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Research article

Causal associations between systemic lupus erythematosus and primary biliary cholangitis: A bidirectional Mendelian randomization study

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ABSTRACT

Objectives: The association between systemic lupus erythematosus (SLE) and primary biliary cholangitis (PBC) has been increasingly recognized. However, the existence of causal connections between SLE and PBC has yet to be established. In this study, we aimed to investigate the bidirectional causation between SLE and PBC utilizing Mendelian randomization (MR) analysis.
Methods: We acquired summary data from Genome-wide association studies (GWAS) for SLE and PBC from the IEU Open GWAS and FinnGen database. The inverse variance weighted (IVW) was employed as the key method to ascertain the causality between SLE and PBC. Subsequently, a range of sensitivity analyses were applied. We also performed a fixed-effects model meta-analysis to combine the MR results from different databases. Moreover, multivariable MR were conducted to clarify the roles of potential confounding factors.
Results: Our univariable MR investigation provided compelling evidence supporting a causal relationship between SLE and PBC in both directions. Specifically, the IVW method demonstrated a strong casual effect of SLE on PBC (odds ratio (OR) = 1.17, 95 % confidence interval (CI) = 1.09–1.25, $p < 0.001$). In addition, the results of reverse MR analysis revealed that genetically predicted PBC was associated with an increased risk of SLE (OR = 1.39, 95 % CI = 1.32–1.45, $p < 0.001$). The sensitivity analyses indicated the absence of horizontal pleiotropy and heterogeneity. Furthermore, the causality between SLE and PBC remained significant even after adjusting for common risk factors in the multivariable MR analysis.
Conclusions: Our study provides statistical evidence of a potential causal relationship between SLE and PBC, but further research is needed to the explore of the underlying mechanisms of these disorders.

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1. Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is characterized by the loss of small-to-medium-sized intrahepatic bile ducts [1]. If left controlled, PBC can progress to fibrosis, cholestasis, and eventually liver cirrhosis [2]. Women are nine times more likely to develop PBC than men, with a notably high incidence in those of European and North American descent [3,4]. The prevalence of PBC is on the rise worldwide, with increasing rates reported in various regions. According to incomplete statistics, the prevalence of PBC in China and Japan has been documented to 55/100,000 and 49/100,000, respectively [5,6]. Treatment with ursodeoxycholic acid (UDCA) has shown promising results in improving serum liver examination results, histological characteristics, and the survival rate of PBC patients [7,8]. Nevertheless, a sizable of PBC patients—roughly 40%—fail to respond favorably to UDCA treatment [8]. PBC and immune-mediated diseases outside the liver, such as inflammatory bowel disease, Sjögren's syndrome, and rheumatoid arthritis, have been reported in earlier studies [9–11].

Systemic lupus erythematosus (SLE) is a longstanding diffuse connective tissue disease with unknown causes that can have multiple systems throughout the body, including the cardiovascular, hematologic, renal, liver, and central nervous system [12,13]. The prevalence of SLE is estimated to range from 13 to 7713.5 cases per 100,000 individuals worldwide [14]. In recent years, an emerging group of studies has reported the co-occurrence of SLE and PBC. Several published research have demonstrated an incidence of PBC in SLE patients of less than 2 % [15–18]. In addition, another large-scale study revealed that individuals with PBC had a considerably

