Exploratory Research and Hypothesis in Medicine **2026** vol. 11(3) | e00013
DOI: 10.14218/ERHM.2026.00013

Original Article

Potential Genetic Causal Associations of Systemic Lupus Erythematosus with Five Hematologic Disorders in the European-ancestry Population: A Bidirectional Two-sample Mendelian Randomization Study

Tianyang Guo[#], Hui Zhou[#], Lili Zhang and Rong Chen*

Department of Clinical Laboratory, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing, Jiangsu, China

[#]*These authors contributed equally to this work.*

Received: April 01, 2026 | **Revised:** April 29, 2026 | **Accepted:** June 25, 2026 | **Published online:** July 27, 2026

Abstract

Background and objectives: Observational studies indicate frequent associations between systemic lupus erythematosus (SLE) and various hematologic disorders, yet causal inferences are limited by confounding and reverse causality. We therefore applied a bidirectional Mendelian randomization (MR) design to assess potential genetic causal associations of SLE with specific hematologic conditions.

Methods: We used European-ancestry GWAS summary statistics for SLE (5,201 cases, 9,066 controls) and five hematologic outcomes (vitamin B12 deficiency anemia (B12DA), myelodysplastic syndrome (MDS), immune thrombocytopenia (ITP), agranulocytosis (AGC), iron deficiency anemia (IDA)) from FinnGen. The primary analysis used inverse-variance weighting, supplemented by MR-Egger and weighted median methods, with comprehensive sensitivity analyses, including heterogeneity tests, pleiotropy assessment, and leave-one-out analysis.

Results: Bidirectional MR analysis revealed that genetically predicted SLE increased the risk of B12DA (odds ratio (OR) = 1.08, $P < 0.001$), and genetically predicted B12DA was associated with an increased risk of SLE (OR = 2.22, $P = 1.6 \times 10^{-29}$). The MDS → SLE association was nominally significant ($P = 0.023$) but did not survive Bonferroni correction ($P < 0.005$) and was inconsistent across MR methods. No significant genetic associations were found between SLE and ITP, AGC, or IDA in either direction (all $P > 0.005$).

Conclusions: This bidirectional MR study provides genetic evidence that SLE increases the risk of B12DA, whereas the reverse direction (B12DA → SLE) should be interpreted cautiously because it was based on only five instruments and was not supported by the Steiger directionality test. No robust genetic associations were found for ITP, AGC, IDA, or MDS. Clinically, monitoring B12DA in SLE patients may be warranted, although screening recommendations await prospective validation.

Keywords: Systemic lupus erythematosus; Hematologic disorders; Mendelian randomization; Causality; Genome-wide association study; Vitamin B12 deficiency anemia; Myelodysplastic syndrome; Immune thrombocytopenia; Agranulocytosis; Iron deficiency anemia.

***Correspondence to:** Rong Chen, Department of Clinical Laboratory, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing, Jiangsu210029, China. ORCID: https://orcid.org/0009-0007-6801-0546. Tel: +86-18362956526, E-mail: 944051949@qq.com

How to cite this article: Guo T, Zhou H, Zhang L, Chen R. Potential Genetic Causal Associations of Systemic Lupus Erythematosus with Five Hematologic Disorders in the European-ancestry Population: A Bidirectional Two-sample Mendelian Randomization Study. *Explor Res Hypothesis Med* 2026;11(3):e00013. DOI: https://doi.org/10.14218/ERHM.2026.00013.

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease resulting from perturbations in the immune system, characterized by the production of diverse autoantibodies, immune complex deposition, and chronic inflammation, and it ultimately leads to multi-organ damage.[1] SLE affects approximately 3.4 million people worldwide, with a higher prevalence in females than in their male counterparts.[2] Patients with SLE face a 2–3 times higher mortality risk than the general

© 2026 The Author(s). This article has been published under the terms of Creative Commons Attribution-Noncommercial 4.0 International License (CC BY-NC 4.0), which permits noncommercial unrestricted use, distribution, and reproduction in any medium, provided that the following statement is provided. "This article has been published in *Exploratory Research and Hypothesis in Medicine* at https://doi.org/10.14218/ERHM.2026.00013 and can also be viewed on the Journal's website at https://www.xiahepublishing.com/journal/erhm".

population and are at elevated risk for fatal infections and cardiovascular events.[3] Patients with SLE frequently present with various hematologic abnormalities, including immune thrombocytopenia (ITP), characterized by thrombocytopenia resulting from increased autoantibody-mediated platelet destruction and insufficient platelet production[4]; agranulocytosis (AGC), defined by a selective reduction in peripheral blood neutrophils due to autoimmune antibody attack[5]; vitamin B12 deficiency anemia (B12DA), caused by impaired DNA synthesis due to vitamin B12 deficiency, leading to megaloblastic changes in the bone marrow and macrocytic anemia[6]; iron deficiency anemia (IDA), arising from depleted body iron stores, resulting in insufficient hemoglobin synthesis and manifesting as microcytic hypochromic anemia[7]; and myelodysplastic syndrome (MDS), a group of clonal hematopoietic stem cell disorders characterized by dysplastic hematopoiesis, ineffective blood cell production, peripheral blood cytopenias, and an increased risk of transformation to acute myeloid leukemia.[8] The pathogenesis of these diseases is closely linked to the complex immune dysregulation in SLE through multiple mechanisms: (1) direct autoantibody-mediated damage, such as anti-platelet antibodies in ITP or anti-neutrophil antibodies in AGC[9]; (2) cytokine-induced myelosuppression, where pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interferon-gamma suppress hematopoietic progenitor cell function[10]; (3) complement activation leading to erythrocyte or platelet lysis[11]; (4) drug effects, as certain immunosuppressive agents may directly or indirectly cause myelosuppression or impair nutrient absorption[12]; and (5) chronic inflammation and disruption of the hematopoietic microenvironment, which may disturb iron metabolism or vitamin B12 homeostasis.[13] Although these clinical associations are well documented, the temporal sequence of their onset varies among individuals. Traditional observational studies are susceptible to confounding from socioeconomic, lifestyle, and treatment-related factors and cannot definitively establish the direction of causality. Consequently, these complex pathological mechanisms make it extremely difficult to clarify the causal direction between SLE and hematologic disorders based on observational studies. It remains unclear whether immune dysregulation in SLE triggers these hematologic complications or whether underlying hematopoietic or metabolic abnormalities exacerbate inflammation in SLE.

In recent years, Mendelian randomization (MR) has emerged as a powerful method for causal inference in epidemiology. This approach uses genetic variants, predominantly single nucleotide polymorphisms (SNPs), typically associated with an exposure, as instrumental variables. Given that genetic alleles are randomly allocated during gamete formation and fixed at conception, MR can mitigate confounding and reverse causality bias, thereby mimicking a natural randomized controlled trial,[14-16] MR studies have been successfully applied to identify causal factors for SLE risk, including cardiovascular traits,[17] psychiatric disorders,[18] gut microbiota,[19] and thyroid diseases.[20] MR studies have also investigated causality in hematologic disorders—for instance, the role of blood lipids in deep vein thrombosis and associations between cardiovascular diseases and anemia-related biomarkers.[21,22] However, evidence specifically examining the causal associations between SLE and disorders such as ITP, B12DA, AGC, MDS, and IDA through bidirectional MR analysis remains scarce. Therefore, research employing a bidirectional MR design to evaluate the causal associations between SLE and these clinically defined hematologic disorders is crucial to elucidate their potential etiological interplay.

Based on their prominent clinical significance and distinct pathophysiological underpinnings, this study selected the above five hematologic disorders for focused investigation. They encompass a spectrum ranging from direct autoimmune attack (ITP, AGC) to nutrition-deficiency-related anemias (B12DA, IDA) to clonal hematopoietic disorders (MDS). Each condition represents a potential pathway through which SLE-related immune dysregulation may interact with hematopoietic homeostasis, yet the genetic causal direction of these associations remains to be elucidated.

The present study aimed to investigate potential genetic causal associations of SLE with these five specific hematologic disorders by conducting a bidirectional two-sample MR analysis.

Materials and methods

Data sources

All genetic data used in this study were derived from publicly available summary statistics of genome-wide association studies (GWAS) conducted in populations of European ancestry. The genetic data for SLE were sourced from a 2015 GWAS (GWAS Catalog ID: ebi-a-GCST003156).[23] This study comprised 5,201 cases and 9,066 controls. Using the genome-wide significance threshold ($P < 5 \times 10^{-8}$), a total of 4,163 SNPs associated with SLE were initially identified as candidate instrumental variables prior to linkage disequilibrium (LD) clumping. The detailed filtering pipeline—including SNP counts at each selection step—is provided in Supplementary Table. 1.

