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Rosacea and autoimmune liver diseases: a two-sample Mendelian randomization study

Wei Wu[1] · Huo-mu Tong[2] · Yun-sheng Li[1] · Jia Cui[2]

Abstract
Rosacea and autoimmune liver diseases (AILDs) are diseases closely associated with immune system abnormalities. AILDs primarily includes autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Currently, research on the association between these two conditions is limited. Therefore, this study employed the bidirectional Mendelian randomization (MR) method to investigate potential causal relationships between rosacea and AILDs based on genetic predictions. Summary data related to Rosacea, AIH, PSC, and PBC were obtained from public genome-wide association studies (GWAS). The inverse variance weighted (IVW) method was used as the primary analytical approach, supplemented by the MR-Egger, weighted mode method, weighted median, and simple mode. A series of sensitivity analyses were also conducted to identify heterogeneity and pleiotropy effects. The MR analysis results indicated a significant increase in the risk of rosacea being associated with PBC (OR = 1.09, 95% CI = 1.02–1.18, P = 0.014), but no such association was found with AIH or PSC. Furthermore, this study did not find a significant impact of rosacea on the risk of AILDs. This study represents the first in-depth exploration of the potential causal relationship between rosacea and AILDs using MR analysis. Thes findings suggest an increased risk of rosacea among PBC patients.

Keywords Rosacea · Autoimmune liver disease · Mendelian randomization · Autoimmune hepatitis · Primary sclerosing cholangitis · Primary biliary cholangitis

Introduction

Rosacea is a common chronic inflammatory skin disease prevalent among individuals aged 30–50 years and is characterized primarily by persistent erythema, recurrent papules, and pustules [1]. It is typically classified into four subtypes: papulopustular, phymatous, erythematotelangiectatic, and ocular rosacea [2, 3]. The pathogenesis of rosacea is complex and not fully understood, involving intrinsic factors such as genetics, psychological factors, and obesity, as well as extrinsic factors such as smoking, alcohol consumption, ultraviolet radiation, and specific microbes such as Demodex folliculorum, Propionibacterium acnes, and Helicobacter pylori infections. These factors contribute to neurovascular dysregulation, immune system abnormalities, and meibomian and sebaceous gland dysfunction, thereby triggering the disease. It not only leads to emotional issues such as low self-esteem and depression in patients, but also negatively impacts their quality of life, posing a significant burden on societal health.

Autoimmune liver diseases (AILDs) encompasses a group of chronic liver diseases characterized by abnormal immune responses that target the liver cells or bile ducts. These diseases are typically categorized into three types [4]. Autoimmune hepatitis (AIH) is characterized by hepatocellular damage, elevated liver enzymes, serum autoantibodies, and immunoglobulins [5]. Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease primarily caused by autoimmune-mediated injury to the intrahepatic bile duct epithelia, predominantly affecting middle-aged women [6]. Primary sclerosing cholangitis (PSC), on the other hand, is a relatively rare cholestatic liver disease characterized by multilayered fibrosis and bile duct obstruction

✉ Jia Cui
    cuijiadl@outlook.com

1   Department of Geriatrics, Chun'an First People's Hospital (Chun'an Branch of Zhejiang Provincial People's Hospital), Hangzhou 311700, Zhejiang Province, China

2   Department of Endocrinology, Chun'an First People's Hospital (Chun'an Branch of Zhejiang Provincial People's Hospital), Hangzhou 311700, Zhejiang Province, China

both intrahepatically and extrahepatically, more commonly affecting young to middle-aged men [6]. AILDs may initially be asymptomatic, but as the disease progresses, it can lead to complications, such as cirrhosis and hepatocellular carcinoma. Currently, there is no cure, and recurrence rates after liver transplantation are high, imposing substantial economic and medical burdens on patients and society. The etiology of AILDs is complex and involves factors such as immune responses, environment, and genetics [7]. Despite the identification of some risk factors, the exact pathogenic mechanisms remain unclear. AILDs are often associated with other autoimmune diseases, further exacerbating their severity.

