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RESEARCH ARTICLE

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Systemic lupus erythematosus is associated with lower risk of hepatitis B virus infection: A multivariable Mendelian randomization study in East Asian population

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Abstract

The relationship between systemic lupus erythematosus (SLE) and hepatitis B virus (HBV) infection is still unclear. We conducted a two-sample Mendelian randomization (MR) analysis using summary statistics from genome-wide association studies for SLE and HBV infection in individuals of East Asian ancestry. The inverse-variance weighted (IVW) method, weighted median (WM) method, and MR-Egger method were used to estimate the causal effect of SLE on HBV infection. Additionally, we performed a multivariable MR analysis adjusting for the effects of body mass index and rheumatoid arthritis. This MR study included a total of 225 106 individuals of East Asian ancestry, comprising 5616 cases and 219 490 controls. The IVW method (OR: 0.79, $p = 3.34E{-}08$) and the WM method (OR: 0.79, $p = 9.09E{-}06$) revealed a causal relationship between genetically predicted SLE and a low risk of HBV infection. The multivariable MR analysis still suggested a low risk of HBV infection associated with SLE (OR: 0.83, $p = 2.89E{-}06$). Our MR analysis supports a causal relationship between SLE and a low risk of HBV infection in individuals of East Asian ancestry.

KEYWORDS
causal relationship, GWAS, HBV, Mendelian randomization, SLE

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder that manifests itself in a wide range of symptoms.[1,2] These may encompass skin rashes, joint pain, and inflammation (arthritis), as well as damage to internal organs.[1,2] This chronic disease impacts multiple bodily systems, and the precise etiology of SLE remains incompletely understood.[2] Current research posits that a combination of genetic, environmental, and immunological factors likely contribute to its development.[3,4] Among environmental factors, infections, particularly those caused by viruses, have been extensively documented as potential triggers for SLE.[3,4]

Hepatitis B virus (HBV) infection has surfaced as a significant global health concern.[5,6] It is estimated that approximately 360 million individuals worldwide are afflicted with chronic HBV infection.[5,6] HBV is a virus that targets the liver and can lead to severe illness.[5] Cirrhosis and liver cancer account for the primary causes of death in approximately 25% of individuals with chronic HBV infection.[7] Autoimmune diseases have been closely linked to viral infections, with studies connecting Epstein–Barr virus to SLE and rheumatoid arthritis (RA).[8] Over several decades, a multitude of

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studies have reported a potential association between SLE and HBV infection, with the majority of observational studies demonstrating a reduced HBV infection rate among SLE patients.[9–11] Some observational studies support the notion that SLE may decrease the risk of HBV infection,[10] while others suggest that HBV may exert a protective effect on SLE.[12,13] Traditional research approaches are hindered by confounding variables and reverse causation, making it difficult to establish a causal relationship between SLE and HBV.

Mendelian randomization (MR) is a statistical technique that employs genetic variants as instrumental variables (IVs) to evaluate the causal effect of an exposure on an outcome.[14] This method assumes that genetic variants are randomly assigned at conception and are not subject to confounding factors or reverse causation.[15,16] MR has been utilized to infer causal associations between SLE and various conditions, including tumors, neurological disorders, and cardiovascular diseases.[17–19] Consequently, in the absence of randomized controlled trials examining the relationship between SLE and HBV, this study employs both univariable and multivariable MR approaches to investigate the causal link between SLE and HBV.

2 | METHODS

2.1 | Study design

We conducted a bidirectional and multivariable MR study following the most up-to-date STROBE-MR (Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization) guidelines.[20] We selected relevant single nucleotide polymorphisms (SNPs) by performing quality control procedures on the genome-wide association study (GWAS) summary results. MR was used to assess the causal relationship between SLE and HBV, with SNPs as the IVs, and three assumptions of MR studies needed to be met: (1) IVs directly affect exposure; (2) IVs do not correlate with confounders; (3) IVs affect the outcome by affecting exposure (Figure S1).[15,16] Figure 1 illustrated the process of MR.

2.2 | Data sources

Biobank Japan (BBJ) is a national biobank established in 2003, comprising data on 200 000 individuals of East Asian descent, making it a large-scale and long-term project.[21] It aims to collect, store, and distribute biological samples and associated data from Japanese citizens. More than 5800 items of screened information are available for research, including the patients' survival information, and 95% of the patients are tracked over an average of 10 years.[21] The GWAS summary statistics for HBV from the BBJ were obtained from 1394 cases and 211 059 controls, containing 8 885 805 variant sites. Clinical information and biological samples were collected from Japanese patients from 12 medical institutions and population-based controls in Japan.[22] The diagnoses of HBV were made by physicians at cooperating hospitals.[22,23]

The summary-level statistical data for SLE were extracted from another large meta-analysis of GWAS in East Asia, which included 4222 cases and 8431 controls and contained 5 691 661 variant sites.[24] The study included subjects of Han Chinese descent from three different regions: Hong Kong, Guangzhou, and Central China.[24] SLE patients in the study were classified using the 1997 revised SLE diagnostic criteria of the American College of Rheumatology.[25,26] All the data sources are provided in Supporting Information S2: Table 1.

