighted mode	19	0.110236424	1.06(0.99 to 1.12)

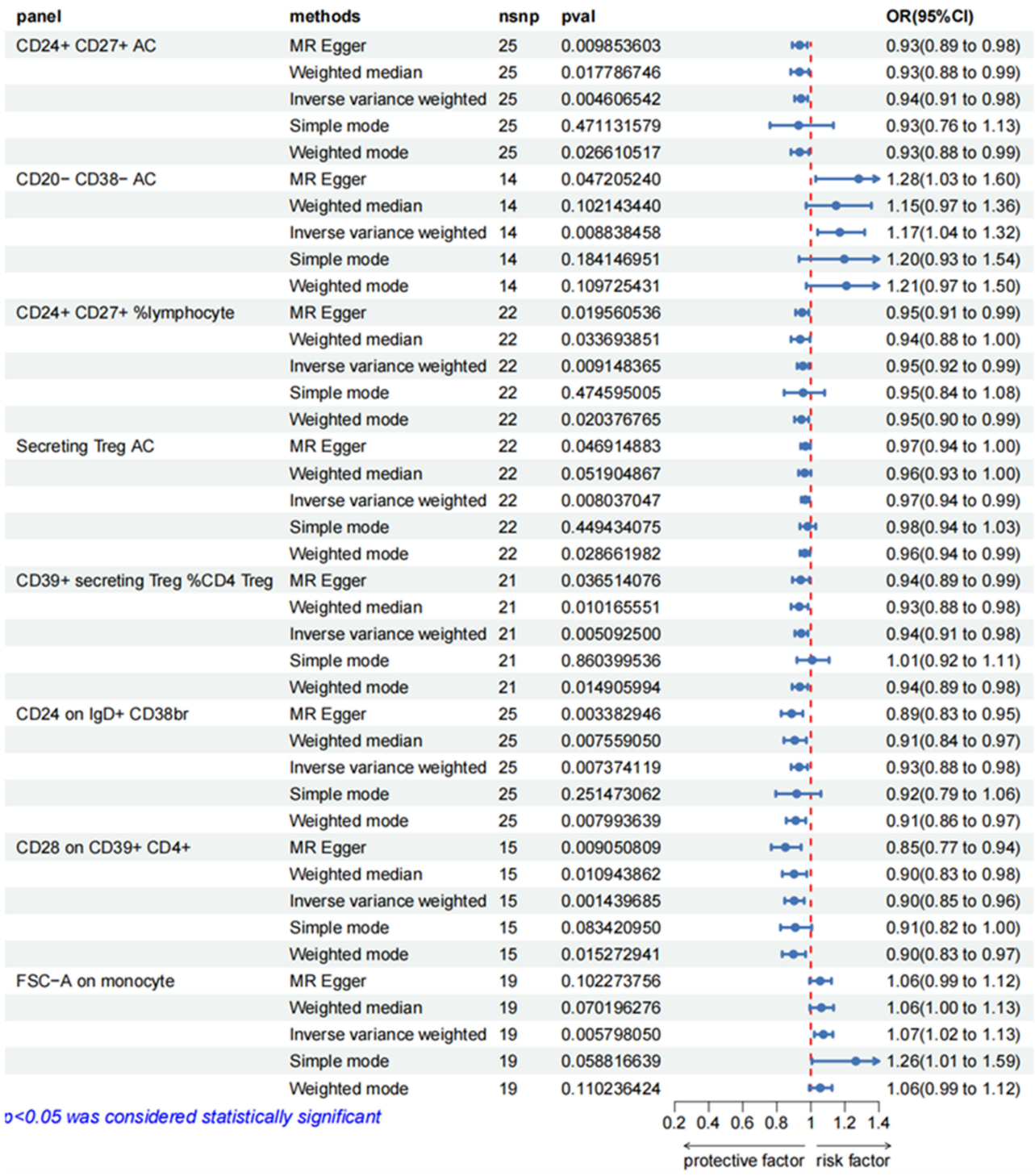

Figure 2 MR forest plot.