Therefore, to elucidate the potential causal relationship between rosacea and AILDs, this study utilized the bidirectional Mendelian randomization (MR) method. MR has gained prominence in genetic and epidemiological research, owing to its unique advantages. Compared with traditional observational studies, MR leverages genetic variants naturally occurring at birth to significantly mitigate the influence of confounding factors, ensuring the objectivity and independence of research results. This technique relies on publicly available genome-wide association study (GWAS) data and utilizes genetic variations as instrumental variables (IVs) to assess the potential causal relationships between exposures and outcomes [8]. Because genes are immutable and follow Mendelian inheritance laws, MR effectively circumvents issues commonly encountered in observational studies, such as confounding factors, reverse causation, and measurement errors [9]. Thus, in the absence of randomized controlled trials, MR is an efficient and economical method to explore causal associations. This study employed bidirectional two-sample MR analyses supplemented by comprehensive sensitivity analyses to delve deeper into the causal relationship between rosacea and AILDs.

Material and methods

Study design

This study aimed to explore the potential causal relationship between rosacea and AILDs using bidirectional two-sample MR analysis. We utilized GWAS datasets of European ancestry, structured around three core hypotheses: first, IVs must be significantly associated with rosacea and other exposure factors; second, these IVs must be independent of confounding factors that could interfere with the exposure-outcome relationship and IVs can only affect outcomes through exposure factors, without other causal pathways. We meticulously selected single nucleotide polymorphisms (SNPs) associated with rosacea, AIH, PBC, and PSC as IVs, adhering strictly to the guidelines of the STROBE-MR (Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization) statement [10]. The datasets used in this study were obtained from public databases and had prior ethical approval, thereby obviating the need for additional ethical clearance. The MR design is illustrated in Fig. 1.

Data source

The FinnGen project, initiated in 2017, aims to collect biological samples from 500,000 participants in Finland to provide scientific insights into health improvements through genetic research. By leveraging resources from the FinnGen biobank, we investigated the genetic variations associated with rosacea. This biobank comprised 16,380,452 SNPs and 212,334 European samples, including 1195 rosacea cases and 211,139 controls (GWAS ID: finn-b-L12_ROSA-CEA). IVs related to AIH were sourced from 220 human

Fig. 1 The flowchart of the MR analysis. IVs, instrumental variables; *MR*, Mendelian randomization; *ROS*, rosacea; *AIH*, autoimmune hepatitis; *PBC*, Primary biliary cholangitis; *PSC*, Primary sclerosing cholangitis
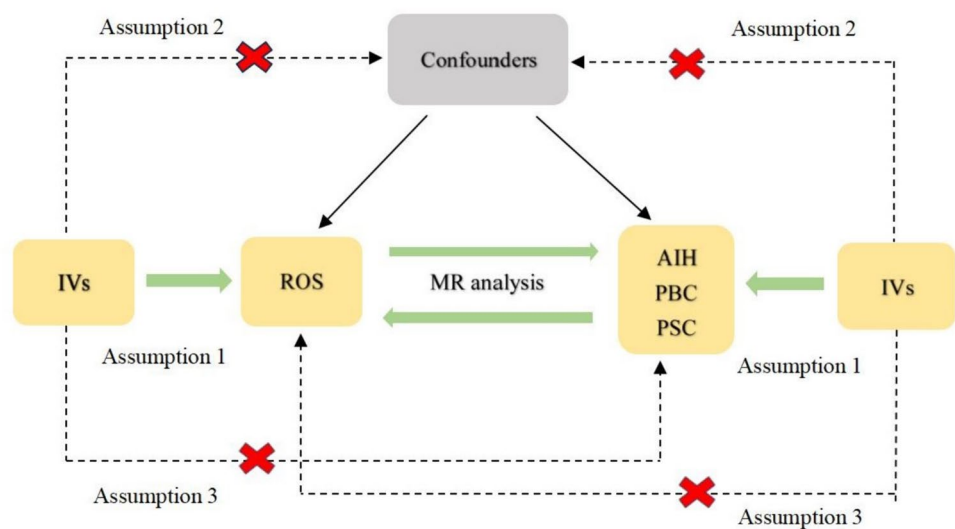
phenotype genetic correlation maps, encompassing 821 European patients and 484,413 European controls, involving 24,198,482 SNPs (GWAS ID: ebi-a-GCST90018785). The IVs for PBC were derived from the largest international genome-wide meta-analysis to date, including 8021 European patients and 16489 European controls, with 5,004,018 SNPs (GWAS ID: ebi-a-GCST90061440). IVs for PSC were obtained from the most comprehensive PSC GWAS conducted by the International PSC Study Group (IPSCSG), comprising 2871 European PSC patients and 12019 European controls, involving 7,891,603 SNPs (GWAS ID: ieu-a-1112). Detailed information regarding the GWAS data used in this study is presented in Table 1.