2.3 | IV

To ensure close association with SLE, we selected SNPs that were significantly associated with SLE with a p value of 5×10^{-8} as IVs. To remove linkage disequilibrium, we chose a clumping distance of 10 000 kb and an r^2 threshold of <0.001. We also calculated the F and R^2 values for each SNP to ensure its adequate validity in the study. The R^2 and F values were calculated using the formula: $F = (R^2 \times [N-2])/(1-R^2)$, where $R^2 = (2 \times \beta^2 \times EAF \times [1-EAF])/(2 \times \beta^2 \times EAF \times [1-EAF] + 2 \times SE^2 \times N \times EAF \times [1-EAF])$.[27] Here, N and EAF represent the sample size and the effect allele frequency, β is the estimated effect of the SNP, and SE is the standard error of the SNP on SLE.[27] SNPs with F less than 10 were excluded, and palindromic SNPs with a moderate allele frequency were removed.[27]

2.4 | Bidirectional and multivariate MR analysis

In the analysis, we conducted forward MR with SLE as the exposure and HBV as the outcome. We employed five different methods for this analysis, including the inverse variance weighted (IVW) method, MR-Egger, and the weighted median (WM) methods, as well as the simple mode and weighted mode approaches. The IVW method served as the primary analysis method for assessing causality. To clarify the causal relationship between HBV and SLE, we conducted reverse MR. We selected SNPs associated with HBV ($p < 1 \times 10^{-5}$) as IVs and performed a reverse MR study using the same MR methods as those used for the forward MR. In addition, body mass index (BMI) is an important factor affecting both autoimmune diseases and HBV, and there have been studies reporting associations between RA and both SLE and HBV.[28] Therefore, BMI and RA are potential confounding factors in studying the genetic susceptibility of SLE to HBV, and we used a multivariable MR approach to adjust for their effects. We utilized complete data on BMI and RA from the BBJ database.[22] All RA cases met the American College of Rheumatology 1987 RA diagnostic criteria or were diagnosed as having RA by professional rheumatologists.[22,29]

2.5 | Sensitivity analyses

To ensure the reliability of the MR results, we conducted sensitivity analyses, which included Cochran's Q test, MR-pleiotropy residual sum

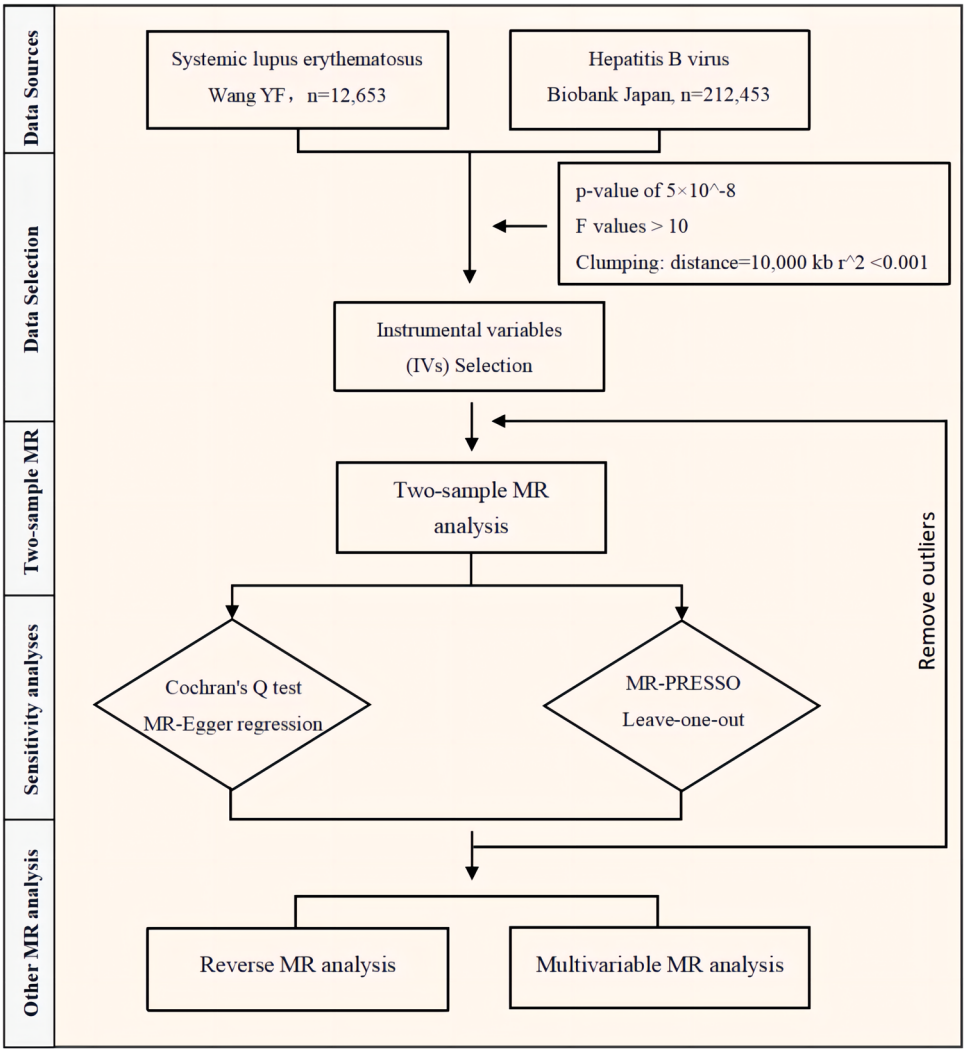

FIGURE 1 Flowchart of this MR study. IVs, instrument variables; MR, Mendelian randomization; MR-PRESSO, MR-pleiotropy residual sum and outlier.