P=0.0088) and FSC-A on monocytes (OR=1.07, 95%CI: 1.02−1.13, P=0.0058) were positively correlated with acne presentation. Our results except for the Simple mode method result in the group of "CD39+ secreting Treg %CD4 Treg" exhibited some deviation from other results; however, the findings from other groups supported the IVW result which enhanced the robustness of our analysis outcomes. MR forest plot is presented in Figure 2, and MR effect plot can be observed in Figure 3. Detailed data for all five detection methods are provided in Supplementary Table S2.

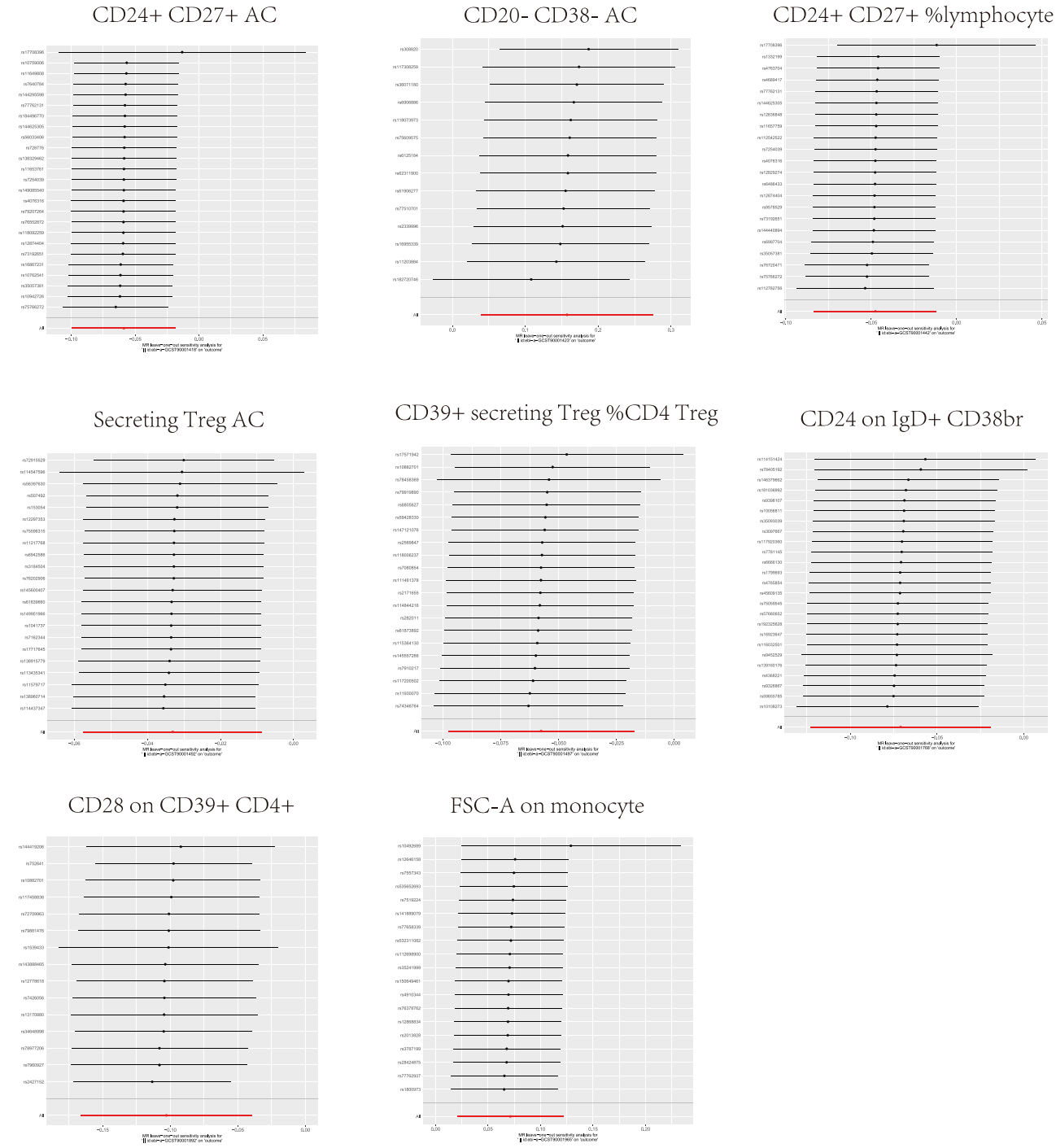

Figure 3 MR effect plot.