Instrumental variable selection

Before conducting the MR analysis, we rigorously screened the IVs to ensure that they were both significant and independent. First, we selected SNPs with genome-wide significance ($P < $5e-8) [11]. Given the limited number of SNPs meeting the criteria for rosacea and AIH, we appropriately relaxed the P-value threshold to $<$5e-6 to ensure an adequate sample size. Second, to ensure the independence of SNPs, we set a linkage disequilibrium (LD) threshold such that the LD r^2 value within 10000 base pairs was less than 0.001, excluding SNPs with palindromic sequences. As we were unable to use PhenoScanner V2, we manually removed SNPs related to confounding factors using multiple online databases, such as IEU Open GWAS and GWAS Catalog. Subsequently, we used MR-polynomial residuals and outliers (MR-PRESSO) to identify and remove outlier SNPs and further corrected the results to ensure that no horizontal pleiotropy existed among selected SNPs. Finally, we calculated the F value $=$ [beta/SE]^2 for each SNP, requiring an F-value $>$ 10 to ensure sufficient instrument strength and to minimize potential bias. These carefully selected SNPs served as IVs for subsequent MR analyses.

MR analysis

MR analysis primarily employed the inverse variance weighted (IVW) method to explore the correlations between rosacea and the risks of AIH, PBC, and PSC. We assessed the heterogeneity among the IVs using Cochran's Q test. When the P-value of Cochran's Q test was $<$ 0.05, indicating heterogeneity, we used the IVW random effects model for analysis; if the P-value was $\geq$ 0.05, we employed the fixed effects model. To ensure the robustness of our findings, we complemented the IVW with MR-Egger, weighted median, simple mode, and weighted mode for validation. Additionally, we utilized various methods such as MR-PRESSO, MR-Egger intercept, funnel plots, and forest plots to examine potential pleiotropy and comprehensively assess the robustness of the results. Furthermore, to determine whether specific SNPs influenced the causal estimates, we conducted leave-one-out analyses. Statistical analyses were conducted using R software (version 4.3.2) with the "TwoSampleMR" (v.0.5.8) and "MR-PRESSO" (v.1.0) packages, with a significance level set at $P < 0.05$.

Results

Selection of IVs

Using rosacea as an exposure factor, we successfully identified and selected 13 SNPs through a rigorous screening process. After further analysis, we excluded the confounding factor rs79440702, ultimately determining 12 SNPs as IVs for the subsequent in-depth analysis. Similarly, using AIH, PBC, and PSC as exposure factors, and based on the screening method described in detail earlier, this study identified 10, 35, and 11 SNPs associated with these exposure factors, respectively. The F-values of all included SNPs were significantly greater than 10, which is a strict criterion that avoids potential bias introduced by weak IVs. Detailed information on the SNPs is provided in the Table S1–S6.
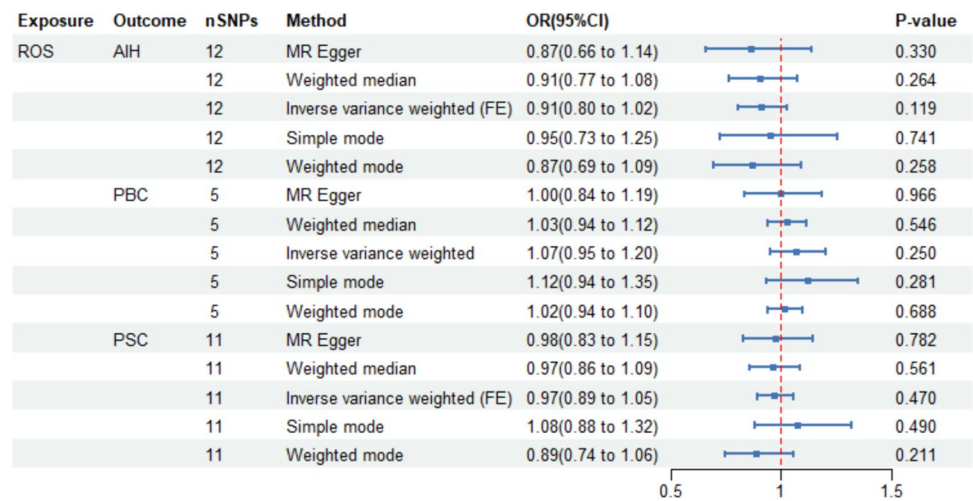
Causal effects of *rosacea* on AILDs