and outlier (MR-PRESSO), MR-Egger regression, and leave-one-out sensitivity. Cochran's Q test was used to evaluate the presence of heterogeneity among the estimated effects of each individual genetic variant used in the analysis.[30] A *p* value greater than 0.05 indicates the absence of heterogeneity.[30,31] MR-PRESSO was utilized to identify and correct for horizontal pleiotropy, which occurs when a genetic variant affects the outcome of interest through pathways other than the exposure of interest.[32] It detects genetic variants with pleiotropic effects and corrects for their impact on the causal estimates.[32] MR-Egger regression was also applied to determine the presence of horizontal pleiotropy, but it does not assume that all genetic variants are valid IVs.[33] It estimates a linear regression of the genetic variants on the outcome, and a statistically significant intercept indicates the presence of horizontal pleiotropy.[33] To evaluate the impact of individual genetic variants on the overall causal estimate, we performed leave-one-out sensitivity.[34] This method involves removing one genetic variant at a time from the analysis and recalculating the causal estimate to determine the impact of each individual variant.[34]

The MR analysis was conducted using the "TwoSampleMR" R package. All statistical analyses and data visualization were carried out using R software version 4.2.0.

3 | RESULTS

3.1 | Instrument variables selection

This MR study included a total of 225 106 individuals of East Asian ancestry, comprising 5616 cases and 219 490 controls. We selected 8453 IVs that showed a strong correlation with SLE. We then removed those that were in linkage disequilibrium (LD) ($r^2 < 0.001$, 10 000 KB) (8417 IVs) and retained only those with *F*-statistics greater than 10, indicating the absence of weak instruments. After harmonization with HBV and the removal of palindromic SNPs with intermediate allele frequencies (rs11059928, rs11185603, rs12575600, rs4844538, and rs5749502), we included 30 SNPs in

the two-sample MR study of SLE and HBV. Detailed information on these SNPs that are significantly associated with SLE is provided in Table 1 and Supporting Information S2: Table 2.

3.2 | MR analysis of SLE and HBV

As shown in Table 2, using the IVW method, we found a causal relationship between genetically predicted SLE and a low risk of HBV infection in individuals of East Asian ancestry (OR: 0.79, 95% CI: 0.72–0.86, $p = 3.34E{-}08$). The same result was obtained using the WM method (OR: 0.79, 95% CI: 0.71–0.87, $p = 9.09E{-}06$). The MR-Egger result was consistent with the above two methods (OR: 0.67, 95% CI: 0.53–0.86, $p = 3.38E{-}03$) (Figures 2 and 3).

3.3 | Sensitivity analysis of the two-sample MR

To test for directional pleiotropy, which can introduce bias in MR results, we conducted an MR-Egger regression (Supporting

TABLE 1 Characteristics of the genetic instrumental variables used in the two sample MR analysis.

SNP	A1	A2	β	SE	p	N	F	R^2
rs11889341	T	C	4.16E−01	2.95E−02	3.33E−45	12 653	199.21	1.55E−02
rs4731532	A	G	3.72E−01	3.34E−02	8.15E−29	12 653	123.76	9.69E−03
rs4916315	T	C	3.36E−01	3.11E−02	4.12E−27	12 653	116.57	9.13E−03
rs2618473	T	C	3.59E−01	3.39E−02	2.89E−26	12 653	112.13	8.79E−03
rs5029937	T	G	6.84E−01	6.76E−02	4.32E−24	12 653	102.48	8.04E−03
rs143821594	C	T	−4.95E−01	5.52E−02	3.08E−19	12 653	80.34	6.31E−03
rs13385731	C	T	−3.65E−01	4.21E−02	4.19E−18	12 653	75.32	5.92E−03
rs3734266	C	T	3.34E−01	3.99E−02	6.09E−17	12 653	70.06	5.51E−03
rs7097397	A	G	−2.39E−01	3.10E−02	1.32E−14	12 653	59.18	4.66E−03
rs4134466	G	A	−2.14E−01	3.06E−02	3.09E−12	12 653	48.72	3.84E−03
rs6941112	A	G	2.22E−01	3.26E−02	1.01E−11	12 653	46.24	3.64E−03
rs12599402	C	T	−1.98E−01	2.92E−02	1.02E−11	12 653	46.11	3.63E−03
rs4930642	G	A	−2.34E−01	3.44E−02	1.10E−11	12 653	46.11	3.63E−03
rs76571753	T	G	2.79E−01	4.14E−02	1.46E−11	12 653	45.47	3.58E−03
rs9938016	T	C	−3.97E−01	5.91E−02	1.78E−11	12 653	45.21	3.56E−03
rs2841281	T	C	1.93E−01	2.92E−02	3.56E−11	12 653	43.82	3.45E−03
rs6941485	G	A	2.03E−01	3.14E−02	9.53E−11	12 653	41.95	3.31E−03
rs10516487	A	G	−2.55E−01	3.98E−02	1.64E−10	12 653	40.95	3.23E−03
rs10953792	C	T	1.99E−01	3.20E−02	4.69E−10	12 653	38.82	3.06E−03
rs2524058	G	A	−1.86E−01	3.00E−02	5.31E−10	12 653	38.60	3.04E−03
rs10896045	G	A	−1.73E−01	2.88E−02	1.78E−09	12 653	36.20	2.85E−03
rs7486387	A	G	−1.89E−01	3.14E−02	1.98E−09	12 653	36.07	2.84E−03
rs10036748	T	C	2.02E−01	3.38E−02	2.29E−09	12 653	35.75	2.82E−03
rs7650774	C	T	−1.80E−01	3.06E−02	4.07E−09	12 653	34.52	2.72E−03
rs55701306	T	C	1.66E−01	2.93E−02	1.38E−08	12 653	32.17	2.54E−03
rs2431697	C	T	−2.54E−01	4.51E−02	1.84E−08	12 653	31.66	2.50E−03
rs9387400	A	C	−2.97E−01	5.36E−02	3.14E−08	12 653	30.64	2.42E−03
rs244689	G	A	−1.60E−01	2.91E−02	4.29E−08	12 653	30.04	2.37E−03
rs201036579	C	T	−2.88E−01	5.27E−02	4.85E−08	12 653	29.82	2.35E−03
rs3750996	G	A	−2.04E−01	3.74E−02	4.91E−08	12 653	29.75	2.35E−03