Summary statistics for the five hematologic disorders—ITP, B12DA, AGC, MDS, and IDA—were obtained from the FinnGen consortium (Release 10). Each phenotype was defined by specific ICD codes within the database: MDS: Phenocode C3_MYELODYSP_SYNDR_EXALLC. Cases were sourced from the Finnish Cancer Registry using ICD-O-3 coding to ensure pathological specificity. To minimize confounding, the control group excluded all other cancer patients, thereby enhancing the specificity of the genetic signal. The following four phenotypes, classified under the broader category of hematologic diseases, were defined based on clinical diagnoses (ICD-10 codes) recorded in inpatient and outpatient visits, representing patient populations diagnosed in clinical practice: B12DA: Phenocode D3_ANAEMIA_B12_DEF. This phenotype was a core outcome of this study. ITP: Phenocode D3_ITP. AGC: Phenocode D3_AGRANULOCYTOSIS. IDA: Phenocode D3_ANAEMIA_IRONDEF. Following significance filtering, the initial numbers of identified SNPs for each phenotype were: ITP (n = 771), B12DA (n = 3,828), AGC (n = 2,085), MDS (n = 611), and IDA (n = 505). Detailed characteristics of all datasets, including sample sizes, SNP counts, and access links, are summarized in Table 1. This study exclusively utilized GWAS data from populations of European ancestry. This approach aimed to maximize population homogeneity for instrumental variable selection (LD reference) and exposure–outcome association estimates, thereby reducing bias due to population stratification.

Table 1. Summary of GWAS data sources and instrumental variable information

Trait	Data source	Accession number URL / Link	Sample size	Cases/Controls	Total GWAS variants	SNPs passing P threshold	Mean F-statistic	*P*-value threshold
SLE	Bentham *et al.*[23] / ebi-a-GCST003156	ebi-a-GCST003156	14,267	5,201/9,066	7071163	4,163	71.13921	5×10^{-8}
ITP	FinnGen R10 / finn-b-ITP	D3_ITP	406644	882/405762	21306266	771	18.30696	5×10^{-5}
B12DA	FinnGen R10 / finn-b-B12DA	D3_ANAEMIA_B12_DEF	397378	3694/393684	21306091	3,828	52.37448	5×10^{-8}
AGC	FinnGen R10 / finn-b-AGC	D3_AGRANULOCYTOSIS	408201	3462/404739	21306280	2,085	19.40945	5×10^{-5}
MDS	FinnGen R10 / finn-b-MDS	C3_MYELODYSP_S YNDR_ EXALLC	314302	206/314096	21303816	611	18.25706	5×10^{-5}
IDA	FinnGen R10 / finn-b-IDA	D3_ANAEMIA_IRONDEF	408837	15153/393684	21306290	505	60.38724	5×10^{-8}

This table presents the key characteristics of the genome-wide association study (GWAS) datasets used for each trait in the Mendelian randomization analysis. For each trait, the following information is provided: the original study or consortium source, the GWAS accession number, sample size, number of cases and controls, total number of GWAS variants, number of single nucleotide polymorphisms (SNPs) passing the predefined *P*-value threshold (before linkage disequilibrium (LD) clumping), the mean F-statistic indicating instrument strength, and the *P*-value threshold used for SNP selection. Traits include systemic lupus erythematosus (SLE), immune thrombocytopenia (ITP), vitamin B12 deficiency anemia (B12DA), agranulocytosis (AGC), myelodysplastic syndromes (MDS), and iron deficiency anemia (IDA). The *P*-value threshold is 5×10^{-8} for SLE, B12DA, and IDA, and 5×10^{-5} for ITP, AGC, and MDS. These counts are before LD clumping. The final numbers of instrumental variables used in each bidirectional MR analysis are provided in Supplementary Table. 3. MR, Mendelian randomization; URL, uniform resource locator.

We acknowledge that this limits the generalizability of the findings to other ethnic groups, a limitation that will be further discussed.

Selection of genetic instrumental variables

Significance filtering

In principle, SNPs associated with the exposure at the genome-wide significance level ($P < 5 \times 10^{-8}$) were selected. Given the limited GWAS sample sizes for certain hematologic disorders (e.g., ITP, AGC, MDS), the significance threshold for these exposures was relaxed to $P < 5 \times 10^{-5}$ to ensure a sufficient number of instrumental variables for robust analysis.[24] The potential risk of weak instrument bias introduced by this relaxed threshold was rigorously evaluated by calculating and reporting the F-statistic.

Independence clumping

To satisfy the independence requirement for instrumental variables, SNPs were clumped for LD using the European population reference panel (1000 Genomes Project Phase 3), with parameters set at $r^2 < 0.001$ and a distance window > 10,000 kb.

Exclusion of potential confounding SNPs

To satisfy the independence assumption, all filtered instrumental SNPs were queried using the PhenoScanner V2 database. Any SNP associated with known confounding factors for SLE or hematologic diseases at $P < 5 \times 10^{-8}$ was removed. These confounders included smoking, alcohol consumption, obesity, vitamin D deficiency,[25] HCV/HIV infection, *Helicobacter pylori* infection,[26] advanced age, poor health status, specific comorbidities, chemotherapy,[27] and exposure to pesticides, radiation, or benzene.[28] A list of removed confounding SNPs and the rationale is provided in Supplementary Table. 2.

Allele harmonization and ambiguous SNP handling

The harmonise_data() function from the TwoSampleMR package (version 4.3.2) was used to ensure that the effect alleles in the exposure and outcome datasets referred to the same nucleotide. For SNPs with ambiguous alleles (i.e., A/T or C/G base pairs), we first attempted to infer the strand by comparing allele frequencies with the European population reference panel (1000 Genomes). If reliable inference was not possible (e.g., frequency close to 0.5), the SNP was excluded.

MR core assumptions and verification

This study strictly adhered to the three core MR assumptions, with corresponding operational and statistical verification, as illustrated in Figures 1 and 2.

Relevance assumption

To verify the assumption that instrumental variables are strongly associated with the exposure and to quantify potential weak instrument bias, a systematic genetic instrument strength analysis was performed. First, the F-statistic (calculated as $F = \beta^2\_exposure / SE^2\_exposure$) was computed for each SNP to measure its individual strength. The mean F-statistic for all SNP sets in this study exceeded 10, indicating a low risk of weak instrument bias.[29] Second, the phenotypic variance (R^2) explained by each SNP was calculated using the formula $R^2 = \beta^2 / (\beta^2 + SE^2 \times N)$, where β is the allele effect size, SE is its standard error, and N is the corresponding exposure sample size.[30] All SNPs included in the final analysis, along with their corresponding F-statistics and R^2 values, are summarized in Supplementary Table. 3. Finally, the statistical power of this MR analysis was estimated using the online tool mRND,[31] with results presented in Supplementary Table. 4.

Independence assumption

This requires that instrumental variables are independent of any confounders of the exposure–outcomeassociation. This assumption was primarily satisfied through the systematic confounding SNP exclusion procedure described in the Exclusion of Potential Confounding SNPs section.

Exclusion restriction assumption

This requires that instrumental variables influence the outcome solely through the exposure, with no horizontal pleiotropy. To test this assumption, multiple sensitivity analyses were conducted, including the MR-Egger intercept test and the MR-PRESSO global test (detailed in the Sensitivity analysis and pleiotropy testing section below).

Primary causal inference analysis

The inverse-variance weighted (IVW) method was used as the primary analytical approach. The IVW method combines Wald ratios from each genetic variant by meta-analyzing SNP-specific causal estimates, using the inverse of their variances as weights to obtain an overall causal estimate. This method provides the most precise estimate when all genetic variants are valid instrumental variables. Heterogeneity among SNP-specific estimates was assessed using Cochran's Q test. If P_Q > 0.05, a fixed-effects IVW model was applied; otherwise, a random-effects model was used.[32,33] To control the false-positive rate arising from multiple testing, a Bonferroni correction was applied. Given the bidirectional design, a total of 10 directional tests were performed (5 hematologic outcomes × 2 directions). These 10 tests were considered a single family, and the statistical significance threshold was set at 0.005 (i.e., 0.05/10).[34]

Sensitivity analysis and pleiotropy testing

All MR analyses were performed using the TwoSampleMR package (version 4.3.2) and the MR-PRESSO package (version 1.0) in R software (version 4.3.1). To ensure the robustness of causal estimates, comprehensive sensitivity analyses were performed. The weighted median estimator (WME) and MR-Egger regression were used as complementary methods to validate the IVW results.

Horizontal pleiotropy was assessed using two methods. The MR-Egger regression intercept test was used to examine directional pleiotropy, with an intercept *P*-value > 0.05 indicating no significant pleiotropy.[35] Additionally, the MR-PRESSO global test was applied to identify potential outlier SNPs. MR-PRESSO identified and removed all outlier SNPs to provide more accurate estimates.[36] Details are listed in Supplementary Table. 5. IVW analysis was repeated using the dataset after outlier removal. To assess the plausibility of the assumed causal directions, Steiger directionality tests were performed for the bidirectional associations between SLE and B12DA.[37] The test compares the variance explained (R^2) by the genetic instruments in the exposure versus the outcome. A significantly larger R^2 for the exposure supports the assumed causal direction. R^2 values were calculated using the formula $R^2 = \beta^2 / (\beta^2 + SE^2 \times N)$.

