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Systemic lupus erythematosus Association between Osteomyelitis: A two-sample Mendelian randomization study in European population

Minhua Hu [a,c], Zhizhong Sun [a,c], Xintao Tang [a,c], Wenxing Zeng [a,c], Hongsong Yan [a,c], Ziwei Jiang [a,b], Feng Huang [a,b,*]

[a] Guangzhou University of Chinese Medicine, Guangzhou, China
[b] The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China
[c] The First Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, China

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) has been correlated with osteomyelitis (OM), yet the underlying causal relationship remains poorly understood. This study aims to investigate the causal association between SLE and OM using Mendelian randomization (MR) analysis.
Methods: Genetic instrumental variables (IVs) correlated with SLE were extracted from a comprehensive genome-wide association study (GWAS) summary database (5201 cases and 9066 controls). OM was considered a SLE phenotype, and summary data from the fast GWA data portal were utilized for the analysis. Eligible IVs were extracted following rigorous quality control measures ($P < 5 \times 10\text{-}8$, LD r2>0.001, distance 1 Mb, and $F > 10$). MR analysis was conducted using the Inverse Variance Weighted (IVW), MR-Egger, and Weighted Median (WM) methods after excluding potential confounders. Cochran's Q was applied for heterogeneity test. Pleiotropy was evaluated through MR-Egger intercept, MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) method, and Leave-one-SNP-out analysis.
Result: A total of 40 eligible IVs were included for MR analysis. IVW results demonstrated a positive causal association between SLE and OM ($P = 0.049$, $OR = 1.167$). Heterogeneity analysis reveal no significant heterogeneity in the IVW analysis ($P = 0.5503$). Pleiotropy tests, including MR-PRESSO global test and MR-Egger intercept, indicated no evidence of pleiotropy in our findings ($P > 0.05$). Additionally, the Leave-one-SNP-out analysis showed no substantial deviations when removing individual SNPs, thus supporting the robustness of our results.
Conclusion: This study establishes a genetic causal relationship between SLE and OM, indicating an increased risk of developing OM in individuals with SLE. Therefore, proactive management of SLE is advised to mitigate the risk of developing OM.

1. Introduction

Osteomyelitis (OM) is a pathological condition characterized by inflammatory bone disease caused by microorganisms. Clinically, it presents as the destruction of skeletal structures, involving trabeculae, cortical bone, bone marrow, and periosteum, leading to local

* Corresponding author. Guangzhou University of Chinese Medicine, Guangzhou, China.
E-mail address: m13427641014@163.com (F. Huang).

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pain, swelling, and even the formation of sinus tracts in the skin [1]. The incidence of OM has exhibited an upward trend over time. In the United States, the estimated incidence of OM increased from 11.4 cases per 100,000 person-years between 1969 and 1979 to 24.4 cases per 100,000 person-years between 2000 and 2009 [2]. The conventional treatment strategy for OM involves systemic or local antibiotic administration combined with surgical intervention to address devitalized bone. However, the negative prognosis of OM, often marked by recurrence and eventual development into chronic OM, poses significant challenges for patients and surgeons [3]. The emergence of OM is intricately linked with external infectious determinants, wherein diverse sources of infection give rise to distinct OM classifications. Prevalently, traumatic OM constitutes the predominant clinical archetype, accounting for approximately 80 % of cases. This form predominantly stems from the localized transmission of persistent infectious agents, typically ensuing open fractures or arthroplasty procedures. In contrast, hematogenous OM, although less frequent, is primarily attributed to bacteremia, resulting in infection of the vertebral body and epiphysis. Additionally, a subset of OM cases arises secondarily due to vascular insufficiency, with a substantial portion originating from complications of diabetic foot infections [4]. Beyond environmental influences, the evolution of OM is inextricably tied to host-related factors. Among these, the genetic dimension, which has historically been understated in prior investigations, emerges as a pivotal determinant in OM development and progression. A burgeoning body of evidence underscores the potential role of genetic variants, specifically single nucleotide polymorphisms (SNPs), in shaping the susceptibility to OM. Noteworthy instances include genetic variants at loci such as Bax-Gene G (-248) (rs4645878), IFN-γ (rs2430561), IL-1β (rs1143634), and TLR-2 (rs3804099), which have demonstrated associations with heightened vulnerability to hematogenous or traumatic OM across diverse ethnic cohorts [5–7].