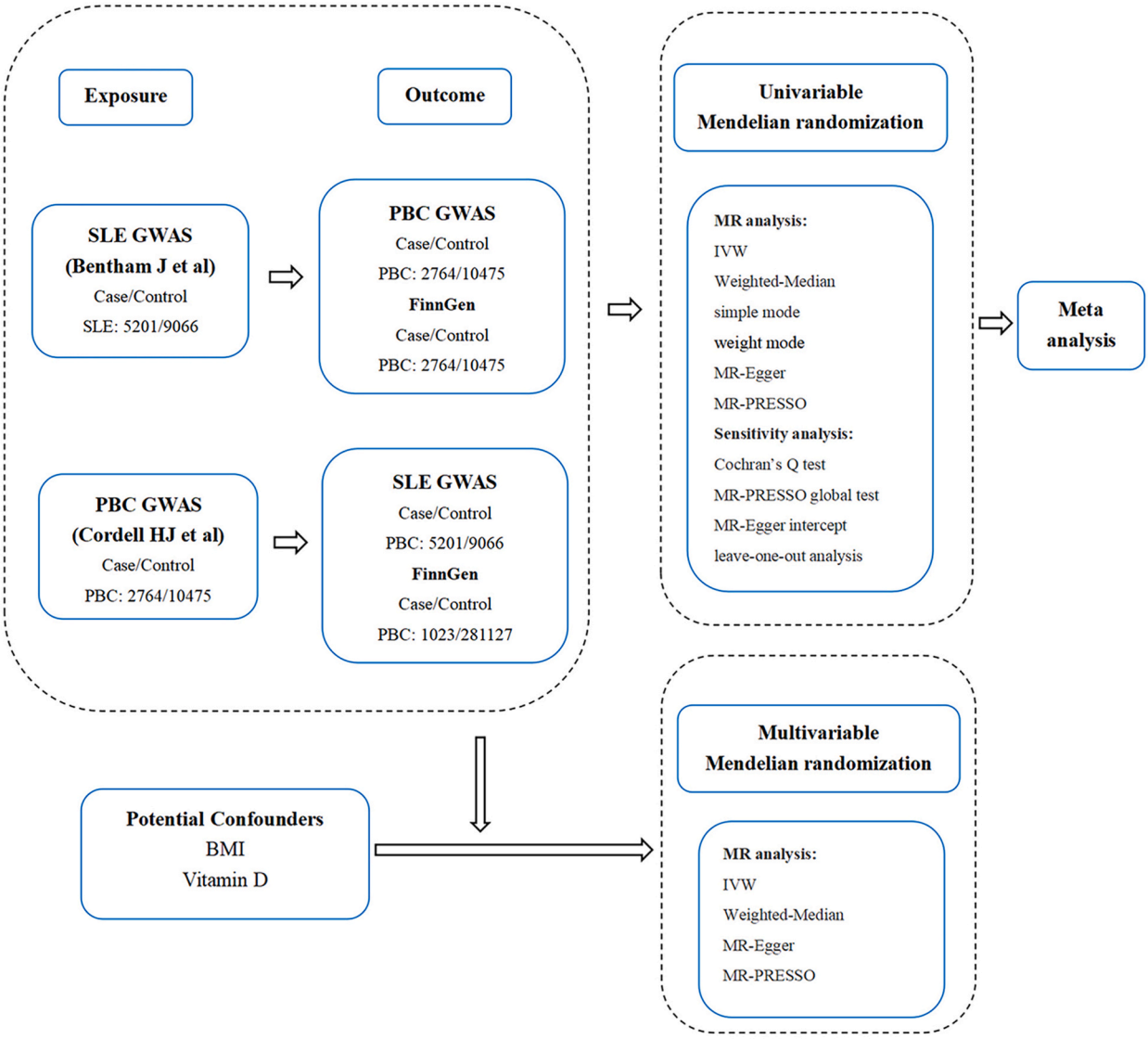

Fig. 1. Schematic overview of the present study. SLE, Systemic lupus erythematosus; PBC, Primary biliary cholangitis; IVW, inverse variance weighted; MR-PRESSO, MR Pleiotropy residual sum and outlier; BMI, body mass index.

greater incidence of SLE compared to controls [19]. However, the presence of unmeasured confounding factors and potential reverse causality can weaken the link between exposure and outcome in typical epidemiological research. Therefore, it is imperative to conduct additional studies to assess the causality between these illnesses.

Mendelian randomization (MR), similar to randomized controlled trials (RCTs), utilizes genetic variations as instrumental variables to detect and quantify causality [20]. Unlike observational epidemiologic studies, MR studies are not subject to the general confounders or reverse causality issues. To the authors' knowledge, MR between SLE and PBC has not been investigated. In the present research, a bidirectional MR examination was carried out to ascertain the existence of a causal relationship between the two conditions. Investigating the causal relationship between SLE and PBC is important for better understanding the pathogenesis of these two diseases and facilitating early detection and treatment.

2. Materials and methods

2.1. Study design and data resources

Fig. 1 depicts a detailed explanation of the current study design. Single-nucleotide polymorphisms (SNPs) were employed as instrumental variables (IVs) in our MR analysis to evaluate the causal relationships between SLE and PBC [21]. Three suppositions are met by MR studies: (a) IVs have a strong relationship with exposure; (b) IVs are unaffected by confounding factors; (c) IVs do not directly impact the outcome but may do so indirectly through the exposure. The initial MR analysis explored the association between SLE and PBC result in terms of causality, while the subsequent MR analysis examined the reverse causality. Since our analysis was built on summary data from ethically approved published studies [22–24], no additional approval was necessary. This study was performed according to the most recent (STROBE-MR) guidelines [25].