Abbreviations: A1, effect_allele; A2, other_allele; β, beta; F, F-statistics; MR, Mendelian randomization; N, sample size; SE, standard error; SNP, single-nucleotide polymorphism.

TABLE 2 MR results of causal links between SLE and HBV ($p < 1 \times 10^{-8}$).

Exposure	Outcome	Method	nSNP	SE	p	OR (95% CI)
SLE	HBV	MR-Egger	30	0.12	3.38E−03	0.67 (0.53–0.86)
		Weighted median	30	0.05	9.09E−06	0.79 (0.71–0.87)
		Inverse variance weighted	30	0.04	3.34E−08	0.79 (0.72–0.86)
		Simple mode	30	0.12	9.40E−03	0.73 (0.58–0.91)
		Weighted mode	30	0.11	8.96E−03	0.74 (0.60–0.91)

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; MR, Mendelian randomization; OR, odds ratio; SE, standard error; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.

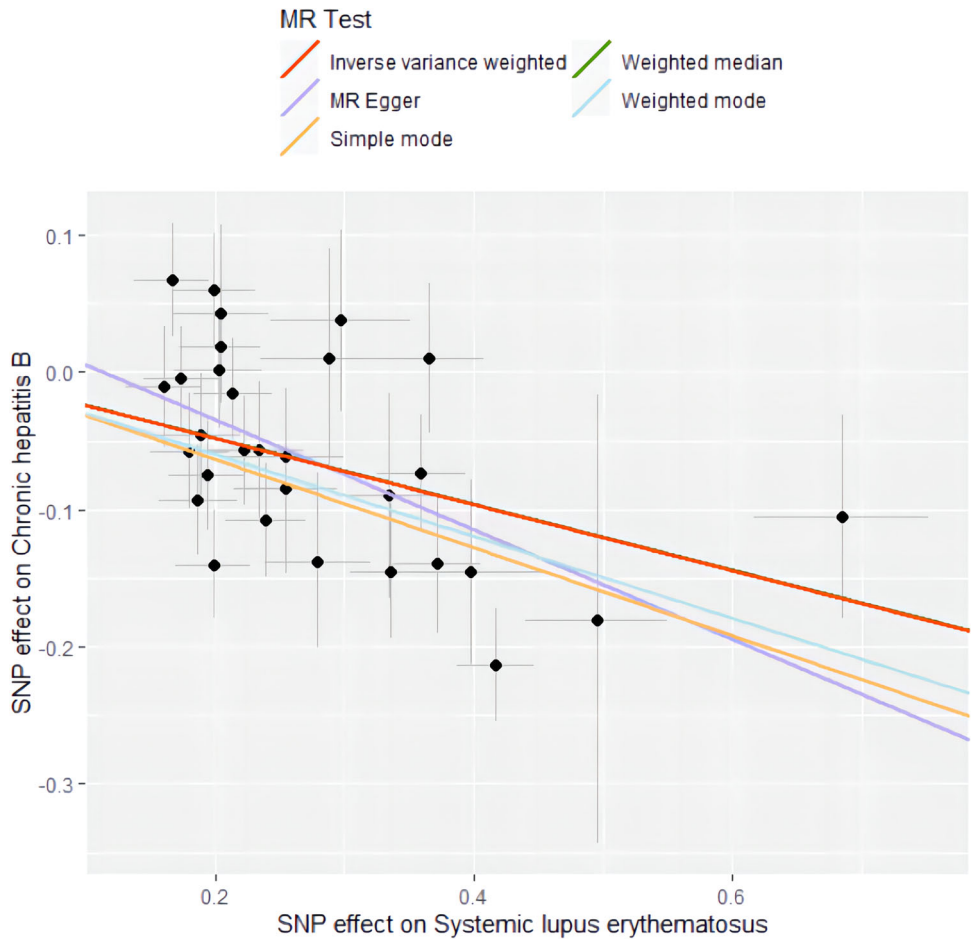

FIGURE 2 Scatter plots for effect sizes of SNPs for SLE on HBV. HBV, hepatitis B virus; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.