A leave-one-out analysis was also performed by iteratively removing each instrumental SNP and re-running the IVW analysis with the remaining SNPs to determine whether the overall causal estimate was driven by a single influential SNP. Heterogeneity was assessed using Cochran's Q test and its *P*-value. The results of all sensitivity analyses, including effect estimates, confidence intervals, *P*-values for each method, and statistics for heterogeneity and pleiotropy tests, are fully reported in Tables 2 and 3.

Ethics statement and data availability

All GWAS summary statistics used in this study are publicly available. The original SLE GWAS (Bentham *et al.*, 2015[23]) was approved by the relevant institutional review boards, and all participants provided informed consent. The FinnGen study (Release 10) was approved by the Finnish Ethics Committee (permit number: TUKO 118/2021). As this study involved secondary analysis of de-identified summary-level data, no additional ethical approval was required.

Reporting guideline

This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline. The completed checklist is provided as Supplementary File 1.

Results

Overview of genetic instrument selection

All GWAS summary statistics used in this study were derived from populations of European ancestry. Table 1 details the data sources, GWAS accession links, sample sizes, case/control counts, initial SNP numbers, mean F-statistics, and significance thresholds (SLE, B12DA, IDA: $P < 5 \times 10^{-8}$; ITP, AGC, MDS: $P < 5 \times 10^{-5}$) for SLE and the five hematologic disorders: ITP, B12DA, AGC, MDS, and IDA. Following LD clumping ($r^2 < 0.001$, window > 10,000 kb), allele harmonization, and confounder filtering via PhenoScanner V2, the number of instrumental variables was reduced from 4,163 candidate SNPs to between 20 and 25 for the SLE-to-outcome analyses, depending on the specific outcome

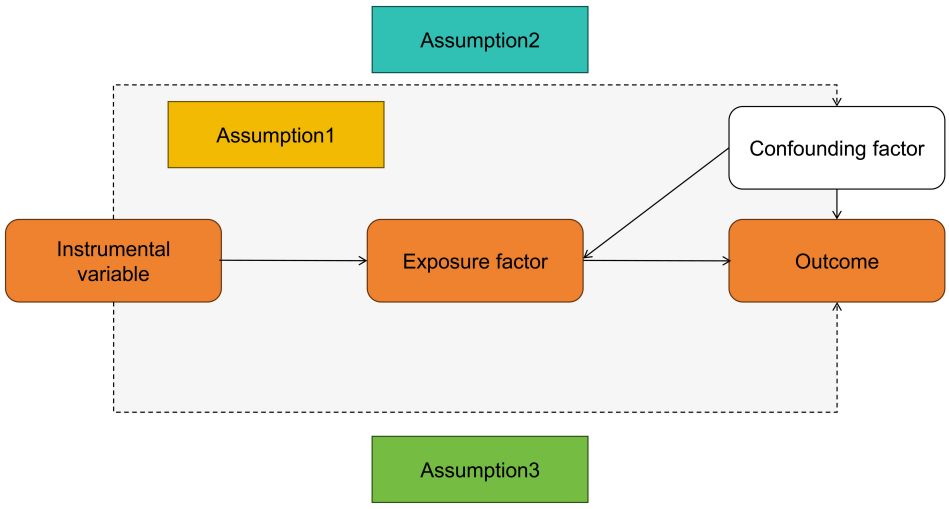

Fig. 1. Schematic overview of the core assumptions in Mendelian randomization. This figure illustrates the three core assumptions of Mendelian randomization (MR) analysis. Genetic variants used as instrumental variables (IVs) must satisfy the following criteria: Assumption 1 (Relevance): The IV is robustly associated with the exposure of interest. Assumption 2 (Independence): The IV is not associated with any confounder that influences the exposure–outcome relationship. Assumption 3 (Exclusion restriction): The IV influences the outcome solely through the exposure and not via alternative causal pathways. Solid arrows represent causal relationships, while dashed arrows indicate prohibited associations that would violate MR assumptions.

(Supplementary Table. 1). The mean F-statistic for all final genetic instruments included in the analyses exceeded 10 (see Supplementary Table. 3), indicating a low risk of weak instrument bias. Sufficiently powered genetic instruments were obtained for most analyses (see Supplementary Table. 4). All *P*-values reported in this study are two-sided. A Bonferroni correction was applied to control the family-wise error rate for the 10 directional tests performed (5 hematologic outcomes × 2 directions). Accordingly, associations with $P < 0.005$ were considered statistically significant. A nominally significant inverse association was observed between genetically predicted MDS and SLE risk (IVW odds ratio (OR) = 0.96, 95% CI: 0.93–0.99, $P = 0.023$). However, this did not survive correction for multiple testing ($P < 0.005$) and was not consistent across MR methods, indicating a lack of robust evidence.

Primary MR findings

Effect of SLE on B12DA risk

As shown in Figure 3a, genetically predicted SLE was significantly associated with an increased risk of B12DA (IVW OR = 1.08, 95% CI: 1.04–1.13, $P = 0.00023$). This association remained significant after Bonferroni correction for multiple testing (corrected significance threshold $P < 0.005$). The WME (OR = 1.07, 95% CI: 1.01–1.14, $P = 0.023$) and MR-Egger regression (OR = 1.09, 95% CI: 1.00–1.19) yielded effect estimates consistent in direction with the IVW result. The MR-Egger intercept test indicated no evidence of horizontal pleiotropy ($P = 0.832$). Cochran's Q test indicated no significant heterogeneity ($P = 0.610$), suggesting relative homogeneity in the effects of the 20 selected SLE instruments on B12DA. Furthermore, the MR-Egger intercept test again showed no evidence of horizontal pleiotropy ($P = 0.832$). Leave-one-out analysis (Supplementary Fig. 1) confirmed that the association was not driven disproportionately by any single SNP, and the symmetry of the funnel plot (Supplementary Fig. 2) further supported the robustness of the result.

Effect of B12DA on SLE risk

Reverse MR analysis revealed a stronger effect. As shown in Figure 3b, genetically predicted B12DA was significantly associated with an increased risk of SLE (IVW OR = 2.22, 95% CI: 1.93–2.55, $P = 1.6 \times 10^{-29}$), a result that also survived multiple testing correction. The WME (OR = 2.13, 95% CI: 1.76–2.59, $P = 1.2 \times 10^{-14}$) and MR-Egger regression (OR = 1.92, 95% CI: 1.25-2.95) were directionally consistent with the IVW estimate. However, given the limited number of instruments (n = 5), the MR-Egger estimate should be interpreted with caution, and the MR-Egger intercept test detected no horizontal pleiotropy ($P = 0.538$). The analyses showed no evidence of heterogeneity (Cochran's Q $P = 0.355$) or horizontal pleiotropy (MR-Egger intercept $P = 0.538$). Both leave-one-out analysis (Supplementary Fig. 3) and the funnel plot (Supplementary Fig. 4) confirmed the robustness of this association. Of note, this reverse-direction analysis was based on only five genetic instruments. The MR-Egger regression estimate, while directionally consistent, did not reach statistical significance ($P = 0.058$). Given the limited number of instruments, these results should be interpreted with appropriate caution. To further validate the assumed causal directions, Steiger directionality tests were performed for the bidirectional associations between SLE and B12DA. For SLE → B12DA, the genetic instruments explained significantly more variance in SLE ($R^2 = 0.105$) than in B12DA ($R^2 = 4.4 \times 10^{-5}$), supporting the causal direction (Supplementary Table. 6). For