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disorder distinguished by the generation of autoantibodies and widespread inflammation affecting multiple organ systems [8]. The malady encompasses a spectrum of organs, including but not limited to the skin, joints, kidneys, lungs, central nervous system, and hematopoietic system, and is accompanied by an array of complications [8]. Similar to OM, the etiology of SLE is inherently linked to both environmental and genetic factors. The interaction between susceptibility genes and environmental triggers in individuals with SLE leads to an irreversible breakdown of immune self-tolerance, resulting in the clinical presentation of the disease [9]. Within this immunologic context, SLE commonly gives rise to various complications. Among these complications, skeletal system involvement emerges as a recurring issue, leading to bone-related impairments like arthritis, rheumatoid arthritis, femoral head necrosis, and OM, prominently observed in SLE patients [10]. Osteomyelitis, a condition strongly linked to genetic factors, has been extensively studied for its connection to SLE. The association between SLE and OM has been firmly established, with several investigators reporting cases of SLE patients presenting with concurrent acute septic OM or chronic Garre's sclerosing OM [11–13]. Furthermore, a comprehensive retrospective cohort study with stronger evidence demonstrated a significantly higher incidence of OM in SLE patients compared to the control group [14]. However, due to potential residual confounders and disruptions in acquired behaviors like smoking, immunosuppression, and hormone use, along with the possibility of reverse causality, previous observational studies have offered limited insights into the causal link between SLE and OM. It remains challenging to determine whether OM in SLE patients arises from acquired behaviors or is genetically rooted from birth, leaving the genetic causality behind this relationship uncertain.

In recent years, Mendelian randomization (MR) studies have gained prominence as a means to assess causality in observed associations between modifiable exposures or risk factors and clinically relevant outcomes. MR employs genetic variants as instrumental variables (IVs). As the alleles of these genetic variants are assigned to individuals prior to any exposure or outcome, they are largely associated with acquired potential confounders independently of environmental exposure. Consequently, the genetic-disease association remains unaffected by common confounding factors such as environment, socioeconomic factors, and individual behavior [15].

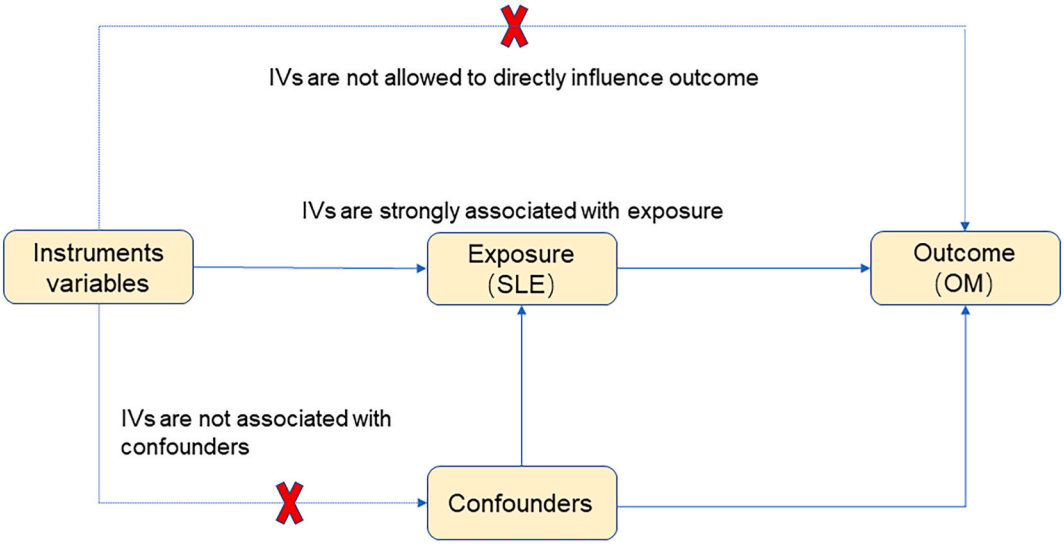

Fig. 1. A comprehensive examination of the three assumptions of MR study.