The results of the IVW estimation indicated that there was no significant association between genetically predicted rosacea and the risk of AIH (OR $=$ 0.91, 95% CI $=$ 0.80–1.02, $P =$ 0.119) (Fig. 2). Additionally, the results from the MR-Egger method (OR $=$ 0.87, 95% CI $=$ 0.66–1.14, $P =$ 0.330), weighted median (OR $=$ 0.91,

Table 1 Baseline characteristics of the rosacea and autoimmune liver diseases database

Phenotype	Year	GWAS ID	Population	Sex	Ncase	Ncontrol	Number of SNPs
Rosacea	2021	finn-b-L12_ROSACEA	European	F/M	1195	211,139	16,380,452
AIH	2021	ebi-a-GCST90018785	European	F/M	821	484,413	24,198,482
PBC	2021	ebi-a-GCST90061440	European	F/M	8021	16489	5,004,018
PSC	2017	ieu-a-1112	European	F/M	2871	12019	7,891,603

GWAS genome-wide association studies; *SNPs* single nucleotide polymorphisms; *AIH* autoimmune hepatitis; *PBC* primary biliary cholangitis; *PSC* primary sclerosing cholangitis; *F/M* female/male

Fig. 2 MR estimates the causal effect of rosacea on AILDs. *ROS* rosacea; *AILDs* autoimmune liver diseases; *AIH* autoimmune hepatitis; *PBC* Primary biliary cholangitis; *PSC* Primary sclerosing cholangitis; *SNPs* single nucleotide-polymorphisms; *MR* Mendelian randomization; *FE* fixed effect; *OR* odds ratio; *CI* confidence interval

Exposure	Outcome	nSNPs	Method	OR(95%CI)	P-value
ROS	AIH	12	MR Egger	0.87(0.66 to 1.14)	0.330
		12	Weighted median	0.91(0.77 to 1.08)	0.264
		12	Inverse variance weighted (FE)	0.91(0.80 to 1.02)	0.119
		12	Simple mode	0.95(0.73 to 1.25)	0.741
		12	Weighted mode	0.87(0.69 to 1.09)	0.258
	PBC	5	MR Egger	1.00(0.84 to 1.19)	0.966
		5	Weighted median	1.03(0.94 to 1.12)	0.546
		5	Inverse variance weighted	1.07(0.95 to 1.20)	0.250
		5	Simple mode	1.12(0.94 to 1.35)	0.281
		5	Weighted mode	1.02(0.94 to 1.10)	0.688
	PSC	11	MR Egger	0.98(0.83 to 1.15)	0.782
		11	Weighted median	0.97(0.86 to 1.09)	0.561
		11	Inverse variance weighted (FE)	0.97(0.89 to 1.05)	0.470
		11	Simple mode	1.08(0.88 to 1.32)	0.490
		11	Weighted mode	0.89(0.74 to 1.06)	0.211

95% CI = 0.77–1.08, $P = 0.264$), simple mode (OR = 0.95, 95% CI = 0.73–1.25, $P = 0.741$), and weighted mode (OR = 0.87, 95% CI = 0.69–1.09, $P = 0.258$) suggested no significant correlation between genetic variations in rosacea and AIH (Fig. 2 and Fig. S1). We did not detect significant heterogeneity (Cochran's Q test: $P = 0.115$) or pleiotropy (MR-PRESSO global test: $P = 0.162$; MR-Egger regression: intercept = 0.019, $P = 0.690$) (Table 2). No association was found between genetically predicted rosacea (OR = 1.07, 95% CI = 0.95–1.20, $P = 0.250$) and the risk of PBC (Fig. 2 and Fig. S2). Although heterogeneity was observed in this analysis (P-value < 0.05 in Cochran's Q test), it was acceptable because this study primarily employed a random-effects IVW for analysis. For PBC, no pleiotropy was detected (MR-PRESSO global test: $P = 0.185$; MR-Egger regression: intercept = 0.048, $P = 0.369$) (Table 2). Similarly, no association was found between genetically predicted rosacea (OR = 0.97, 95% CI = 0.89–1.05, $P = 0.470$) and the risk of PSC, and no heterogeneity was detected in this analysis (Cochran's Q test: $P = 0.823$) or pleiotropy (MR-PRESSO global test: $P = 0.768$; MR-Egger regression: intercept = − 0.003, $P = 0.916$) (Fig. 2, Fig. S3 and Table 2).