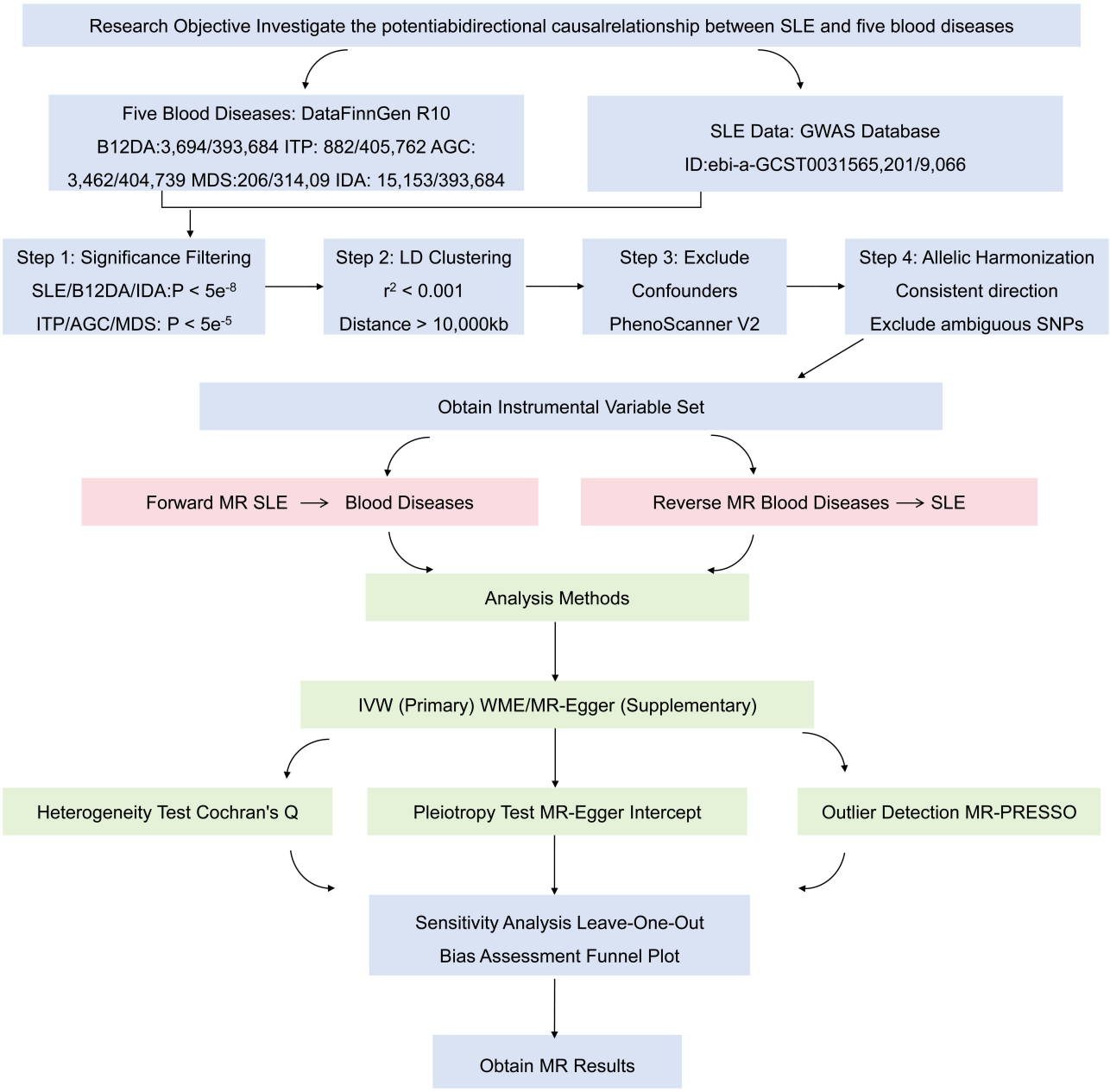

Fig. 2. Study design and workflow of the bidirectional Mendelian randomization analysis. This figure illustrates the overall study design and analytical workflow for the bidirectional Mendelian randomization (MR) analysis investigating the causal relationships between systemic lupus erythematosus (SLE) and five blood-related disorders: vitamin B12 deficiency anemia (B12DA), immune thrombocytopenia (ITP), agranulocytosis (AGC), myelodysplastic syndromes (MDS), and iron deficiency anemia (IDA). Data sources: SLE GWAS data were obtained from the Bentham *et al.*[23] study (ebi-a-GCST003156, 5,201 cases and 9,066 controls). Summary statistics for the five blood diseases were sourced from the FinnGen R10 consortium, with sample sizes as indicated. Instrumental variable selection: single nucleotide polymorphisms (SNPs) significantly associated with each exposure were selected using trait-specific *P*-value thresholds (5×10^{-8} for SLE, B12DA, and IDA; 5×10^{-5} for ITP, AGC, and MDS). Linkage disequilibrium (LD) clumping was performed ($r^2 < 0.001$, distance > 10,000 kb) to obtain independent instruments. Potential confounding variants were identified and removed using PhenoScanner V2, followed by allele harmonization to ensure effect allele consistency and exclusion of palindromic SNPs with ambiguous strand. MR analysis: Bidirectional MR analyses were conducted using inverse-variance weighted (IVW) as the primary method, with weighted median (WME) and MR-Egger as complementary approaches. Sensitivity analyses included Cochran's Q test for heterogeneity, MR-Egger intercept test for directional pleiotropy, MR-

PRESSO for outlier detection and correction, and leave-one-out analysis for assessing influential SNPs. Interpretation: Causal estimates were presented as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were performed using the TwoSampleMR package in R. GWAS, genome-wide association study; ID, identifier; kb, kilobase; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

B12DA → SLE, the test did not support the assumed direction (R^2_exposure = 0.00105, R^2_outcome = 0.01008), likely due to the limited number of instruments (n = 5) and the large disparity in GWAS sample sizes.

Robustness and triangulation of evidence

For the bidirectional associations described above, estimates from different MR methods were highly consistent in direction, with overlapping confidence intervals (Tables 2 and 3). All sensitivity tests, including the MR-PRESSO global test ($P > 0.05$) and re-analysis after outlier removal, supported the reliability of the primary findings. In summary, this bidirectional MR analysis provides genetic evidence supporting a potential bidirectional causal relationship between SLE and B12DA.

MR analysis results for other hematologic disorders

After multiple testing correction (corrected significance level set at $P < 0.005$), no statistically significant genetically predicted causal associations were identified between SLE and ITP, AGC, or IDA in this study (all IVW $P > 0.005$). Regarding MDS, the MR analyses suggested a non-robust association with SLE. In the reverse analysis (MDS → SLE), the IVW method showed a nominally significant negative correlation (OR = 0.96, 95% CI: 0.93–0.99, $P = 0.023$). However, this result did not survive multiple testing correction, and neither the WME nor MR-Egger regression showed significance ($P > 0.05$), indicating weak consistency across methods. Conversely, in the forward analysis (SLE → MDS), the IVW result was only marginally significant (OR = 1.18, 95% CI: 1.00–1.40, $P = 0.056$) and also failed to meet the corrected threshold. As none of these findings satisfied the pre-defined stringent significance criteria, and with confidence intervals that were broad and included 1, the present study concludes that the current results do not support a robust genetic causal association between MDS and SLE.

Assessment of heterogeneity and pleiotropy

As shown in Tables 2 and 3, Cochran's Q test indicated no significant heterogeneity in any of the analyses (all $P > 0.05$), suggesting good consistency in the effect estimates of the selected genetic instruments. The MR-Egger intercept test did not detect significant horizontal pleiotropy (all intercept *P*-values > 0.05). The SNPs excluded during instrument selection were primarily associated with inflammatory, metabolic, or infectious risk factors (Supplementary Table. 2). This suggests that some genetic effects may operate through shared pathways involving systemic inflammation or metabolism, rather than being specific to SLE or individual hematologic disorders.

Discussion

This bidirectional MR study provides a novel genetic causal perspective for understanding the heterogeneity of hematologic complications in SLE. Our core finding reveals a potential bidirectional genetic association between SLE and B12DA,[38] whereas no robust evidence emerged for similar links between SLE and ITP, AGC, IDA, or MDS.

The SLE–B12DA bidirectional association: mechanistic implications

SLE patients exhibit a high prevalence of B12DA, as documented in observational studies.[39] For the first time, the genetic causal evidence provided by our MR analysis suggests that this association may be partly driven by shared genetic susceptibility, rather than being entirely explained by confounding or reverse causality. This finding carries significant pathophysiological implications. On one hand, the chronic systemic inflammation of SLE could contribute to conditions that lead to a clinical diagnosis ofB12DA, such as impaired absorption related to autoimmune gastritis or alterations in the intestinal microenvironment. However, these mechanistic hypotheses require direct validation in studies measuring serum vitamin B12 or other metabolic biomarkers, as our MR analysis is based on the clinical diagnosis of B12DA.[40,41] On the other hand, reverse MR analysis indicates that genetically predicted vitamin B12 deficiency is associated with an increased risk of SLE. As a crucial cofactor for DNA synthesis and methylation reactions, vitamin B12 deficiency could potentially affect immune cell development and functional regulation. However, it is important to note that our study used the clinical diagnosis of B12DA as the exposure, not direct measurements of serum vitamin B12 levels. Therefore, while the genetic association is robust, the specific metabolic pathways involved remain to be elucidated. Recent studies indicate that the vitamin B12 transporter TCN2 can drive monocyte proliferation and exacerbate TLR4-mediated inflammatory responses in SLE patients by regulating one-carbon metabolism.[42] Furthermore, vitamin B12 supplementation is being investigated *in vitro* to modulate persistently dysregulated inflammatory gene expression in leukocytes from patients with lupus.[43] Therefore, this bidirectional association may point to a potential "inflammation–metabolic dysregulation" interaction pathway.[44] It must be emphasized that MR evidence indicates a potential causal relationship at the genetic level; however, it represents a genetically inferred causal hypothesis rather than proof of established clinical pathways. Consequently, the implicated molecular mechanisms require direct experimental validation. It should also be emphasized that the reverse direction (B12DA → SLE) was based on only five genetic instruments, and the MR-Egger estimate, though directionally consistent, did not reach statistical significance ($P = 0.058$). Therefore, these findings should be interpreted as hypothesis-generating rather than definitive causalevidence. Recent bidirectional MR studies have also demonstrated causal associations between SLE and other conditions. Using a bidirectional MR approach, Ding *et al.*[45] found no significant causal effect between vitamin D deficiency and SLE, suggesting that previously observed associations may be due to confounding rather than direct causality. Chen *et al.*[46] reported causal effects of certain autoimmune diseases on aplastic anemia,