The most recent and comprehensive genome-wide association studies (GWAS) meta-analysis conducted by three consortiums provided the summary statistics for SLE, including 5,201 cases and 9,066 controls [22]. Another GWAS data for SLE came from the FinnGen release R9 [23], with 1,023 cases and 281,127 controls. Genetic instruments for the PBC were sourced from a large meta-analysis (2,764 cases and 10,475 controls) [24] and FinnGen release R9 (557 cases and 281,127 controls) [23] provided the genetic tools for the PBC dataset. There were no overlap populations between the exposures and outcomes.

2.2. Instrumental variable selection

To ensure the robustness of our MR analysis, SNPs were rigorously selected based on specific criteria aligned with the three core assumptions. First, SNPs that exhibited significantly correlations to SLE and PBC at a threshold of $p < 5 \times 10-8$ were selected. Besides, we eliminated SNPs in linkage disequilibrium (LD) ($r2 < 0.001$, $kb = 10,000$) to guarantee the independence of the SNPs. In addition, SNPs linked to confounding factors were deleted by scanning PhenoScannerV2 [26]. The strength of the selected SNPs was evaluated using F statistics, which were calculated as $[beta/SE]^2$ [27,28]. The SNP was excluded from the analysis when the F statistic was below 10. Finally, we calculated the statistical power for this MR [29].

2.3. Univariable mendelian analysis

Prior to analysis, the exposure and outcome data were harmonized to ensure that every IV had been matched to the same effect alleles [30]. Subsequently, outlier SNPs were removed based on MR pleiotropy residual sum and outlier (MR-PRESSO) analysis to obtain a consistent outcome [31]. The MR analysis was then conducted in two directions: examining the causality of SLE to PBC, followed by investigating the causal outcome of PBC to SLE. The inverse variance weighted (IVW) method was applied as the key procedure of analyses [32]. To further improve accuracy and stability, other techniques such as the weighted median, simple mode, weight mode, MR-Egger regression, and MR-PRESSO method were utilized [33,34]. Causative estimates were expressed using odds ratios (ORs) with 95 % confidence intervals (CIs), and significance was defined as $p < 0.05$.

2.4. Multivariable mendelian analysis

Multivariable MR analysis, an advanced form of MR, was utilized to conduct a more comprehensive examination of the causal relationship between SLE and PBC while accounting for confounding factors [35]. Specifically, in our study, multivariate MR analysis was employed to confirm the credibility of causality after adjusting for common risk factors such as smoking, alcohol consumption, Body Mass Index (BMI), vitamin D, inflammatory bowel disease and its subtypes, and celiac disease, previously identified in the literature as associated with both SLE and PBC [11,36–40]. For the multivariable MR (MVMR) analysis, IVW served as the primary analysis method, supported by MR-Egger, weighted median, and MR-PRESSO approaches.

2.5. Sensitivity analyses

We performed multiple sensitivity studies in order to understand the potential pleiotropy. First, Cochran's Q test was used to assess where heterogeneity existed [41]. A fixed-effects IVW model was included if there was no heterogeneity ($P > 0.05$) [42]. Furthermore, the horizontal pleiotropy of SNPs was assessed using the MR-Egger and MR-PRESSO global tests [34]. No horizontal pleiotropy was found when the intercept of MR-Egger did not deviate from zero, and findings were shown by scatter plots. Moreover, the

leave-one-out analysis was employed to examine the influence of individual SNPs on the outcomes. Finally, the results obtained from each outcome study were pooled by fixed-effects meta-analysis.

All statistics were analyzed by using TwoSampleMR (0.5.7), MRPRESSO (1.0), and meta package (6.5.0) in R software (Version 4.3.0).

3. Results

3.1. Univariable MR analysis

3.1.1. Causal effect of SLE on PBC

According to the IVs screening criteria in our study, 6 SNPs related to PBC (Cordell HJ et al.) and 35 SNPs related to PBC (FinnGen) were selected. The F-statistic of the instrumental SNPs for SLE on PBC in two datasets were above the threshold 10. Specific data are described in Table S1. Supplementary Fig. S1 provided detailed information about the statistical power.