Therefore, MR designs can effectively mitigate the influence of potential confounders or reverse causality on experimental results [16]. In the present study, we employed a MR approach to examine the causal association between SLE and OM.

2. Methods

2.1. Study design

This study employed a MR design, utilizing publicly available datasets derived from large-sample genome-wide association studies (GWAS). Genetic variants (SNPs) were chosen as IVs for the analysis. The MR analysis was conducted based on three key assumptions (Fig. 1): 1). The correlation assumption: The selected IVs exhibit a significant association with the exposure of interest, SLE. 2). The independence assumption: The selected IVs are not associated with any confounding factors that may influence the relationship between the exposure and the outcome. 3). The exclusivity assumption: The selected IVs exert an exclusive impact on the outcome through their effect on the exposure and do not directly influence the outcome [17].

2.2. Data source

Genetic summary data associated with SLE were obtained from GWAS on SLE published in Nat Genet by Bentham et al. [18]. A total of 14,267 individuals with European ancestry were encompassed in the study, contained 5201 SLE patients and 9066 controls. All cases met the criteria for SLE diagnosis by the American College of Rheumatology.

Jiang LD [19] et al. applied fast GWA or fast GWA GLMM to 3000 traits on 456,422 array-genotyped and 49,960 whole-exome-sequenced individuals of the European ancestry in the UK Biobank. GWAS summary data (GCST90044537) associated with OM can be downloaded from the fast GWA data portal. (https://yanglab.westlake.edu.cn/data/ukb_fastgwa/imp/), contained 122 OM patients and 456,225 controls.

The data used in this study are published public data and therefore do not require further ethical approval.

2.3. Extraction of genetic IVs

To identify SNPs that were robustly associated with SLE, we applied a genome-wide significance threshold, considering SNPs with a *P*-value less than 5×10^{-8}. In order to obtain independent SNPs for use as exposure variables, we performed clumping and discarded SNPs that exhibited linkage disequilibrium (LD) with an r^2 value greater than 0.001 within a 1 Mb distance, utilizing the European reference panel. For the reliability of the IVs, we calculated the F-statistics, which quantifies the strength of the genetic variant ($F =$ beta^2/se^2) [20]. SNPs with F-statistics below 10 were excluded to mitigate any bias arising from weak instruments. R^2 refers to the cumulative explained variance of the selected SNP during exposure, We calculated the total R^2-value of the study based on the formula: $R^2 = 2 \times MAF \times (1\text{-MAF}) \times (\beta/SD)^2$. Then, we used the mRnd calculation tool (https://shiny.cnsgenomics.com/mRnd/) to assess the power of our research.

Next, we extracted SNPs associated with OM characteristics while also removing SNPs with palindromic properties and intermediate allele frequencies. Furthermore, to minimize the influence of known confounding factors on the estimation of causality, SNPs that were associated with OM confounders at a significance threshold of $P < 5 \times 10^{-8}$ were manually excluded using PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk).

2.4. MR analysis

Data processing and statistical analyses were conducted using the Two-sample MR package (version 0.5.6) in the R software environment (version 4.3.0). Three different methods, namely the Inverse Variance Weighted (IVW, random effects), MR-Egger, and Weighted Median (WM) methods, were employed to analyze the causal relationship between systemic lupus erythematosus (SLE) and osteomyelitis (OM).