Table 2. Mendelian randomization analysis of immune-related exposures on blood-related outcomes (SLE as exposure)

Exposure	nSNPs	Method	β (SE)	*P*-value	OR (95% CI)	Cochran's Q (Q/df/ *P*)	MR-Egger intercept (β/SE/*P*)	F-statisticrange	Leave-one-out conclusion	Total R^2
ITP	23	MR Egger	–0.16 (0.12)	0.209	0.85 (0.67–1.08)	25.04 / 21 / 0.246	0.06 / 0.03 / 0.109	30.4-374.85	Robust	0.0819643
	23	Weighted median	–0.04 (0.07)	0.534	0.96 (0.83–1.10	–	–	–		
	23	Inverse variance weighted	0.03 (0.05)	0.632	1.03 (0.92–1.14	28.37 / 22 / 0.164	–	–		
	–	MR-PRESSO	–	0.171	–	*P* = 0.274	–	–		
B12DA	20	MR Egger	0.09 (0.04)	0.053	1.09 (1.00–1.19)	16.61 / 18 / 0.550	–0.003 / 0.01 / 0.832	29.97-453.21	Robust	0.105077843
	20	Weighted median	0.07 (0.03)	0.023	1.07 (1.01–1.14	–	–	–		
	20	Inverse variance weighted	0.08 (0.02)	0.00023	1.08 (1.04–1.13	16.66 / 19 / 0.610	–	–		
	–	MR-PRESSO	–	0.541	–	–	–	–		
AGC	22	MR Egger	0.065 (0.058)	0.280	1.07(0.95–1.20)	15.66 / 20 / 0.737	-0.0163 / 0.0163 / 0.330	29.97-453.21	Robust	0.080534819
	22	Weighted median	0.030 (0.036)	0.415	1.03 (0.96–1.11	–	–	–		
	22	Inverse variance weighted	0.012 (0.025)	0.628	1.01 (0.96–1.06)	16.66 / 21 / 0.732	–	–		
	–	MR-PRESSO	–	0.755	–	–	–	–		
MDS	25	MR Egger	0.02 (0.17)	0.919	1.02 (0.73–1.43)	22.77 / 23/ 0.474	–0.05 / 0.05 / 0.326	29.97-453.21	Robust	0.115649093
	25	Weighted median	0.12 (0.12)	0.316	1.13 (0.89–1.44)	–	–	–		
	25	Inverse variance weighted	0.17 (0.09)	0.056	1.18 (1.00–1.40)	23.78 / 24 / 0.474	–	–		
	–	MR-PRESSO	–	0.526	–	–	–	–		

Table 2. Mendelian randomization analysis of immune-related exposures on blood-related outcomes (SLE as exposure) (*continued*)

Exposure	nSNPs	Method	β (SE)	*P*-value	OR (95% CI)	Cochran's Q (Q/df/ *P*)	MR-Egger intercept (β/SE/*P*)	F-statisticrange	Leave-one-out conclusion	Total R^2
IDA	24	MR Egger	-0.011 (0.033)	0.742	0.99 (0.93–1.05)	31.28 / 22 / 0.091	0.0047 / 0.0090 / 0.611	29.97-374.85	Robust	0.084860605
	24	Weighted median	0.007 (0.018)	0.707	1.01 (0.97–1.04)	–	–	–		
	24	Inverse variance weighted	0.004 (0.014)	0.750	1.00 (0.98–1.03)	31.66 / 23/ 0.107	–	–		
	–	MR-PRESSO	–	0.131	–	–	–	–		

This table summarizes the MR estimates for the effects of systemic lupus erythematosus (SLE) on five blood-related outcomes: immune thrombocytopenia (ITP), vitamin B12 deficiency anemia (B12DA), agranulocytosis (AGC), myelodysplastic syndromes (MDS), and iron deficiency anemia (IDA). For each exposure–outcome pair, the number of instrumental variables (nSNPs), MR methods applied (MR-Egger, weighted median, inverse-variance weighted [IVW], and MR-PRESSO), beta coefficients (β) with standard errors (SE), *P*-values, odds ratios (ORs) with 95% confidence intervals (CIs), Cochran's Q statistics (Q, degrees of freedom [df], and *P*-value) for heterogeneity assessment, MR-Egger intercept test for directional pleiotropy (β/SE/P), range of F-statistics, leave-one-out sensitivity conclusion, and total R^2 of the instruments are provided. The MR-Egger effect *P*-value is based on the t-distribution, whereas the 95% CI is based on the normal distribution. In analyses with a limited number of genetic instruments, these two approaches may yield inconsistent results; therefore, the MR-Egger effect estimate should be interpreted with caution. MR, Mendelian randomization; MR-Egger, Mendelian randomization–Egger regression; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

highlighting genetic links between autoimmune conditions and hematologic disorders. These findings, together with our results, underscore the value of bidirectional MR in disentangling complex associations between autoimmune diseases and hematologic conditions and in identifying potential therapeutic targets.

Interpretation of results for other hematologic disorders

This study did not detect genetic causal links between SLE and ITP, AGC, or IDA. In contrast, the results suggest that these clinically common hematologic complications are more likely driven by acquired factors, such as disease-specific autoantibody production during periods of high disease activity, metabolic changes secondary to chronic inflammation, or therapeutic agents, rather than by a shared genetic predisposition. This implies that the clinical approach to these abnormalities in SLE patients should prioritize investigation of underlying acquired etiologies, including disease activity and pharmacological adverse effects.

Particularly noteworthy is the nominally significant inverse association observed between MDS and SLE (IVW $P = 0.023$). However, this *P*-value did not survive Bonferroni correction for 10 directional tests (corrected threshold $P < 0.005$), and the estimates were inconsistent across different MR methods (weighted median $P = 0.279$, MR-Egger $P = 0.372$). Therefore, our data do not provide sufficient support for a robust genetic causal association between MDS and SLE. Previous research suggests that elevated inflammatory cytokines (e.g., TNF-α, IL-6), common to both diseases, may represent a shared pathological background; however, the causal direction remains unclear and requires investigation in larger studies.

Strengths and limitations

Strengths

The primary strength of this study is the application of an MR framework, which effectively controls for confounding and reverse causality inherent in observational research. This is further supported by a set of comprehensive sensitivity analyses.

Limitations

Heterogeneity in statistical power

As shown in Supplementary Table. 4, the available sample size of the SLE GWAS (N = 14,267) limited our ability to detect weak effects. Consequently, reverse MR analyses with SLE as the outcome (e.g., ITP, AGC, MDS → SLE) were underpowered (~20–22%). Therefore, the null

Table 3. Mendelian randomization analysis of hematologic outcomes on SLE (blood-related traits as exposures)

Exposure	nSNPs	Method	β (SE)	*P*-value	OR (95% CI)	Cochran's Q (Q/df/*P*)	MR-Egger intercept (β/SE/*P*)	F-statistic range	Leave-one-out conclusion	Total R^2
ITP	36	MR Egger	0.07 (0.04)	0.103	1.08 (0.99–1.18	29.92 / 34 / 0.668	-0.0287 / 0.0145 / 0.056	16.46-24.38	Robust	0.001665487
	36	Weighted median	–0.02 (0.03)	0.405	0.98 (0.92–1.03)	–	–	–		
	36	Inverse variance weighted	–0.004 (0.020)	0.851	1.00 (0.96–1.04)	33.83 / 35 / 0.524	–	–		
	–	MR-PRESSO	–	0.542	–	–	–	–		
B12DA	5	MR Egger	0.655 (0.219)	5.8e-02	1.92 (1.25–2.95)	3.786 / 3 / 0.285	0.0372 / 0.0537 / 0.538	30.3-149.58	Robust	0.001047713
	5	Weighted median	0.758 (0.098)	1.2e-14	2.13 (1.76–2.59)	–	–	–		
	5	Inverse variance weighted	0.797 (0.071)	1.6e-29	2.22 (1.93–2.55)	4.393 / 4 / 0.355	–	–		
	–	MR-PRESSO	–	0.555	–	–	–	–		
AGC	47	MR Egger	0.071 (0.096)	0.466	1.07 (0.89–1.30)	51.24 / 45 / 0.242	-0.0066 / 0.0164 / 0.691	16.51-27.22	Robust	0.002104012
	47	Weighted median	0.075 (0.058)	0.192	1.08 (0.96–1.21)	–	–	–		
	47	Inverse variance weighted	0.036 (0.040)	0.373	1.04 (0.96–1.12	51.42 / 46 / 0.270	–	–		
	–	MR-PRESSO	–	0.265	–	–	–	–		
MDS	17	MR Egger	-0.058 (0.063)	0.372	0.94 (0.83–1.07)	16.04 / 15 / 0.380	0.0121 / 0.0369 / 0.748	16.59-25.44	Robust	0.000998946
	17	Weighted median	-0.026 (0.024)	0.279	0.97 (0.93–1.02)	–	–	–		
	17	Inverse variance weighted	-0.038 (0.017)	0.023	0.96 (0.93–0.99)	16.15 / 16 / 0.443	–	–		
	–	MR-PRESSO	–	0.457	–	–	–	–		
IDA	3	MR Egger	–1.34 (1.35)	0.502	0.26 (0.02–3.68)	0.591 / 1 / 0.442	0.1822 / 0.1294 / 0.393	30.21-42.57	Robust	0.000257219
	3	Weighted median	0.38 (0.36)	0.300	1.46 (0.71–2.99)	–	–	–		
	3	Inverse variance weighted	0.52 (0.31)	0.098	1.68 (0.91–3.11	2.575 / 2 / 0.276	–	–		