Causal effects of AILDs on *rosacea*

This study also conducted a reverse MR analysis to evaluate the potential causal effects of AILDs on rosacea. Genetic prediction indicated a causal relationship between PBC and the risk of rosacea. Using IVW estimation, we observed that having PBC might increase the risk of rosacea by 9.0% (OR = 1.09, 95% CI = 1.02–1.18, $P = 0.014$) (Fig. 3 and Fig. 4). In the pleiotropy analysis, we detected no significant pleiotropy (MR-PRESSO global test: $P = 0.099$; MR-Egger regression: intercept = 0.037, $P = 0.209$) and no heterogeneity (Cochran's Q test: $P = 0.084$) (Table 2). There was no association between AIH (OR = 1.07, 95% CI = 0.97–1.17,

$P = 0.175$) and the risk of rosacea, and no pleiotropy (MR-PRESSO global test: $P = 0.813$; MR-Egger regression: intercept = − 0.015, $P = 0.727$) or heterogeneity (Cochran's Q test: $P = 0.822$) was detected in this analysis (Fig. 3, Fig. S4 and Table 2). Similarly, no correlation was found between PSC (OR = 0.94, 95% CI = 0.84–1.06, $P = 0.308$) and risk of rosacea (Fig. 3 and Fig. S5). In subsequent analyses, we detected no pleiotropy (MR-PRESSO global test: $P = 0.306$; MR-Egger regression: intercept = − 0.031, $P = 0.477$) or heterogeneity (Cochran's Q test: $P = 0.326$) (Table 2).

Discussion

This study employed the bidirectional two-sample MR method to investigate the causal relationship between rosacea and AILDs for the first time. The study findings demonstrated a positive association between PBC and rosacea, indicating an increased risk of rosacea with PBC, but no reverse causation was found. However, when analyzing other AILDs such as AIH and PSC, no significant statistical correlation with rosacea was observed. Similarly, rosacea did not significantly influence the prevalence of AIH or PSC.

Despite the distinct primary sites of rosacea (predominantly affecting the central facial skin) and AILDs (primarily affecting the hepatobiliary system), both conditions are closely associated with immune dysfunction. Rosacea, as an inflammatory skin disease, shares mechanistic links with immune system dysregulation, while AILDs, as autoimmune diseases, also involve immune response dysfunctions. Nevertheless, research on the association between these two diseases remains insufficient, highlighting the importance of further investigation in this field.

Whereas AIH, PBC, and PSC fall under category of AILDs, each has unique pathological characteristics. AIH is mainly characterized by hepatocellular damage, PBC by

Table 2 Heterogeneity and pleiotropic test results

Exposure	Outcome	Heterogeneity						Pleiotropy			MR-PRESSO (global test)	
		MR-Egger			IVW			MR-Egger				
		Q	Q_df	Q_pval	Q	Q_df	Q_pval	Intercept	SE	P-value	RSSOBs	P-value
Rosacea	AIH	16.48520795	10	0.086559792	16.76249848	11	0.115099758	0.018627124	0.045417737	0.69035991	19.69803	0.162
	PBC	8.204397743	3	0.041971003	11.24317567	4	0.0239628	0.047849301	0.045392996	0.369226798	24.2202	0.185
	PSC	5.89786793	9	0.750095019	5.909697123	10	0.822792153	−0.00272353	0.02504117	0.915777487	7.891347	0.768
AIH	Rosacea	5.011021113	8	0.756497533	5.141648619	9	0.821789645	−0.014747491	0.04080382	0.72714158	6.367918	0.813
PBC	Rosacea	41.35292427	31	0.101271438	43.55581236	32	0.083609301	0.03669979	0.028558778	0.208289538	46.18636	0.099
PSC	Rosacea	10.75928167	9	0.292570553	11.41788441	10	0.325900562	−0.030675006	0.041327894	0.476868411	14.32989	0.306