To ensure the absence of heterogeneity and validate the robustness of our findings, we performed Cochran's Q test for heterogeneity and Leave-one-out analysis. The results demonstrated no evidence of heterogeneity or multiple testing issues, thereby confirming the stability of our findings. Furthermore, the Leave-one-out analysis substantiated that our results were not influenced by a single SNP. Detailed information regarding heterogeneity and multiple testing can be found in Supplementary Table S3. Please refer to Figure 4 for the Leave-one-out plot.

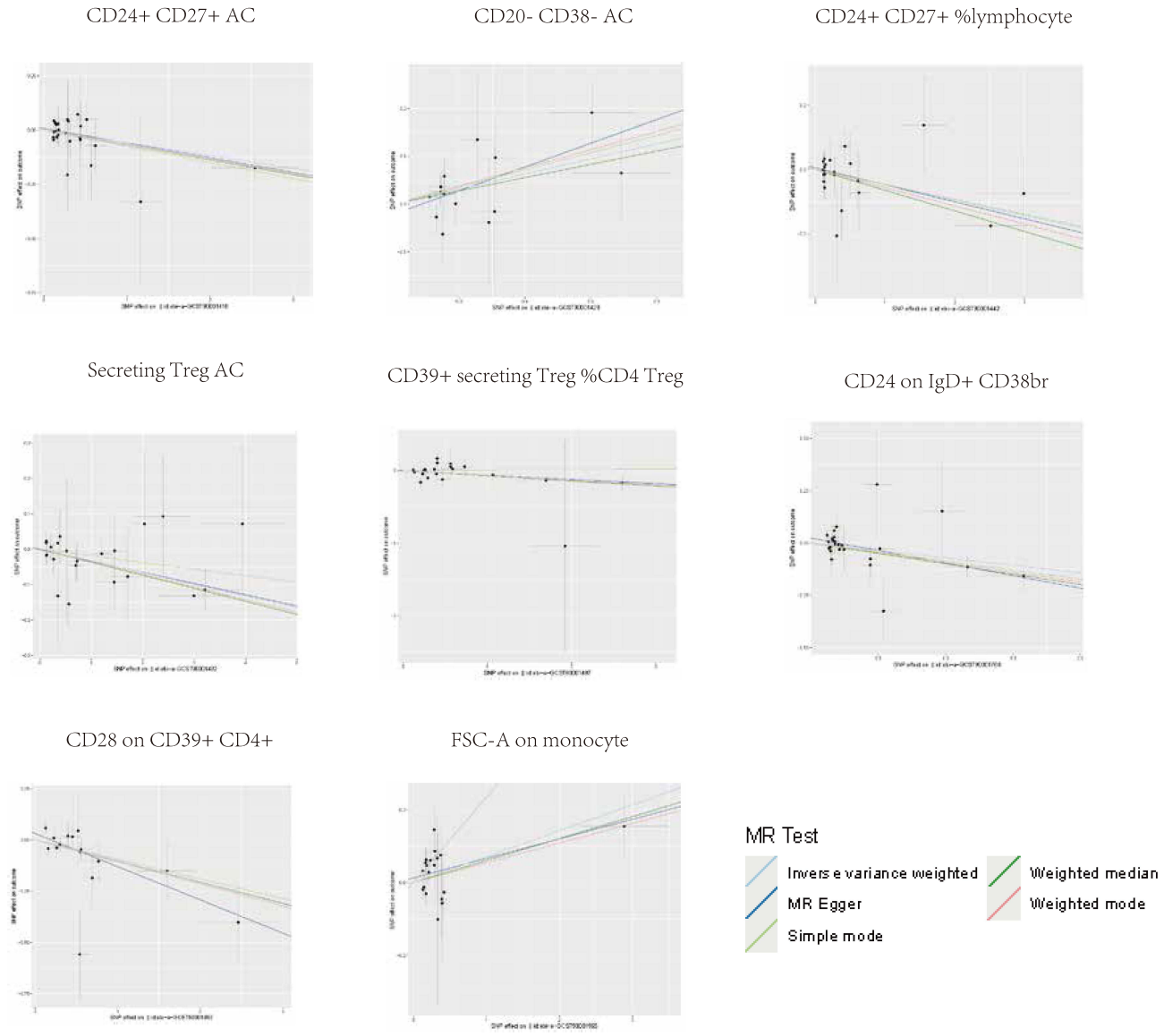

Figure 4 Leave-one-out plot.

Results of MVMR Analysis

No duplicate single nucleotide polymorphisms (SNPs) were identified upon merging the SNP data for immune cell phenotypes, thus obviating the need for conducting multivariable Mendelian randomization (MVMR).

Reverse MR Analysis Results

Following rigorous screening, no significant associations were observed between the remaining SNPs and 731 immune cell phenotypes in the acne dataset.

Discussion

Acne, an inflammatory skin disease affecting the hair follicle sebaceous gland unit, is clinically characterized by the presence of comedones, papules, nodules, and cysts. Inflammation and immune reactions represent the primary pathological features of acne that persist throughout its course. In this study, through comprehensive exploration of

genetic data, we have identified causal relationships between 731 types of immune cell phenotypes and acne. We observed close associations between eight specific immune cell types and acne: CD28 on CD39+ CD4+ T cell, CD39+ secreting CD4+ regulatory T cell, secreting CD4+ regulatory T cell, CD24+ CD27+AC, CD24 on IgD+ CD38br. FSC-A monocytes, as well as AC lacking expression for both CD20-CD38 markers. These findings suggest potential protective effects against acne for certain populations of immune cells while indicating a positive correlation between FSC-A monocytes orCD20-CD38-AC with acne risk.