Table 3. Mendelian randomization analysis of hematologic outcomes on SLE (blood-related traits as exposures) (*continued*)

Exposure	nSNPs	Method	β (SE)	*P*-value	OR (95% CI)	Cochran's Q (Q/df/*P*)	MR-Egger intercept (β/SE/*P*)	F-statistic range	Leave-one-out conclusion	Total R^2
	–	MR-PRESSO	–	–	–	–	–	–		

This table summarizes the MR estimates for the effects of five blood-related traits (ITP, B12DA, AGC, MDS, and IDA) on systemic lupus erythematosus (SLE). The same set of MR methods and diagnostic metrics as described in Table 2 are reported for each exposure–outcome pair. All analyses were conducted using consistent quality control and sensitivity analysis procedures to ensure the robustness of the causal inferences. The MR-Egger effect *P*-value is based on the t-distribution, whereas the 95% CI is based on the normal distribution. In analyses with a limited number of genetic instruments, these two approaches may yield inconsistent results; therefore, the MR-Egger effect estimate should be interpreted with caution. AGC, agranulocytosis; B12DA, vitamin B12 deficiency anemia; CI, confidence interval; df, degrees of freedom; IDA, iron deficiency anemia; ITP, immune thrombocytopenia; MDS, myelodysplastic syndromes; MR, Mendelian randomization; MR-Egger, Mendelian randomization–Egger regression; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; nSNPs, number of single nucleotide polymorphisms; OR, odds ratio; SE, standard error.

findings for genetic associations between ITP or AGC and SLE risk should be interpreted with caution. Weaker causal relationships cannot be ruled out due to underpowered analyses. Similarly, the results for the MDS–SLE association must be viewed in the context of low statistical power. While the IVW method yielded a nominally significant *P*-value of 0.023, this result did not pass the predefined multiple testing correction threshold ($P < 0.005$). More importantly, the results from the weighted median and MR-Egger methods were non-significant, indicating a lack of consistency across MR methods. Given the low statistical power, this nominal significance likely reflects a false-positive signal or chance variation rather than a true causal effect. Therefore, our data do not provide evidence supporting a genetic causal association between MDS and SLE. It is important to emphasize that the core finding of this study—the bidirectional association between SLE and B12DA—was supported with extremely high statistical confidence (>99%). This is primarily due to the large sample size of the B12DA GWAS (for the SLE → B12DA direction) and the strong genetic effect of B12DA on SLE (for the B12DA → SLE direction).

Limited number of instruments for B12DA

The reverse MR analysis examining the effect of B12DA on SLE was conducted using five genetic instruments. Although these SNPs were strong instruments (F > 10) and the IVW result was highly significant after multiple testing correction, the small number of instruments may limit the ability to test for potential pleiotropy and reduce the precision of the estimate. The MR-Egger regression did not reach statistical significance ($P = 0.058$), and therefore, while the IVW estimate suggests an association, causal inference should be made with caution.

Use of a relaxed *P*-value threshold for certain exposures

For ITP, AGC, and MDS, we adopted a relaxed significance threshold ($P < 5 \times 10^{-5}$) instead of the conventional genome-wide threshold ($P < 5 \times 10^{-8}$). This was necessary because the available GWAS for these conditions had limited sample sizes, and applying a stricter threshold would have resulted in an insufficient number of instrumental variables (often fewer than three) to perform valid MR analysis. To control the false-positive rate arising from multiple testing across the five hematologic outcomes, a Bonferroni correction was applied, setting the statistical significance level at 0.005. Nevertheless, we acknowledge that the relaxed threshold may increase the risk of weak instrument bias and false-positive findings. To mitigate this risk, we ensured that all selected instruments had F-statistics > 10, a widely accepted threshold indicating a low risk of weak instrument bias. Additionally, we performed a sensitivity analysis using a more stringent threshold ($P < 1 \times 10^{-6}$) for these exposures; as shown in Supplementary Table. 7, the number of remaining SNPs was too small (ITP: 2 SNPs, AGC: 0 SNPs, MDS: 1 SNP) to yield reliable MR estimates, confirming the necessity of the relaxed threshold. Therefore, the null findings for ITP, AGC, and MDS should be interpreted with caution. Furthermore, while the Steiger directionality test supported SLE → B12DA, it did not support the reverse direction. However, this result should be interpreted with caution given the limited number of instruments (n = 5) and the substantial disparity in GWAS sample sizes between B12DA (N = 397,378) and SLE (N = 14,267), which reduces the power of the Steiger test.

Potential pleiotropy and residual confounding

Despite employing various methods (e.g., MR-Egger and MR-PRESSO) to test for horizontal pleiotropy, residual confounding due to pleiotropy via unknown or unmeasured pathways remains a possibility, which is an inherent limitation of MR studies. Certain genetic instruments could influence the outcome by mediating an individual's response to environmental factors such as nutritional status. Such gene–environment interactions represent a form of horizontal pleiotropy that may remain undetected in our analysis. The findings of this study—although supported by rigorous sensitivity analyses—should be interpreted within this conceptual