The IVW method, which combines Wald estimates of specific variables by utilizing the inverse of their approximate variance as corresponding weights, served as the primary approach for the Mendelian randomization (MR) analysis in this study. The MR-Egger method was employed to identify potential violations of IV assumptions; however, it should be noted that this method may introduce bias and potentially amplify type I errors [21]. To address the issue of invalid instruments, the WM method was utilized, as it has the ability to mitigate the impact of such instruments. Importantly, the WM method produces consistent estimates even when up to 50 % of the selected genetic variants are invalid [22].

2.5. Heterogeneity test and pleiotropy test

To assess heterogeneity of statistical results, Cochran's Q statistic was employed as a test. A *P*-value exceeding 0.05 was deemed indicative of non-significant heterogeneity among the analyzed variables. In addition, the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) method were utilized to identify outliers and detect potential pleiotropy. If outliers were identified, they were subsequently excluded from the analysis, and the analysis was performed again. To further examine potential pleiotropy and evaluate influence on the risk estimation, MR-Egger regression was employed. The intercept test was utilized to assess the presence of pleiotropy, with a *P*-value greater than 0.05 indicating the absence of pleiotropy. Leave-one-SNP-out analysis was conducted for

identifying SNPs that conceivably influenced the results and to evaluate the reliability of the findings. The entire MR study process is visually summarized in Fig. 2.

3. Result

3.1. Selection of IV for MR analysis

In the present study, a total of 43 significant and independent SNPs were included as IVs for the MR analysis, meeting the stringent threshold of $P < 5 \times 10^{-8}$ and demonstrating low LD with an LD $r^2 > 0.001$. The F-statistics of the selected candidate SNPs exceeded the threshold of 10, indicating that weak instrument bias was effectively avoided. To ensure the robustness of our analysis, we excluded palindrome SNPs (rs2736332) among the 43 SNPs due to their inherent limitations. Furthermore, two SNPs, namely rs6679677 and rs1270942, exhibited strong associations with confounders (diabetes) of OM. Therefore, to minimize potential confounding effects, these SNPs were also excluded from the study.

Ultimately, a set of 40 SNPs were determined to be the genetic IVs for the MR analysis, as summarized in Table 1. The total R^2 value of these candidate SNPs in the study was 0.070778557 and substituted it into mRnd tool to calculate the power value of the study as 0.68. These SNPs were carefully selected to meet rigorous criteria and serve as reliable instruments for investigating the causal relationship between SLE and OM.

3.2. MR analysis

The IVW analysis revealed a statistically significant positive causal association between SLE and OM ($P = 0.049$, 95 % confidence interval [*CI*]: 1.0001–1.3631, odds ratio [*OR*] = 1.167). In SLE patients, the relative risk of developing OM was increased by 16.7 %. However, the results obtained from the MR-Egger revealed that there was no significant association between OM and the risk of SLE (*OR* = 1.384, 95%*CI*: 0.9824 to 1.9506, $P = 0.070$). Similarly, the Weighted Median also indicated non-significant association (*OR* = 1.245, 95 % *CI*: 0.9881 to 1.5690, $P = 0.063$) between OM and SLE risk. The scatter plot in Fig. 3 visually represents the causal effect of the MR analysis, depicting the relationship between SLE and OM.

3.3. Heterogeneity test and pleiotropy test

The Cochran's Q test results indicated no significant heterogeneity between the effect estimates of the IVs in both the IVW method ($Q = 37.239$, $P = 0.5503$) and MR-Egger method ($Q = 36.0511$, $P = 0.5598$), as illustrated in Fig. 4. The MR-PRESSO test did not detect any outliers among those included SNPs, suggesting the absence of significant horizontal pleiotropy (global test $P = 0.522$).