MR Mendelian randomization; *IVW* inverse variance weighting; *MR-PRESSO* MR Pleiotropy RESidual Sum and Outlier; *SE* standard error; *AIH* autoimmune hepatitis; *PBC* primary biliary cholangitis; *PSC* primary sclerosing cholangitis

non-suppurative destructive cholangitis and chronic cholestasis, and PSC by onion-skin fibrosis of intrahepatic and extrahepatic bile ducts [5, 12, 13]. These differences are likely to stem from the distinct nature of each disease. Furthermore, patients with AILD often present with various skin symptoms, such as butterfly rash, pigmentation, and itching. Patients AIH and PBC are susceptible to conditions like alopecia areata, vitiligo, and psoriasis [14]. However, owing to the frequent association of PSC with inflammatory bowel disease, its relationship with skin diseases remains unclear.

The onset of rosacea is closely linked to keratinocytes, which produce pro-inflammatory factors that recruit and activate immune cells, especially T cells [15]. In rosacea patients, toll-like receptor 2 (TLR2) levels significantly increase, potentially leading to the enhanced expression of kallikrein 5 (KLK5) and antimicrobial peptides [16, 17]. KLK5 promotes the expression of LL-37, which triggers inflammatory responses [18]. LL-37, particularly in mast cells, activates degranulation and the release of inflammatory mediators, and plays a crucial role in leukocyte chemotaxis and inflammation-related angiogenesis. In contrast, specific antibodies, such as anti-smooth muscle antibodies or anti-mitochondrial antibodies (AMA), are often detected in AILDs. These antibodies may activate B and T cells, leading to uncontrolled immune responses to self-antigens. Notably, various HLA alleles are associated with the onset of both rosacea and AILDs, suggesting that individuals carrying predisposing autoimmune genes may be more susceptible to multiple autoimmune diseases [19].

Our results indicate a clear causal impact of PBC on rosacea; however, the influence of rosacea on PBC is not significant. This phenomenon may be due to the limited sample size of rosacea cases in GWAS, potentially biasing the accurate assessment of reverse causality individuals with PBC may be more susceptible to rosacea, but rosacea itself does not drive the progression of PBC. Furthermore, immune dysregulation associated with PBC may be a contributing factor to the onset of rosacea.

The MR method effectively mitigated the biases commonly found in observational studies, such as reverse causation and confounding factors. All SNPs included in our study had F-statistics greater than 10, thus minimizing potential biases from weak IVs. Sensitivity analyses further ensured the accuracy of the causal estimates and the robustness of our results. However, this study has several limitations. Although we focused on the causal relationships between rosacea and subtypes of AILDs, we did not delve into the specific impacts of rosacea subtypes. Additionally, our study population was primarily based on European ancestry, potentially introducing biases due to racial differences. The limited availability of IVs prompted us to set a low *P*-value threshold ($P < 5e\text{-}6$)

Fig. 3 MR estimates the causal effect of AILDs on rosacea. *AILDs* autoimmune liver diseases; *AIH* autoimmune hepatitis; *PBC* Primary biliary cholangitis; *PSC* Primary sclerosing cholangitis; *ROS* rosacea; *SNPs* single nucleotide-polymorphisms; *MR* Mendelian randomization; *FE* fixed effect; *OR* odds ratio; *CI* confidence interval