Information S2: Table 4) and found no evidence of directional pleiotropy ($p > 0.05$). Despite the presence of heterogeneity according to Cochran's Q test (Supporting Information S2: Table 3), the MR-Egger intercept test and funnel plot (Figure 4) symmetry suggested the absence of horizontal pleiotropy. Furthermore, neither the forest plot (Figure 5) nor the leave-one-out plot (Figure 6) showed any outliers. Using the MR-PRESSO method, we identified rs11889341 and rs12599402 as potential outliers. After correction, we repeated the MR analysis, which still suggested a strong association between SLE and a low risk of HBV infection (OR: 0.83, 95% CI: 0.76–0.89, $p = 2.89e{-}06$) and passed the tests for pleiotropy and heterogeneity (Supporting Information S2: Tables 5, 6, and 7).

3.4 | Reverse MR and multivariable MR

We performed reverse MR by using SNPs associated with HBV as instruments, and the IVW analysis did not find evidence (OR: 0.86,

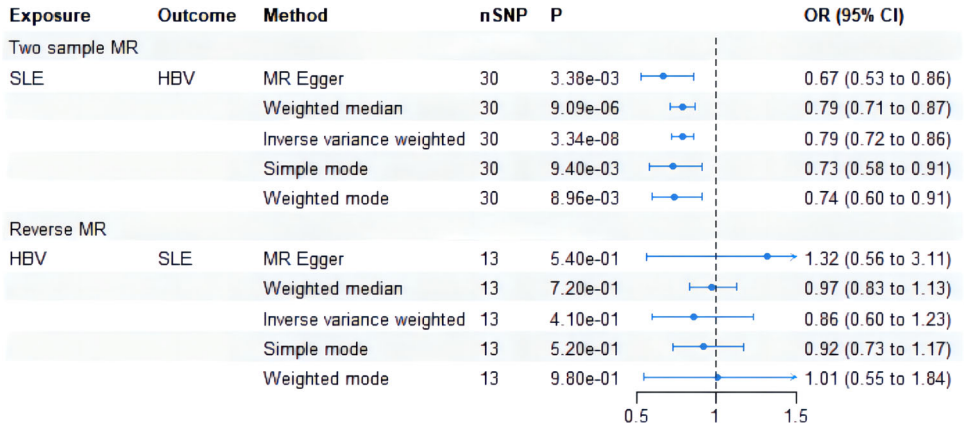

FIGURE 3 Forest plot of two-sample MR analysis and reverse MR analysis. HBV, hepatitis B virus; MR, Mendelian randomization; OR, odds ratio; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.

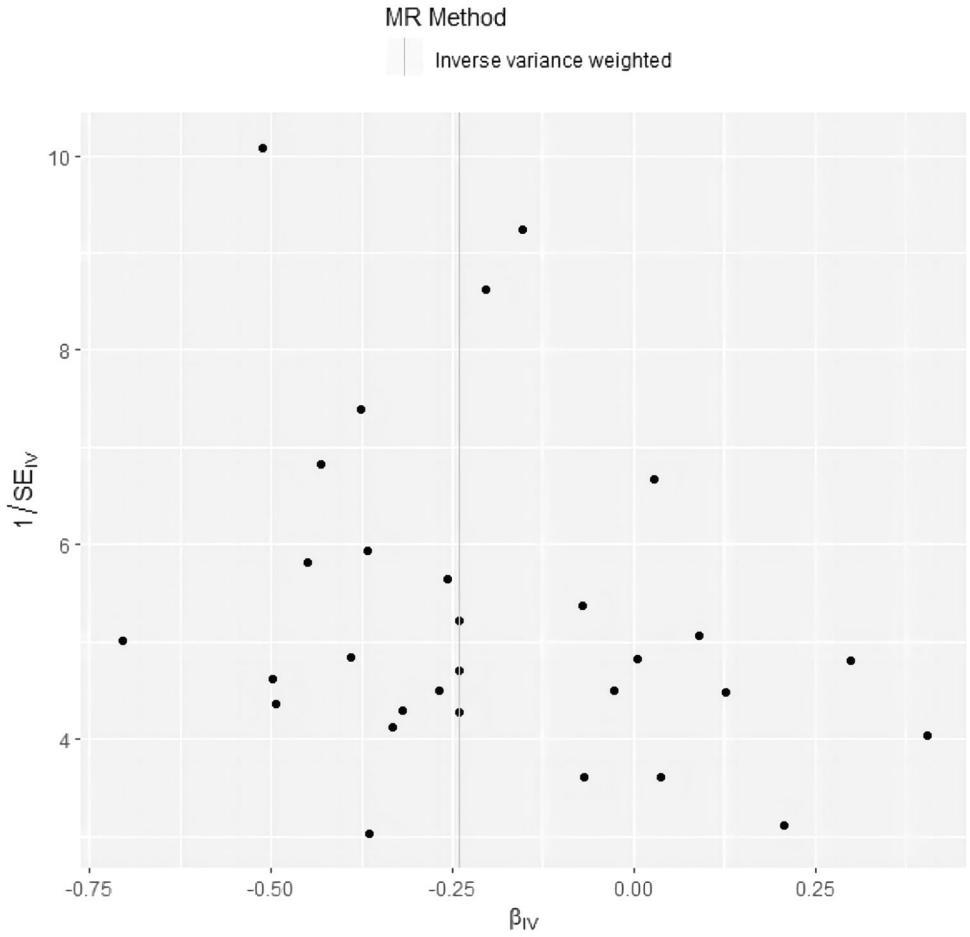

FIGURE 4 Funnel plot for SLE on HBV. *β*, beta; HBV, hepatitis B virus; IV, instrumental variable; MR, Mendelian randomization; SE, standard error; SLE, systemic lupus erythematosus.