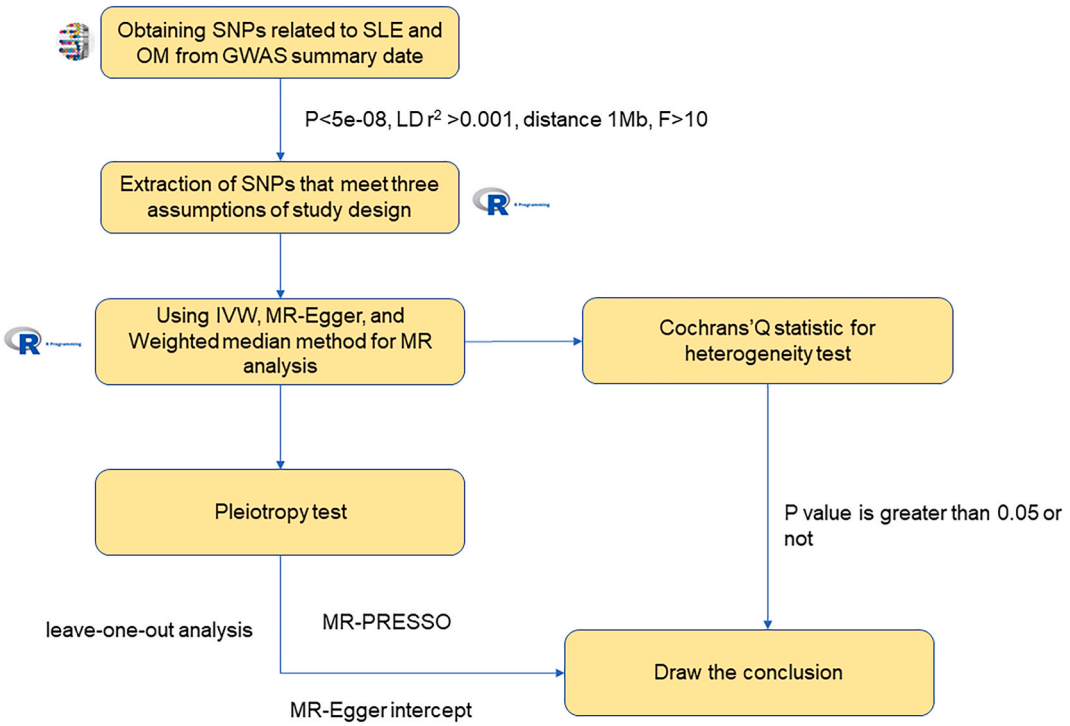

Fig. 2. The whole process of MR study.

Table 1
The detailed information of identified SNPs in exposure and outcomes.