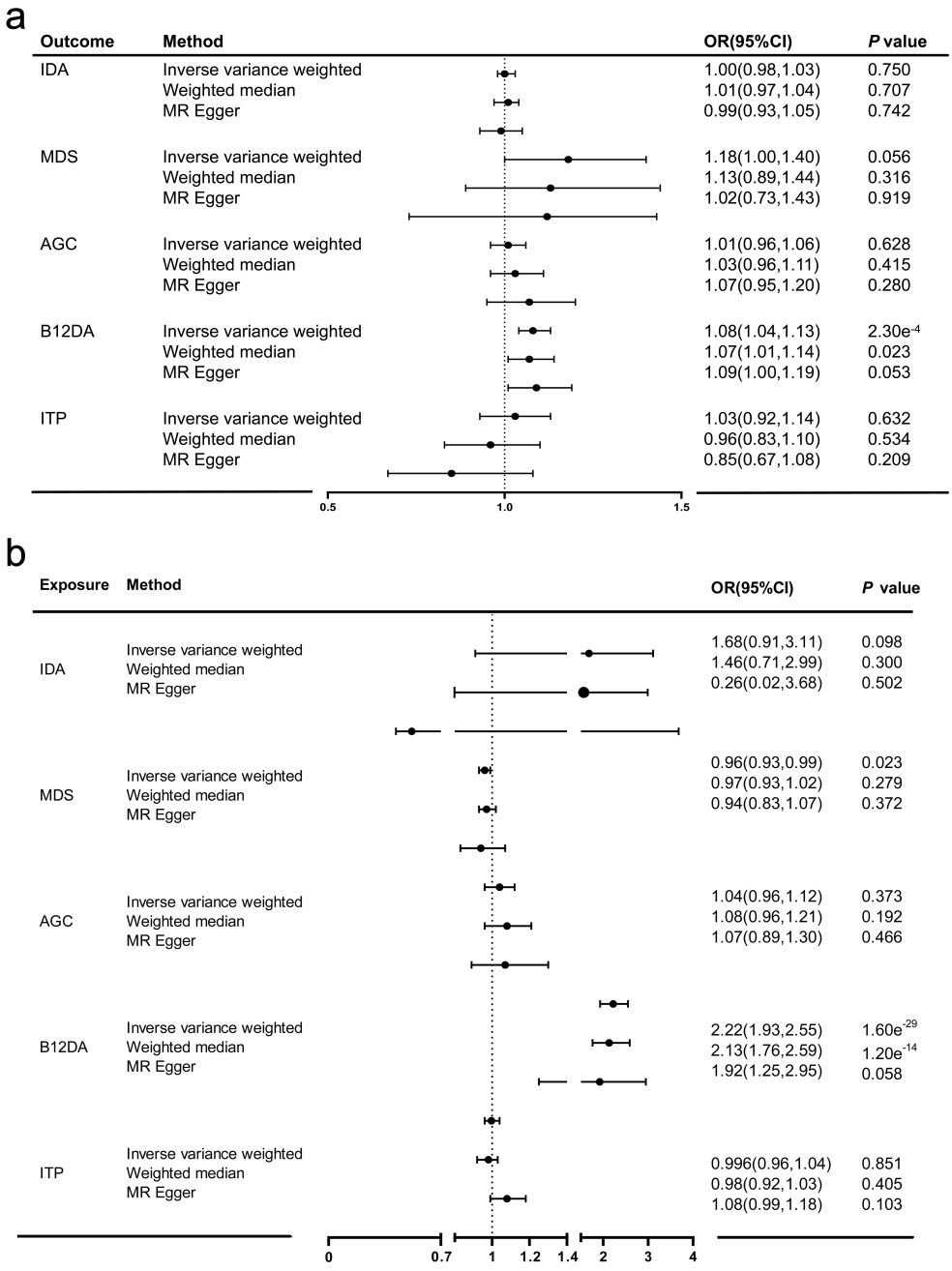

Fig. 3. Bidirectional Mendelian randomization estimates for systemic lupus erythematosus and five blood-related disorders. This figure presents the causal effect estimates from the bidirectional Mendelian randomization (MR) analysis between systemic lupus erythematosus (SLE) and five blood-related outcomes: vitamin B12 deficiency anemia (B12DA), immune thrombocytopenia (ITP), agranulocytosis (AGC), myelodysplastic syndromes (MDS), and iron deficiency anemia (IDA). (a) Forward MR analysis: effect of SLE on blood-related outcomes. Forest plot showing the causal effects of SLE on each blood-related outcome using three MR methods: inverse-variance weighted (IVW), weighted median, and MR-Egger. Effect estimates are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding *P*-values. IVW was used as the primary analysis method. A significant positive causal association was observed between SLE and B12DA (IVW OR = 1.08, 95% CI: 1.04–1.13, $P = 2.30 \times 10^{-4}$). No statistically significant causal effects were detected for ITP, AGC, MDS, or IDA after accounting for multiple testing. (b) Reverse MR analysis: effect of blood-related outcomes on SLE. Forest plot showing the causal effects of each blood-related outcome on SLE, estimated using the same three MR methods. A significant positive causal association

was identified for B12DA on SLE (IVW OR = 2.22, 95% CI: 1.93–2.55, $P = 1.60 \times 10^{-29}$). After correction for multiple testing, no statistically significant causal effects were observed for ITP, AGC, MDS, or IDA on SLE. All analyses were assessed for heterogeneity and pleiotropy through sensitivity analyses. ORs greater than 1 indicate a positive causal effect, while ORs less than 1 indicate a protective effect.

framework.

Population generalizability

Analyses were based on data from populations of European ancestry. This choice was made primarily to ensure genetic homogeneity during instrumental variable selection (e.g., LD clumping) and data analysis, thereby minimizing bias due to population stratification. However, the exclusive use of genetic data from populations of European ancestry limits the generalizability of our findings to other ethnic groups.

Indirect nature of biological mechanisms

MR identifies statistical associations. The specific molecular pathways underlying the observed SLE–B12DA association require direct validation in subsequent experimental studies.

Distance from clinical translation

Based on the current genetic findings, it is premature to recommend routine vitamin B12 screening or supplementation for patients with SLE. Any potential clinical intervention must be evaluated through rigorous prospective studies and clinical trials. Finally, it is important to reiterate that MR provides genetic evidence for causal inference at the population level but does not directly inform individual-level clinical decision-making. Therefore, our findings should be interpreted as hypothesis-generating rather than practice-changing.

Phenotype heterogeneity and potential misclassification bias

The hematologic outcomes (ITP, AGC, B12DA, IDA) were identified from FinnGen registry data using ICD codes. These real-world diagnoses are useful but come with inherent heterogeneity. For example, IDA and B12DA can have multiple secondary causes, and AGC may be drug-induced or infection-related. Such heterogeneity could weaken genetic associations if the instruments capture only specific etiologies. Misclassification bias, such as coding errors or incomplete diagnosticworkups, could also bias results toward the null. Although we used conservative multiple testing correction and sensitivity analyses to address these concerns, the findings should be interpreted in light of potential phenotype heterogeneity and diagnostic misclassification.

Future directions

Larger-scale GWAS of SLE and hematologic disorders are needed to improve statistical power, particularly for reverse MR analyses, and to identify additional genetic instruments for B12DA. Future studies should also validate these findings in populations of diverse ancestries and using more refined phenotypes, such as laboratory-confirmed diagnoses. By combining experimental models with clinical cohorts, future research should further elucidate the biological pathways linking SLE and B12DA. Studies incorporating direct measurements of serum vitamin B12 and related metabolic biomarkers will be particularly valuable. In addition, future work could explore whether closer attention to the clinical diagnosis of B12DA in patients with SLE is warranted, although prospective studies and clinical trials will be required before any clinical recommendations can be made.

Conclusions

This MR study provides genetic evidence consistent with a potential bidirectional association between SLE and B12DA, although the reverse direction requires replication with a larger set of genetic instruments. The findings should be considered hypothesis-generating rather than conclusive, offering new insights into their comorbid mechanisms.At the same time, the study did not support a similar genetic causal basis for associations between SLE and ITP, AGC, IDA, or MDS.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2026.00013.

Acknowledgments

We thank all participants and researchers involved in this Mendelian randomization study.

Funding

This work was supported by the Basic Research Program of Jiangsu (BK20251139) and the Special Project for Cultivating Outstanding Young Doctors in Jiangsu Provincial Hospital of Chinese Medicine (2023QB0127).

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Study design (TG, HZ), drafting of the manuscript (TG, HZ), data collection (LZ), data analysis (RC), and revision of the manuscript (RC). All authors contributed to the article and approved the submitted version.

Ethical statement

All GWAS summary statistics used in this study are publicly available. The original SLE GWAS (Bentham *et al.*, 2015[23]) was approved by the relevant institutional review boards, and all participants provided informed consent. The FinnGen study (Release 10) was approved by the Finnish Ethics Committee (permit number: TUKO 118/2021). As this study involved secondary analysis of de-identified summary-level data, no additional ethical approval was required.

Data sharing statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article (Table 1).

References

[1] Rose NR. Prediction and Prevention of Autoimmune Disease in the 21st Century: A Review and Preview. Am J Epidemiol 2016;183(5):403–406. DOI: 10.1093/aje/kwv292, PMID: 26888748.

[2] Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. Ann Rheum Dis 2023;82(3):351–356. DOI: 10.1136/ard-2022-223035, PMID: 36241363.

[3] Barber MRW, Drenkard C, Falasinnu T, Hoi A, Mak A, Kow NY, *et al*. Global epidemiology of systemic lupus erythematosus. Nat Rev Rheumatol 2021;17(9):515–532. DOI: 10.1038/s41584-021-00668-1, PMID: 34345022.

[4] Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, *et al*. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019;3(22):3780–3817. DOI: 10.1182/bloodadvances.2019000812, PMID: 31770441.

[5] Barcellini W, Fattizzo B, Cortelezzi A. Autoimmune hemolytic anemia, autoimmune neutropenia and aplastic anemia in the elderly. Eur J Intern Med 2018;58:77–83. DOI: 10.1016/j.ejim.2018.05.034, PMID: 30527923.

[6] Sobczyńska-Malefora A, Delvin E, McCaddon A, Ahmadi KR, Harrington DJ. Vitamin B(12) status in health and disease: a critical review. Diagnosis of deficiency and insufficiency - clinical and laboratory pitfalls. Crit Rev Clin Lab Sci 2021;58(6):399–429. DOI: 10.1080/10408363.2021.1885339, PMID: 33881359.

[7] Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, *et al*. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol 2017;92(10):1068–1078. DOI: 10.1002/ajh.24820, PMID: 28612425.

[8] Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, *et al*. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36(7):1703–1719. DOI: 10.1038/s41375-022-01613-1, PMID: 35732831.

[9] Kostopoulou M, Ugarte-Gil MF, Pons-Estel B, van Vollenhoven RF, Bertsias G. The association between lupus serology and disease outcomes: A systematic literature review to inform the treat-to-target approach in systemic lupus erythematosus. Lupus 2022;31(3):307–318. DOI: 10.1177/09612033221074580, PMID: 35067068.

[10] Sowa MA, Sun H, Wang TT, Virginio VW, Schlamp F, El Bannoudi H, *et al*. Inhibiting the P2Y(12) Receptor in Megakaryocytes and Platelets Suppresses Interferon-Associated Responses. JACC Basic Transl Sci 2024;9(9):1126–1140. DOI: 10.1016/j.jacbts.2024.05.014, PMID: 39444926.