In the database by Cordell HJ et al., the genetically predicted SLE had a positive causal influence on PBC risk, and the connections were consistent in direction with the finding from the FinnGen study. The meta-analysis using IVW estimations revealed a total OR of 1.17 (95 % CI = 1.09–1.25, $p < 0.001$) (Fig. 2). Other MR procedures provided results that were qualitatively comparable to those predicted by the IVW method (Table 1, Supplementary Fig. S2).

To validate the accuracy of the MR data, we conducted various sensitivity studies. First, the absence of heterogeneity among SNPs, was performed as Cochran's Q statistic p-value exceeded 0.05 (Table 2). Furthermore, neither the MR-Egger nor the MR-PRESSO global tests identified horizontal pleiotropy. Additionally, no single SNP was found to alter SLE-PBC causality by the leave-one-out analysis, as indicated in Supplementary Fig. S3.

3.1.2. Causal effect of PBC on SLE

After excluding SNPs using rigorous criteria, 17 independent SNPs from the Bentham J et al. database and 16 SNPs from the FinnGen study were utilized. The F statistic values vary from 30 to 154, ruling out the potential of mild instrument bias (Table S2). Detailed information on statistical power can be found in Supplementary Fig. S1.

For the MR examination, we utilized the fixed-effects IVW technique because the Cochran's Q p-value was more than 0.05. According to this research, there is a positive causal connection between the risk of SLE and genetic vulnerability to PBC, with the combined ORs of PBC on SLE were 1.39 (95 % CI = 1.32–1.45, $p < 0.001$) in the meta-analyses (Fig. 2). The weighted median (OR = 1.39, 95 % CI = 1.30–1.49), simple mode (OR = 1.39, 95 % CI = 1.23–1.58), weighted mode (OR = 1.38, 95 % CI = 1.24–1.54), and MR-Egger (OR = 1.47, 95 % CI = 1.24–1.74) approaches yielded similar findings (Table 1, Supplementary Fig. S4).

Results from the sensitivity analysis indicated in the same direction (Table 2). To be specific, the Cochran's Q statistics within each database failed to detect the horizontal pleiotropy in the IVs ($p > 0.05$). Furthermore, the results showed no indication of horizontal pleiotropy from PBC to SLE in each database. The leave-one-out analysis showed no single SNP was responsible for the links (Supplementary Fig. S5).

3.2. Multivariable MR analysis

MVMR was conducted to explore the bidirectional causal relationship between SLE and PBC. The IVW analysis showed that SLE was

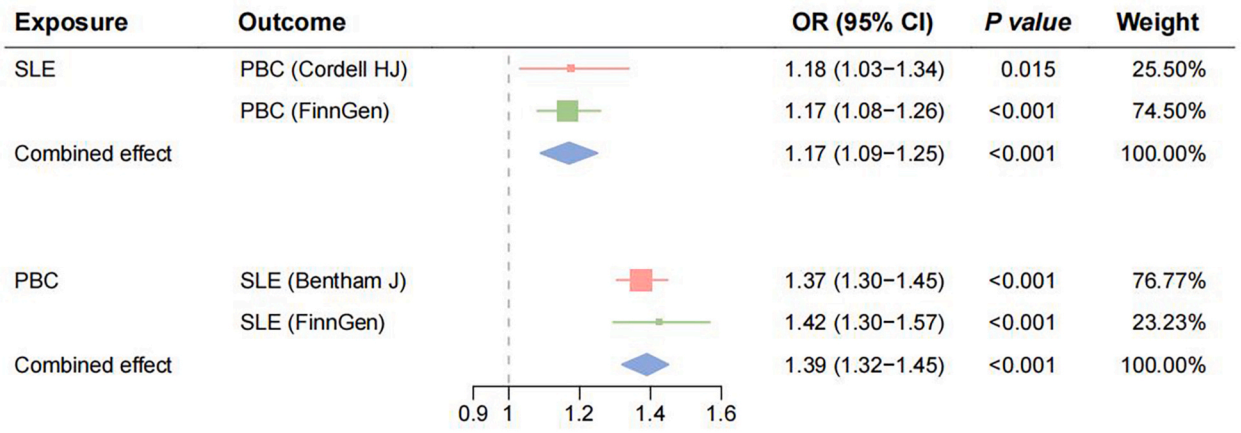

Fig. 2. The bidirectional relationship between SLE and PBC in univariable MR analyses. The estimated ORs represent the effect of per log-OR increase in SLE on PBC, obtained from an inverse-variance weighted analysis, for each outcome database individually and merged across the two databases using fixed-effects meta-analyses. SLE, Systemic lupus erythematosus; PBC, Primary biliary cholangitis; OR: odds ratio; CI: confidence interval.