SNPs	EA	OA	Exposure (Systemic lupus erythematosus)				Outcome (Osteomyelitis)		
			Beta	Se	P	*F*-statistic	Beta	Se	P
rs10048743	G	T	0.231111721	0.0412056	2E-08	31.457983	−0.168821	0.18559	0.36302
rs10200680	T	C	−0.24846136	0.0424835	5E-09	34.204025	−0.005578	0.18064	0.97537
rs1078324	A	C	−0.71334989	0.0781665	7.1E-20	83.284505	−0.289825	0.27751	0.29631
rs10912578	A	G	0.246860078	0.0309918	1.7E-15	63.44657	−0.094531	0.1394	0.49769
rs1143679	A	G	0.58221562	0.0399866	5E-48	212.00105	−0.284402	0.21574	0.18742
rs12094036	C	T	−0.32850407	0.0578595	1.4E-08	32.235351	−0.142981	0.23603	0.54467
rs13019891	T	G	−0.56211892	0.0290336	1.7E-83	374.84758	0.06762	0.13003	0.60304
rs13136219	T	C	−0.17435339	0.027787	3.5E-10	39.371202	−0.021349	0.13235	0.87186
rs13332649	G	A	−0.31471075	0.0375683	5.4E-17	70.174797	−0.16741	0.15289	0.27354
rs143123127	A	G	0.470003629	0.0840342	2.2E-08	31.281695	0.082867	0.35289	0.81435
rs143810596	G	T	−0.61618614	0.1125738	4.4E-08	29.960512	−0.299815	0.42568	0.48123
rs1464446	T	G	−0.32850407	0.0401497	2.8E-16	66.944713	−0.131983	0.16248	0.4166
rs150180633	T	C	0.928219303	0.0689573	2.7E-41	181.19255	1.22272	0.55267	0.02694
rs17849501	T	C	0.810930216	0.0498642	1.8E-59	264.47747	−0.397877	0.28722	0.16597
rs2431697	C	T	−0.22314355	0.0292964	2.6E-14	58.014868	0.070388	0.12871	0.58447
rs2459611	C	T	−0.26136476	0.045245	7.6E-09	33.369744	−0.155706	0.22335	0.48572
rs2573219	C	A	0.587786665	0.0429292	1.1E-42	187.4712	0.489971	0.22222	0.02746
rs268124	C	T	−0.18632958	0.0323703	8.6E-09	33.13379	0.220614	0.14536	0.12909
rs34703115	C	T	−0.61618614	0.1047776	4.1E-09	34.58493	−0.042207	0.40522	0.91704
rs35000415	T	C	0.587786665	0.041539	1.9E-45	200.22962	0.024723	0.20272	0.90293
rs35251378	A	G	−0.23572233	0.0324266	3.6E-13	52.84449	−0.097244	0.14107	0.49061
rs353608	A	G	−0.18632958	0.0280198	2.9E-11	44.221599	0.061052	0.12858	0.63492
rs3747093	A	G	0.262364264	0.0345055	2.9E-14	57.813999	0.029686	0.16552	0.85766
rs4274624	C	T	0.559615788	0.0326791	9.7E-66	293.25088	0.134968	0.1531	0.37801
rs4388254	T	C	0.378436436	0.0603977	3.7E-10	39.259567	0.42848	0.33628	0.2026
rs4661543	T	G	−0.27443685	0.0423755	9.4E-11	41.94267	0.112869	0.19312	0.55892
rs4916215	C	T	−0.22314355	0.0339693	5.1E-11	43.151401	0.089302	0.14376	0.53447
rs58688157	G	A	−0.22314355	0.0335647	3E-11	44.197956	0.012481	0.14322	0.93056
rs58721818	T	C	0.657520003	0.0755941	3.4E-18	75.65585	0.329283	0.37004	0.37354
rs597808	G	A	−0.16251893	0.0294736	3.5E-08	30.40467	−0.0856	0.1282	0.50432
rs6671847	A	G	0.198850859	0.0289651	6.6E-12	47.130869	0.060702	0.12856	0.63681
rs6889239	C	T	0.277631737	0.03174	2.2E-18	76.511271	0.154141	0.15026	0.30498
rs7097397	A	G	−0.18632958	0.0287118	8.6E-11	42.115472	0.165425	0.13228	0.21109
rs73050535	T	C	−0.71334989	0.1241342	9.1E-09	33.023458	−0.681314	0.41733	0.10256
rs73068668	A	G	−0.31471075	0.0574903	4.4E-08	29.966312	0.319953	0.24644	0.19419
rs7768653	C	T	0.207014169	0.0296891	3.1E-12	48.619101	0.040677	0.13086	0.75591
rs7823055	G	T	0.350656872	0.0286208	1.6E-34	150.10667	0.167002	0.13133	0.20349
rs7899626	T	C	0.182321557	0.0332532	4.2E-08	30.061422	0.201591	0.14227	0.15649
rs9274357	C	G	0.457424847	0.0351961	1.3E-38	168.90777	0.258387	0.17007	0.12868
rs9852014	G	A	0.620576488	0.0492727	2.3E-36	158.62739	0.220288	0.2489	0.37614

EA: effect allele; OA: other allele; Se: Standard error; Beta: Beta coefficient.