95% CI: 0.60−1.23, $p = 4.10E{-}01$) for a causal effect of HBV infection on SLE susceptibility (Supporting Information S2: Table 8 and Figure 3). The results of reverse MR analysis do not support the hypothesis that HBV infection affects the risk of developing SLE. We further conducted a multivariable MR analysis by including BMI and RA as covariates. The results showed a strong causal relationship between SLE and a low risk of HBV infection (OR: 0.79, 95% CI: 0.71−0.87, $p = 2.46E{-}06$), while BMI and RA were not causally associated with HBV infection (Supporting Information S2: Table 9). The results are shown in the figure below (Figure 7).

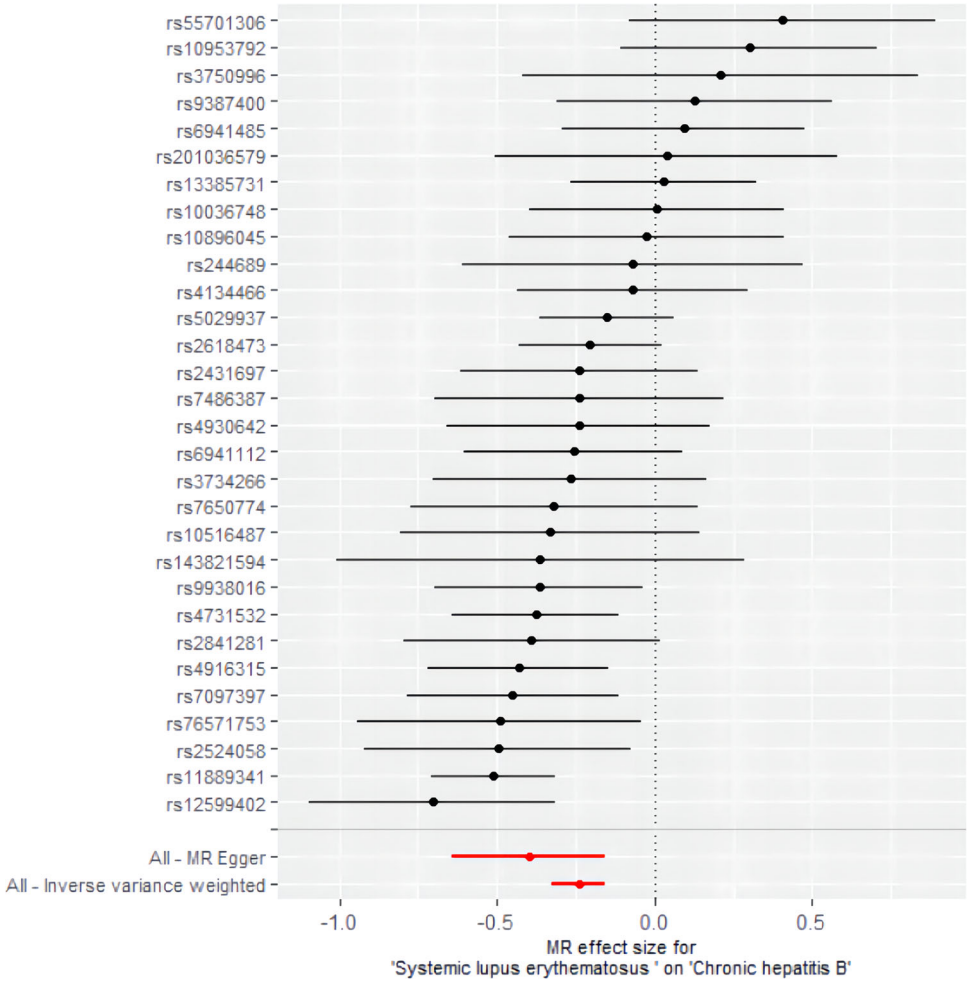

FIGURE 5 Forest plot for effect sizes of SNPs for SLE on HBV. The forest plot shows the estimate of the effect of genetically SLE risk on HBV risk, where each black point represents the log odds ratio (OR) for HBV per standard deviation (SD) in log OR for SLE, and red points showing the combined causal estimate using all SNPs together in a single instrument, using each of the two different methods (inverse-variance weighted [IVW] random effects and MR-Egger). Horizontal lines denote 95% confidence intervals (95% CIs). HBV, hepatitis B virus; MR, Mendelian randomization; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphisms.

4 | DISCUSSION

This is the first study to investigate the potential causal relationship between SLE and HBV using both univariable and multivariable MR methods. Our results support a causal relationship between SLE and a low genetic susceptibility to HBV, while HBV seems to have a protective effect on SLE, although the latter result did not reach statistical significance. Overall, our findings are consistent with previous observational studies and provide genetic evidence supporting the notion that SLE may lower the risk of HBV infection.