Table 1
Mendelian randomization between SLE and PBC.

Exposure	outcomes	No. of SNPs	IVW		Weighted Median		Simple mode		Weighted mode		MR Egger	
			OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
SLE	PBC (Cordell HJ et al.)	6	1.18 (1.03–1.34)	0.015	1.21 (1.03–1.43)	0.022	1.31 (0.99–1.72)	0.117	1.30 (1.01–1.69)	0.102	1.06 (0.67–1.67)	0.814
	PBC (FinnGen)	35	1.17 (1.08–1.26)	<0.001	1.14 (1.02–1.28)	0.021	1.07 (0.86–1.34)	0.523	1.11 (0.95–1.29)	0.184	1.14 (0.93–1.39)	0.206
	M-A	–	1.17 (1.09–1.25)	<0.001	1.17 (1.06–1.28)	0.001	1.16 (0.98–1.38)	0.093	1.16 (1.01–1.32)	0.030	1.13 (0.94–1.35)	0.200
PBC	SLE (Bentham J et al.)	17	1.37 (1.30–1.45)	<0.001	1.36 (1.27–1.47)	<0.001	1.34 (1.16–1.55)	0.001	1.35 (1.19–1.52)	<0.001	1.46 (1.22–1.75)	<0.001
	SLE (FinnGen)	16	1.42 (1.30–1.57)	<0.001	1.48 (1.29–1.70)	<0.001	1.57 (1.21–2.04)	0.004	1.56 (1.22–2.01)	0.003	1.50 (0.99–2.28)	0.760
	M-A	–	1.39 (1.32–1.45)	<0.001	1.39 (1.30–1.49)	<0.001	1.39 (1.23–1.58)	<0.001	1.38 (1.24–1.54)	<0.001	1.47 (1.24–1.74)	<0.001

SNP: single nucleotide polymorphism; IVW: Inverse variance weighted; OR: Odds Ratio; CI: Confidence Interval; SLE, Systemic lupus erythematosus; PBC, Primary biliary cholangitis; M-A: Meta-analysis.

Table 2
Sensitivity analysis of the causal association between SLE and PBC.

Exposure	outcome	Cochran Q test		MR-Egger Pleiotropy test		MR PRESSO (outlier-corrected)		
		Q	p value	Intercept	p value	outlier	OR (95 % CI)	p for global test
SLE	PBC (Cordell HJ et al.)	4.85	0.43	0.03	0.67	4	1.18 (0.96–1.34)	0.478
	PBC (FinnGen)	47.12	0.07	0.01	0.80	5	1.17 (1.07–1.28)	0.065
PBC	SLE (Bentham J et al.)	12.69	0.70	−0.02	0.50	5	1.37 (1.31–1.44)	0.819
	SLE (FinnGen)	17.86	0.27	−0.01	0.80	6	1.42 (1.28–1.58)	0.370

MR PRESSO: MR Pleiotropy residual sum and outlier; OR: Odds Ratio; CI: Confidence Interval; SLE, Systemic lupus erythematosus; PBC, Primary biliary cholangitis.

still associated with an increased risk of PBC after adjusting for smoking, alcohol consumption, BMI, vitamin D, inflammatory bowel disease and its subtypes, and celiac disease (Table 3). In addition, the casual effect of PBC on SLE remained statistically significant after adjusting for these risk factors (Table 4). The other three MR methods revealed similar results (Table S3).

4. Discussion

For the first time, MR analysis is being used to investigate the causal link between SLE and PBC. The results of this study indicate that SLE significantly raises the risk of PBC. Reverse MR analysis also confirmed the causal connection of PBC on SLE. After adjusting for the risk factors, the causality between SLE and PBC remained.