CD28 on CD39+ CD4+ T cell, CD39+ secreting CD4+ regulatory T cell and secreting CD4+ regulatory T cell belong to the regulatory T cell (Treg) family, which suggests that Tregs may play a crucial role in acne development. Following antigen recognition, naive Helper T Cell 0 (Th0) differentiate into various subgroups such as Th1, Th2, Th17, and Treg.[17] In a healthy state, there exists a relative balance between effector cells where they mutually promote and inhibit each other. Whereas, disruption of this homeostasis leads to abnormal immune responses.[18] Studies have revealed an increased proportion of migrating neutrophils, monocytes, and activated mast cells at acne lesions while the infiltration rate of Treg cells significantly decreases.[19] Conversely, non-lesional areas of acne patients exhibit a notable increase in the infiltration rate of Treg cells indicating their potential importance in immunosuppression during acne. Activated T-cells differentiate into functional Tregs that actively regulate self-tolerance and exert anti-inflammatory effects. They secrete immunosuppressive factors such as IL-10 and TGF-β, which inhibit neutrophil chemotaxis and reduce inflammation factor release. Additionally, TGF-β acts as a regulator for activating t-cells by inhibiting their proliferation/activation thereby reducing Th1/Th17 reactions while inducing differentiation towards becoming a Tregs.[20] A reduction in the infiltration of Treg at the site of skin lesions was observed, resulting in an imbalance in the ratio of Th17 cells to Treg cells,[21,22] Th17 cells secrete characteristic cytokines such as interleukin-17 (IL-17), which activates the transcription factor 3 signaling pathway through synergistic interactions with specific cytokines. This activation induces the expression of retinoic acid-related orphan receptor gamma t,[23] thereby promoting the production of cytokines IL-6, IL −17, and IL −22 as well as releasing inflammation mediators to amplify inflammatory responses.[24]