In our study, we extracted 30 SNPs that were strongly correlated with SLE from the GWAS database and used them as IVs for MR analysis. Several SNPs have been identified as potential risk factors for SLE, including rs11889341, which increases STAT1 expression levels and may contribute to immune system dysregulation and the development of SLE.[35] Additionally, rs5029937 in the TNFAIP3 gene has been linked to decreased TNFAIP3 expression, leading to increased inflammation and the development of SLE.[36] rs10516487 in the BANK1 gene has also been linked to increased BANK1 expression, which may contribute to dysregulated B-cell signaling and the production of autoantibodies in SLE.[37,38]

Characteristics of autoimmune diseases include the presence of autoreactive lymphocytes in affected tissues and circulating autoantibodies.[39,40] The ability of the immune system to distinguish self from nonself is crucial for defending the host against microbial agents and protecting self-antigens from autoimmune destruction. When this requirement is not met, autoimmune diseases may develop.[39,40] Environmental triggers, such as exposure to infectious agents, may initiate the development of autoimmune diseases in genetically susceptible individuals.[39,40] While some studies have proposed that HBV infection may be a trigger for the development of systemic autoimmune diseases, recent research has reported a lower incidence of HBV infection in SLE patients than in the general population.[11,41] A meta-analysis of 11 case–control studies suggested that SLE may have a protective effect against HBV,[10] and a study from Colombia collected serum samples from 117 SLE patients and showed

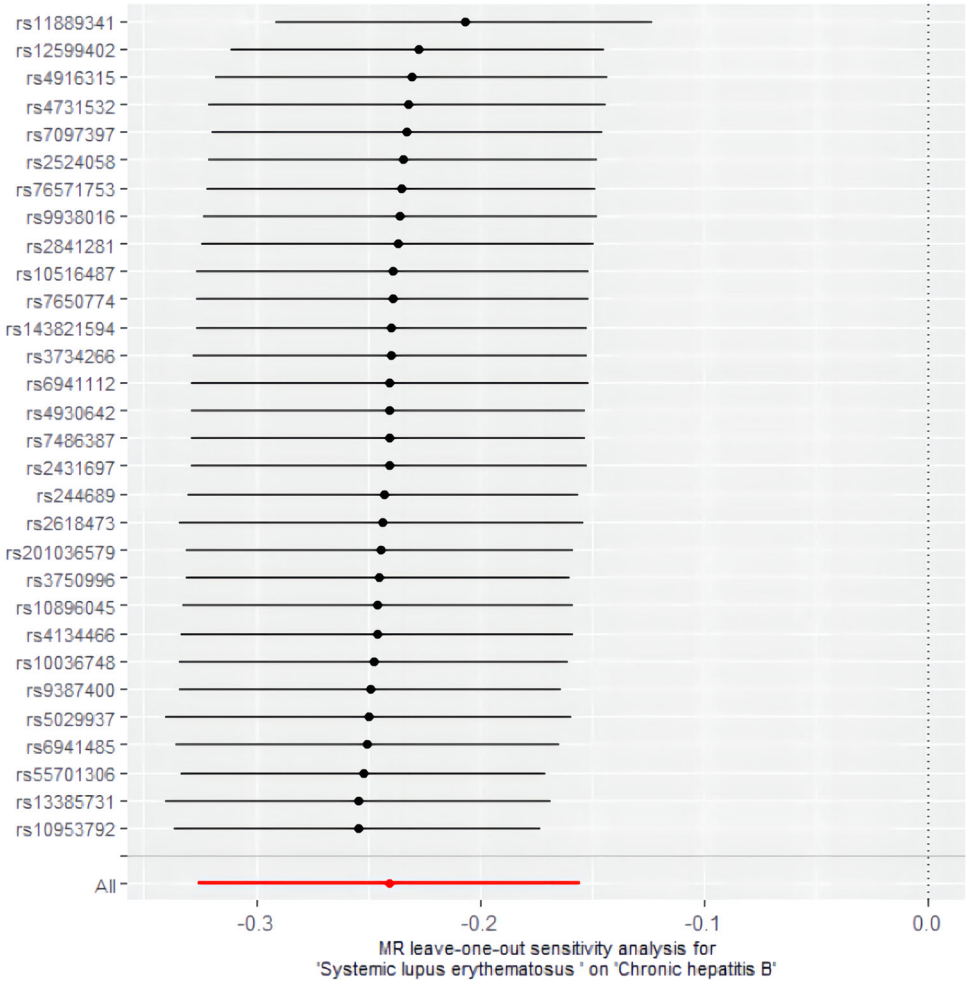

FIGURE 6 Leave-one-out sensitivity analysis for SLE on HBV. Each black point represents the inverse-variance weighted (IVW) method applied to estimate the causal effect of SLE on HBV excluding that particular variant from the analysis. The red point depicts the IVW estimate using all single nucleotide polymorphisms (SNPs). There are no instances where the exclusion of one particular SNP leads to dramatic changes in the overall result. HBV, hepatitis B virus; MR, Mendelian randomization; SLE, systemic lupus erythematosus.