Previous epidemiological observations have reported a close relationship between SLE and PBC. Due to the liver's vulnerability to autoimmune responses, patients with SLE may encounter a variety of liver involvements [12]. It has been noted that up to 60 % of patients with SLE may experience abnormal liver enzyme levels or liver impairment at some point during their illness [17,18,43–45]. Establishing the presence of PBC in SLE patients with hepatic insufficiency is crucial, as it has been estimated that up to 7.5 % of SLE patients with abnormal liver enzyme values or liver dysfunction will develop PBC [17,18,45,46]. The coexistence of SLE and PBC has been demonstrated by a few observational studies, although in a relatively rare incidence [6,15,16,19]. A study by Roberts Cheng C found that combining PBC may worsen the prognosis for SLE [47]. A 3.4 % prevalence of SLE was found in a significant investigation by Gershwin et al., and concomitant SLE may impair the biochemical response to PBC therapy [48]. Moreover, large-scale research by Gershwin et al. revealed that 2.61 % of PBC patients had SLE [19]. Despite the paucity of clinical research on SLE combined with PBC, it is critical to comprehend the causal link between these conditions. Our study confirmed the bi-directional causal relationship between SLE and PBC using MR analysis. Multivariate MR can collectively estimate the causal relationship of various risk factors on

Table 3
Multivariable MR estimates of SLE on PBC.

Exposure	Outcome	Methods	OR (95 % CI)	*P* value
SLE		IVW		
	PBC (Cordell HJ et al.)	a	1.10 (1.01–1.19)	0.021
	PBC (FinnGen)		1.29 (1.15–1.45)	1.00E-04
	M-A		1.16 (1.09–1.24)	1.16E-05
	PBC (Cordell HJ et al.)	b	1.14 (1.02–1.28)	0.027
	PBC (FinnGen)		1.20 (1.10–1.30)	1.56E-05
	M-A		1.18 (1.10–1.26)	1.55E-06
	PBC (Cordell HJ et al.)	c	1.27 (1.10–1.46)	8.69E-04
	PBC (FinnGen)		1.23 (1.09–1.40)	0.001
	M-A		1.25 (1.14–1.37)	2.98E-06
	PBC (Cordell HJ et al.)	d	1.13 (1.00–1.28)	0.052
	PBC (FinnGen)		1.22 (1.09–1.37)	5.82E-04
	M-A		1.18 (1.08–1.28)	1.21E-04
	PBC (Cordell HJ et al.)	e	1.29 (1.12–1.49)	4.63E-04
	PBC (FinnGen)		1.25 (1.12–1.39)	1.10E-04
	M-A		1.26 (1.16–1.38)	1.95E-07
	PBC (Cordell HJ et al.)	f	1.26 (1.09–1.46)	0.002
	PBC (FinnGen)		1.25 (1.12–1.40)	7.39E-05
	M-A		1.25 (1.15–1.37)	5.63E-07
	PBC (Cordell HJ et al.)	g	1.25 (1.06–1.49)	0.010
	PBC (FinnGen)		1.21 (1.09–1.34)	2.74E-04
	M-A		1.22 (1.12–1.33)	8.98E-06
	PBC (Cordell HJ et al.)	h	1.36 (0.94–1.97)	0.099
	PBC (FinnGen)		1.61 (1.27–2.03)	8.38E-05
	M-A		1.53 (1.26–1.87)	2.67E-05

MR: mendelian randomization; IVW: Inverse variance weighted; OR: Odds Ratio; CI: Confidence Interval; SLE, Systemic lupus erythematosus; PBC, Primary biliary cholangitis. a, adjusted for Body Mass Index; b, adjusted for vitamin D; c, adjusted for smoking; d, adjusted for alcohol consumption; e, adjusted for Crohn's diseases; f, adjusted for inflammatory bowel diseases, g, adjusted for ulcerative colitis; h, adjusted for celiac diseases; M-A: Meta-analysis.

Table 4
Multivariable MR estimates of PBC on SLE.