CD24+ CD27+AC, CD24 on IgD+ CD38br as well as CD24+ CD27+lymphocyte are associated with the expression of CD24 and CD27. CD24 is a highly glycosylated protein consisting of 27 amino acids that acts as an effective anti-inflammatory mediator, playing crucial roles in key physiological processes such as cell adhesion, migration, differentiation, and apoptosis.[25] The extensively glycosylated extracellular domain of CD24 facilitates its interaction with various cell surface receptors (including P-selectin, Siglecs, and β1 integrins), thereby playing important roles in mediating intercellular communication, regulating immune responses, and maintaining tissue homeostasis. Studies have demonstrated that CD24 can bind to high mobility group box 1 (HMGB1) protein and heat shock proteins along with downstream Siglec10-SHP1 pathway to inhibit NF-κB signaling activation and suppress downstream inflammatory cytokine expression.[26] It can also negatively regulate T cell activation through the Siglec-15 signaling axis to inhibit T cell activity and proliferation while reducing inflammation factor release.[27] As a member of the tumor necrosis factor receptor superfamily, CD27 interacts with its ligand CD70 and is essential for normal differentiation processes of memory B cells and plasma cells.[28] After binding with CD70, CD27 can activate caspase and induce T cell apoptosis; or mediate memory T cell exhaustion through Smad3 and IL-2/STAT5 signaling.[29] Additionally, CD27 signal transduction can inhibit Treg cell apoptosis, promote the indirect increase of Treg cells, and suppress immune response.[30] Therefore, CD24+ CD27+AC, CD24 on IgD+ CD38br as well as CD24+ CD27+lymphocyte may potentially serve as protective factors for acne development. This protection could be attributed to the negative regulation of inflammation by both CD24 and CD27.

FSC-A monocytes belong to the mononuclear cell population, while CD20-CD38-AC cells are classified as dendritic cells. Both of these cell types are part of the innate immune system and play a crucial role in initiating adaptive immune responses.[31] Monocytes and dendritic cells act as antigen-presenting cells, efficiently internalizing, processing, and presenting antigens. They also serve as potent activators for initial T cell activation and resting T cell activation, promoting T cell proliferation and differentiation to induce adaptive immune responses. In normal conditions, immune cells constitute only 7% of skin cells, including 3.78% Langerhans cells, 0.45% NK cells, 0.24% monocytes, 0.79% dendritic cells, 0.41% T-cells and 1.33% other immune cells; innate immune cells account for more than 80% of skin immune cells.[32] Propionibacterium acnes is considered a significant contributor to acne development due to its strong

pro-inflammatory effects, which predominantly colonizes lipid-rich pilosebaceous units leading to follicular and perifollicular release of IL-6 and IL-8 along with induction of monocyte-dependent toll-like receptor mediated release of IL-1β, IL-12, and chemokines resulting in continuous amplification of inflammatory reactions.[33,34] Research has shown a substantial increase in infiltration by neutrophils, monocytes, and activated mast cells within the first 48 hours after acne occurrence, suggesting an active innate immunity response in acne patients.[19]

Randomized controlled trials are considered the gold standard for establishing causal relationships due to their ability to mitigate various biases and balance confounding factors that may arise during the design and implementation of clinical trials. However, ethical requirements, high costs, and implementation challenges often lead researchers to rely on observational studies for testing causal relationships.[35] Unfortunately, observational studies are susceptible to confounding bias. MR, a newly emerging research method utilizing genotypes to infer associations between phenotypes and diseases, employs single nucleotide SNPs as IVs for assessing causal effects between exposure factors and outcome events.[36] In this study, we employed genome-wide association study data in a comprehensive two-sample bidirectional analysis involving 731 immune cell phenotypes with acne using MR methodology in order to explore potential underlying causal relationships between immune cells and acne. It is important to note that the population included in this study consisted of individuals of European descent; further investigations are required to determine if these findings can be generalized across other ethnicities. Additionally, subgroup analyses based on disease progression or gender-specific susceptibility were not feasible within this study's scope; therefore, larger-scale studies or pooling additional GWAS data will remain necessary for selecting stronger associated genetic variations in MR investigations concerning inflammatory factors.

Disclosure

The authors report no conflicts of interest in this work.

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