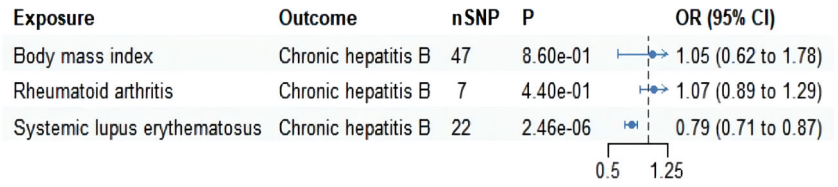

FIGURE 7 Forest plot of multivariable MR analysis. CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism.

unexpectedly lower HBcAg antibody proportions in SLE patients than in healthy controls.[42] These studies suggest that SLE patients have a lower risk of HBV infection. Consistent with previous observational studies, our study provides new genetic evidence confirming that SLE can lower the risk of HBV infection.

The impact of obesity on the development and progression of autoimmune diseases has been established in prior research.[43,44] Additionally, RA, as an autoimmune disease, often cooccurs with SLE.[45] Given multiple exposures and effectors, to further ascertain the causal relationship between SLE and HBV, we included BMI and RA in a multivariable MR analysis. Notably, our findings suggest that the association between SLE and a reduced risk of HBV remained significant even after accounting for BMI. In this study, we conducted a reverse MR analysis to further explore the impact of HBV infection on SLE. Although our results did not reach statistical significance, they still partially support the possibility of a protective effect of HBV on SLE, which is consistent with a previous study involving 1040 SLE patients.[12] That study uncovered HBV DNA-induced CD8 high T-cell apoptosis, which could potentially alleviate SLE symptoms.[12] In our study, we utilized MR methods to reduce potential confounding factors, making our results more compelling. It is important to note that our findings suggest that HBV does not affect the risk of

developing SLE, but this does not necessarily mean that HBV does not impact the development of other autoimmune diseases. Further investigation is needed to better understand the potential mechanisms underlying the relationship between SLE and HBV.

Although the mechanism by which SLE reduces the risk of HBV is still unclear, there are several reasonable explanations. Studies have found that cytokines such as IFN-α, IL-6, and TNF-α are overexpressed in SLE patients compared to healthy controls.[46,47] IFN-α plays a critical role in the immune response to viral infections and is commonly used in the treatment of chronic hepatitis B.[47,48] In addition, IL-6 can inhibit HBV transcription, antigen expression, and replication, making it a key cytokine in the early control of HBV infection.[46] Therefore, SLE patients may not have an increased risk of HBV infection due to abnormal autoimmune regulation. Instead, HBV may lead to an increase in IFN-α and IL-6 levels in the serum of SLE patients, thereby playing a positive role in HBV clearance. Another possible explanation is that testosterone deficiency is associated with SLE,[49,50] and two prospective studies have found that HBV carriers have higher levels of testosterone than healthy controls.[51–53] Therefore, testosterone deficiency may play a role in preventing HBV infection in SLE.[53]

Our study has several strengths. First, it is the first to demonstrate a potential causal relationship between SLE and HBV. Second, there can be significant differences in the incidence and prevalence of SLE among different regions.[54,55] We used two large GWAS meta-analyses from East Asia and Japan for exposure and outcome, these populations share similar dietary and lifestyle habits, and most reside in temperate regions. These factors may reduce the potential for confounding biases due to regional differences. Third, we conducted a multivariable MR study, effectively adjusting for confounding factors such as RA. Fourth, we employed multiple analytical methods and obtained consistent results, which were validated by sensitivity analyses.

However, there are some limitations to our study. Although we used several methods to analyze pleiotropy, we were unable to completely rule out potential pleiotropic effects. It is important to note, however, that multiple methods of analysis produced consistent results. Second, ethnicity can affect the prevalence and mortality of SLE. As all the participants in our MR analysis were from an East Asian population, further studies with different populations are needed to confirm the potential genetic causality between SLE and HBV. Additionally, there are relatively few HBV-related IVs, which may impact the results of reverse MR. Therefore, future studies with larger sample sizes are necessary to explore the effects of HBV on SLE. The current summary-level statistical method does not permit us to perform a covariate-stratified analysis that adjusts for the original GWAS. As a result, we are unable to stratify causal effects by sex or age, which may limit the scope of our findings.

5 | CONCLUSION

In our study, we employed a two-sample MR approach to examine the potential causal link between SLE and HBV infection. Our results indicate that genetically determined SLE is correlated with a decreased risk of HBV infection among individuals of East Asian descent. These findings offer valuable insights into the relationship between SLE and HBV infection, which could have implications for the prevention and treatment of HBV infection in those with SLE. However, additional research is required to confirm our results in other populations and to elucidate the underlying mechanisms.

AUTHOR CONTRIBUTIONS

Shiqiao Luo and Wei Li designed the study. Wei Li and Hua Zhang performed the main data analysis and wrote the draft of the manuscript. Wei Fan, Qiong Qin, Ao Ren, and Ling Zhao conducted the data acquisition and performed the data analysis and manuscript revision. Both Qiufeng Peng and Ruidong Ma contributed to the data analysis and manuscript revision. Shiqiao Luo supervised the whole research and is responsible for the integrity of data analysis. All authors have given consent to the publication of this study.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The GWAS summary statistics used in this study were obtained from published studies and public sources, and ethical approval was obtained for each GWAS. The summary statistics used in this study are deidentified, freely available for download, and can be used without restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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