Exposure	Outcome	Methods	OR (95 % CI)	*P* value
PBC		IVW		
	SLE (Bentham J et al.)	a	1.38 (1.23–1.54)	4.40E-08
	SLE (FinnGen)		1.29 (1.15–1.45)	1.30E-05
	M-A		1.34 (1.23–1.45)	3.42E-12
	SLE (Bentham J et al.)	b	1.44 (1.26–1.64)	8.29E-08
	SLE (FinnGen)		1.35 (1.17–1.55)	3.41E-05
	M-A		1.39 (1.27–1.54)	1.52E-11
	SLE (Bentham J et al.)	c	1.32 (1.10–1.59)	1.84E-11
	SLE (FinnGen)		1.56 (1.37–1.77)	0.003
	M-A		1.48 (1.33–1.64)	6.46E-13
	SLE (Bentham J et al.)	d	1.48 (1.25–1.75)	7.41E-06
	SLE (FinnGen)		1.36 (1.15–1.61)	4.14E-04
	M-A		1.42 (1.26–1.60)	1.45E-08
	SLE (Bentham J et al.)	e	1.60 (1.35–1.90)	1.12E-07
	SLE (FinnGen)		1.54 (1.31–1.82)	2.05E-07
	M-A		1.57 (1.39–1.77)	1.18E-13
	SLE (Bentham J et al.)	f	1.56 (1.36–1.79)	3.11E-10
	SLE (FinnGen)		1.54 (1.34–1.77)	8.84E-10
	M-A		1.55 (1.40–1.71)	1.58E-18
	SLE (Bentham J et al.)	g	1.60 (1.37–1.87)	2.93E-09
	SLE (FinnGen)		1.51 (1.32–1.74)	8.86E-09
	M-A		1.55 (1.40–1.72)	1.60E-16
	SLE (Bentham J et al.)	h	1.63 (1.30–2.06)	3.32E-05
	SLE (FinnGen)		1.43 (1.17–1.74)	3.94E-04
	M-A		1.51 (1.30–1.76)	7.09E-08

MR: mendelian randomization; IVW: Inverse variance weighted; OR: Odds Ratio; CI: Confidence Interval; SLE, Systemic lupus erythematosus; PBC, Primary biliary cholangitis. a, adjusted for Body Mass Index; b, adjusted for vitamin D; c, adjusted for smoking; d, adjusted for alcohol consumption; e, adjusted for Crohn's diseases; f, adjusted for inflammatory bowel diseases, g, adjusted for ulcerative colitis; h, adjusted for celiac diseases; M-A: Meta-analysis.

outcome risk by including exposure in the same model [35,49]. More convincingly, our results show that the association between SLE and PBC was also significant after adjusting for common risk factors.

Genetics may be a key factor in the association between SLE and PBC. Genome-wide research identified risk loci such as including IRF5-TNPO3, possibly indicating a genetic predisposition to both SLE and PBC [50,51]. In addition, Osteopontin (OPN), a multipotent protein that is critical to immune system signaling, has been implicated in SLE and PBC [52,53]. An observational study revealed that OPN has been linked to the etiology of multiple autoimmune disorders, particularly SLE [52,54]. OPN also has a critical role in PBC and has been implicated as a recruiting agent for macrophages and lymphocytes in hepatic granulomas [55]. Our findings suggest a potential causal relationship between SLE and PBC, though the complex etiology remains unclear. Therefore, it is necessary to further explore the specific mechanisms of the relationship between SLE and PBC.

This study is significant as the first to explore the two-way causation between SLE and PBC. First, MR studies were less susceptible to confounding factors compared with observational studies. Second, we used multivariate MR to control for confounding factors to ensure the reliability of the results. Third, meta-analyses were performed to improve the estimates by extracting GWAS summary statistical data for outcomes from various datasets. Despite this, the study still have some limitations. Even though a variety of methods were applied, we cannot completely eliminate potential confounder. Besides, the analysis of SLE on PBC (Cordell HJ) had low statistical power (power <0.8). In addition, we failed to investigate the casual association between SLE and PBC in sex stratification due to the unavailability of sex-specific dataset. The MR analysis solely included participants of European descent. Given that genetic traits to SLE and PBC may be associated with ethnicity [56,57], our findings cannot be generalized to the broader population. Therefore, further research should be done to confirm the findings of this study.

5. Conclusion

Overall, the results of our study suggest a reciprocal relationship between SLE and PBC, with each potentially leading to an increased incidence of the other. Our findings are consistent with prior observational research. It is important for clinicians to have a thorough understanding of this comorbidity, as delayed diagnosis and treatment could lead to irreversible adverse consequences. Further research is imperative to fully comprehend the underlying mechanisms between SLE and PBC.

Data availability statement

The datasets analyzed during the current study are available in the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/)and FinnGen database (https://r9.finngen.fi/).

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Ethics statement

Review or approval by an ethics committee was not needed for this study because the data utilized in our study was built on summary data from ethically approved published studies.

CRediT authorship contribution statement

Min Zhong: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Investigation, Data curation, Conceptualization. **Hongjin An:** Writing – review & editing, Software, Investigation, Data curation. **Huatian Gan:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34971.

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