[11] Fernández-Cladera Y, García-González M, Hernández-Díaz M, Gómez-Bernal F, Quevedo-Abeledo JC, González-Rivero AF, *et al*. Relationship of Hematological Profiles with the Serum Complement System in Patients with Systemic Lupus Erythematosus. Biomedicines 2024;12(5):967. DOI: 10.3390/biomedicines12050967, PMID: 38790929.

[12] Wang CB, Zhang YJ, Zhao MM, Zhao L. Dosage optimization of tacrolimus based on the glucocorticoid dose and pharmacogenetics in adult patients with systemic lupus erythematosus. Int Immunopharmacol 2023;124(Pt A):110866. DOI: 10.1016/j.intimp.2023.110866, PMID: 37678026.

[13] Mitroulis I, Kalafati L, Bornhäuser M, Hajishengallis G, Chavakis T. Regulation of the Bone Marrow Niche by Inflammation. Front Immunol 2020;11:1540. DOI: 10.3389/fimmu.2020.01540, PMID: 32849521.

[14] Park KW, Hwang YS, Lee SH, Jo S, Chung SJ. The Effect of Blood Lipids, Type 2 Diabetes, and Body Mass Index on Parkinson's Disease: A Korean Mendelian Randomization Study. J Mov Disord 2023;16(1):79–85. DOI: 10.14802/jmd.22175, PMID: 36628424.

[15] Castle WE. MENDEL'S LAW OF HEREDITY. Science 1903;18(456):396–406. DOI: 10.1126/science.18.456.396, PMID: 17752783.

[16] Bennett DA, Holmes MV. Mendelian randomisation in cardiovascular research: an introduction for clinicians. Heart 2017;103(18):1400–1407. DOI: 10.1136/heartjnl-2016-310605, PMID: 28596306.

[17] Gao N, Kong M, Li X, Wei D, Zhu X, Hong Z, *et al*. Systemic Lupus Erythematosus and Cardiovascular Disease: A Mendelian Randomization Study. Front Immunol 2022;13:908831. DOI: 10.3389/fimmu.2022.908831, PMID: 35734181.

[18] Xue H, Liu S, Zeng L, Fan W. Causal effect of systemic lupus erythematosus on psychiatric disorders: A two-sample Mendelian randomization study. J Affect Disord 2024;347:422–428. DOI: 10.1016/j.jad.2023.11.033, PMID: 38008292.

[19] Xu Q, Ni JJ, Han BX, Yan SS, Wei XT, Feng GJ, *et al*. Causal Relationship Between Gut Microbiota and Autoimmune Diseases: A Two-Sample Mendelian Randomization Study. Front Immunol 2021;12:746998. DOI: 10.3389/fimmu.2021.746998, PMID: 35140703.

[20] Qin Q, Zhao L, Ren A, Li W, Ma R, Peng Q, *et al*. Systemic lupus erythematosus is causally associated with hypothyroidism, but not hyperthyroidism: A Mendelian randomization study. Front Immunol 2023;14:1125415. DOI: 10.3389/fimmu.2023.1125415, PMID: 36860870.

[21] Zagkos L, Dib MJ, Pinto R, Gill D, Koskeridis F, Drenos F, *et al*. Associations of genetically predicted fatty acid levels across the phenome: A mendelian randomisation study. PLoS Med 2022;19(12):e1004141. DOI: 10.1371/journal.pmed.1004141, PMID: 36580444.

[22] Liu Y, Clarke R, Bennett DA, Zong G, Gan W. Iron Status and Risk of Heart Disease, Stroke, and Diabetes: A Mendelian Randomization Study in European Adults. J Am Heart Assoc 2024;13(6):e031732. DOI: 10.1161/JAHA.123.031732, PMID: 38497484.

[23] Bentham J, Morris DL, Graham DSC, Pinder CL, Tombleson P, Behrens TW, *et al*. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet 2015;47(12):1457–1464. DOI: 10.1038/ng.3434, PMID: 26502338.

[24] Zhang Y, Wang R. A mendelian randomization study on the association between 731 types of immune cells and 91 types of blood cells with venous thromboembolism. Thromb J 2025;23(1):28. DOI: 10.1186/s12959-025-00714-y, PMID: 40181342.

[25] Sakthiswary R, Raymond AA. The clinical significance of vitamin D in systemic lupus erythematosus: a systematic review. PLoS One 2013;8(1):e55275. DOI: 10.1371/journal.pone.0055275, PMID: 23383135.

[26] Wu MC, Leong PY, Chiou JY, Chen HH, Huang JY, Wei JC. Increased Risk of Systemic Lupus Erythematosus in Patients With Helicobacter pylori Infection: A Nationwide Population-Based Cohort Study. Front

Med (Lausanne) 2019;6:330. DOI: 10.3389/fmed.2019.00330, PMID: 32064263.

[27] Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90(3):190–199. DOI: 10.1016/j.critrevonc.2013.12.006, PMID: 24434034.

[28] Garnier R. Environmental and occupational risk factors for myelodysplastic syndrome (in French). Bull Cancer 2023;110(11): 1116–1128. DOI: 10.1016/j.bulcan.2023.02.024, PMID: 37419729.

[29] Staiger D, Stock JH. Instrumental variables regression with weak instruments. Econometrica 1997;65(3):557–586. DOI: 10.2307/2171753.

[30] Palmer TM, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, *et al*. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res 2012; 21(3):223–242. DOI: 10.1177/0962280210394459, PMID: 21216802.

[31] Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. Int J Epidemiol 2013;42(5): 1497–1501. DOI: 10.1093/ije/dyt179, PMID: 24159078.

[32] Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44(2):512–525. DOI: 10.1093/ije/dyv080, PMID: 26050253.

[33] Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum Mol Genet 2018;27(R2):R195–R208. DOI: 10.1093/hmg/ddy163, PMID: 29771313.

[34] Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt 2014;34(5):502–508. DOI: 10.1111/opo.12131, PMID: 24697967.

[35] Li C, Lin J, Yang T, Shang H. Green Tea Intake and Parkinson's Disease Progression: A Mendelian Randomization Study. Front Nutr 2022;9:848223. DOI: 10.3389/fnut.2022.848223, PMID: 35719152.

[36] Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50(5):693–698. DOI: 10.1038/s41588-018-0099-7, PMID: 29686387.

[37] Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet 2017;13(11):e1007081. DOI: 10.1371/journal.pgen.1007081, PMID: 29149188.

[38] Huang S, Wei X, Qin F, Yuan Z, Mo C, Kang Y, *et al*. Assessing causal association of circulating micronutrients and systemic lupus erythematosus susceptibility: a Mendelian randomization study. Front Nutr 2024;11:1359697. DOI: 10.3389/fnut.2024.1359697, PMID: 39161911.

[39] Dułak NA, Rytlewska M, Jaskólska M, Chmielewski M. A new perspective on vitamin B12 deficiency in rheumatology: a case-based review. Rheumatol Int 2024;44(4):737–741. DOI: 10.1007/s00296-024-05539-y, PMID: 38294542.

[40] Pluvinage JV, Ngo T, Fouassier C, McDonagh M, Holmes BB, Bartley CM, *et al*. Transcobalamin receptor antibodies in autoimmune vitamin B12 central deficiency. Sci Transl Med 2024;16(753): eadl3758. DOI: 10.1126/scitranslmed.adl3758, PMID: 38924428.

[41] Matsuda KM, Kotani H, Sato S, Yoshizaki A. Unveiling the hidden syndrome: The enigma of anti-transcobalamin receptor autoantibodies. Immunol Lett 2025;275:107028. DOI: 10.1016/j.imlet.2025.107028, PMID: 40280282.

[42] Liu B, Li A, Liu Y, Zhou X, Xu J, Zuo X, *et al*. Transcobalamin 2 orchestrates monocyte proliferation and TLR4-driven inflammation in systemic lupus erythematosus via folate one-carbon metabolism. Front Immunol 2024;15:1339680. DOI: 10.3389/fimmu.2024.1339680, PMID: 38881906.

[43] da Mota JCNL, Carvalho LM, Ribeiro AA, Souza LL, Borba EF, Roschel H, *et al*. Methyl-donor supplementation in women with systemic lupus erythematosus with different nutritional status: the protocol for a randomised, double-blind, placebo-controlled trial. Lupus Sci Med 2024;11(2):e001279. DOI: 10.1136/lupus-2024-001279, PMID: 39375179.

[44] Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017;542(7640):177–185. DOI: 10.1038/nature21363, PMID: 28179656.

[45] Ding Y, Yang S, Fan S, Tang Y, Teng Y, Tao X, *et al*. Is Vitamin D Deficiency the Cause or the Effect of Systemic Lupus Erythematosus: Evidence from Bidirectional Mendelian Randomization Analysis. J Immunol Res 2022;2022:8689777. DOI: 10.1155/2022/8689777, PMID: 36189146.

[46] Chen Q, Lu C, Wang C, Yu L. Effect of autoimmune diseases on aplastic anemia: a bidirectional two-sample Mendelian randomization study. Hematology 2026;31(1):2617680. DOI: 10.1080/16078454.2026.2617680, PMID: 41572584.