Exposure	Outcome	nSNPs	Method	OR(95%CI)	P-value
AIH	ROS	10	MR Egger	1.10(0.90 to 1.35)	0.365
		10	Weighted median	1.11(0.99 to 1.25)	0.084
		10	Inverse variance weighted (FE)	1.07(0.97 to 1.17)	0.175
		10	Simple mode	1.10(0.91 to 1.35)	0.350
		10	Weighted mode	1.12(0.95 to 1.33)	0.213
PBC	ROS	33	MR Egger	0.94(0.73 to 1.20)	0.628
		33	Weighted median	1.06(0.95 to 1.18)	0.290
		33	Inverse variance weighted (FE)	1.09(1.02 to 1.18)	0.014
		33	Simple mode	1.03(0.83 to 1.28)	0.757
		33	Weighted mode	1.05(0.90 to 1.24)	0.532
PSC	ROS	11	MR Egger	1.01(0.80 to 1.28)	0.912
		11	Weighted median	0.91(0.78 to 1.07)	0.248
		11	Inverse variance weighted (FE)	0.94(0.84 to 1.06)	0.308
		11	Simple mode	1.01(0.76 to 1.33)	0.961
		11	Weighted mode	0.86(0.72 to 1.03)	0.141
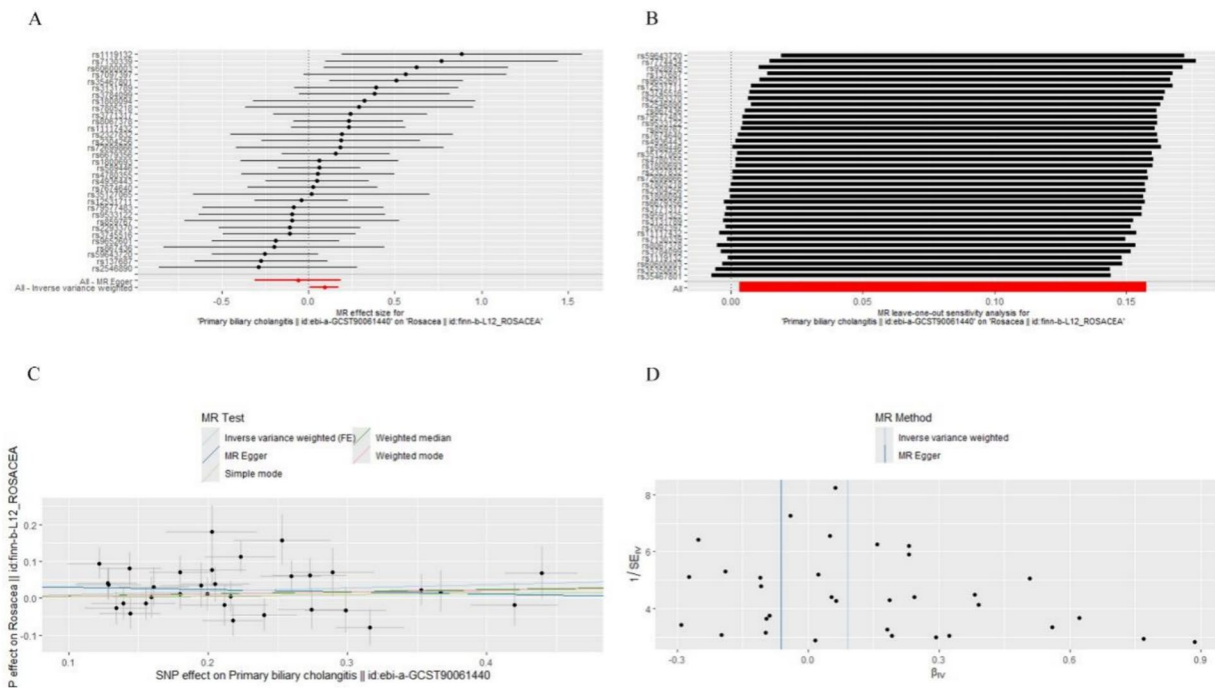
Fig. 4 Forest plot (**A**), leave-one-out analysis (**B**), scatter plot (**C**) and funnel plot (**D**) of the causal effect of primary biliary cholangitis on rosacea

when considering rosacea and AIH as exposure factors. Furthermore, differences between the two sample MR analyses in terms of gender, age, socioeconomic background, etc. may affect the interpretation of causal estimates and potentially weaken causal inferences. Despite efforts to identify potential confounding factors, unmeasured confounders and horizontal pleiotropy effects remain challenging to eliminate. Future research should strive to overcome these limitations to gain a deeper understanding of the complex relationship between rosacea and AILDs.

Conclusion

This study provides evidence of causal relationships between rosacea and AILDs risks. These findings provide new perspectives for the diagnosis and treatment of rosacea and AILDs. The study not only deepens our understanding of the relationship between rosacea and AILDs, but also offers new directions for future research.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Not applicable.

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