Furthermore, the MR-Egger regression analysis demonstrated that the MR results of were not influenced by pleiotropy, as indicated by an intercept of −0.065 ($P = 0.282$). The leave-one-SNP-out analysis, depicted in Fig. 5, demonstrated that the exclusion of individual SNPs did not result in substantial differences in the combined effect estimates between the remaining SNPs and the overall results. This finding underscores the robustness of the MR estimation results. A comprehensive summary of the MR analysis results is provided in Table 2, presenting the effect estimates and corresponding statistical measures.

4. Discussion

In the present study, we conducted a two-sample MR analysis to investigate the causal relationship between SLE and OM. Our MR analysis results demonstrated that patients with SLE carries predisposition gene that have a significantly higher relative risk of developing OM compared to the general population. These findings align with the results of a previous observational study, a retrospective cohort study conducted in Taiwan, China, which reported a significantly higher incidence of OM in SLE patients compared to controls [14]. Notably, our study accounted for confounding factors such as diabetes, allowing us to isolate the specific effect of SLE on the risk of OM. We observed a 16.7 % increase in the relative risk of OM in SLE patients, and the utilization of genetic variants as instrumental variables enhanced the reliability of our findings, as these variants are not influenced by environmental factors, such as the use of immunosuppressants and hormones, and smoking.

The underlying mechanism linking SLE and the increased incidence of OM remains unclear. It has been suggested that the restricted immune function observed in SLE may play a role. Susceptibility genes intimately tied to SLE, such as the Mannose Binding Lectin (MBL) gene, have demonstrated a pivotal role. Notably, the A\B and A\O polymorphisms have been identified as determinants influencing SLE susceptibility, with implications for immune deficiency mechanisms. As a result, the coexistence of SLE and MBL

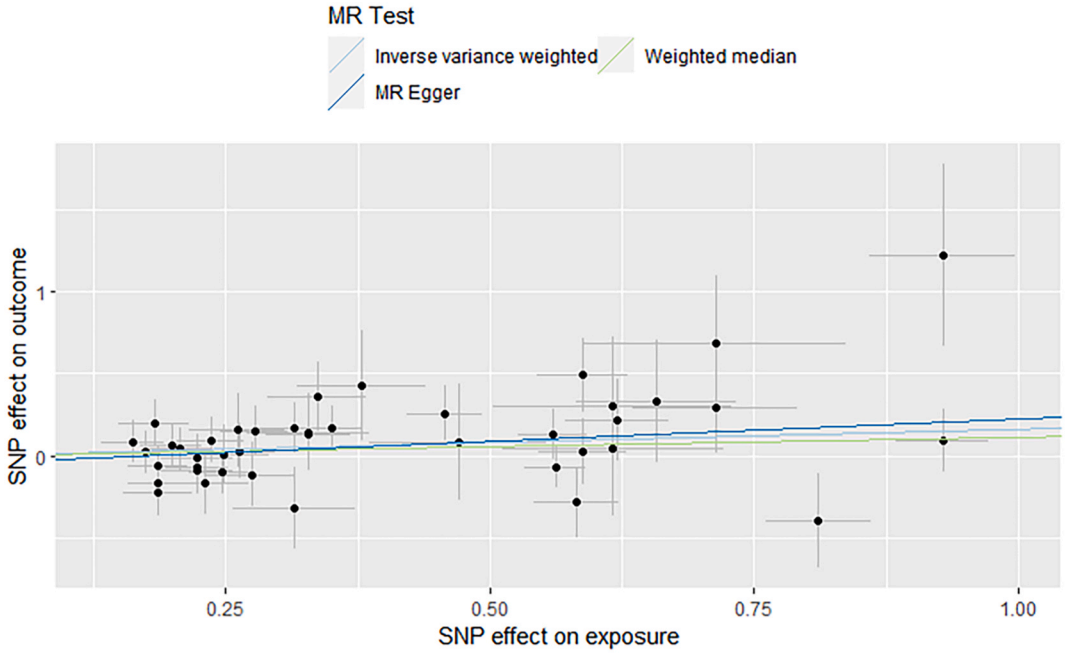

Fig. 3. The scatter plot of the causal effect of OM on SLE risk.

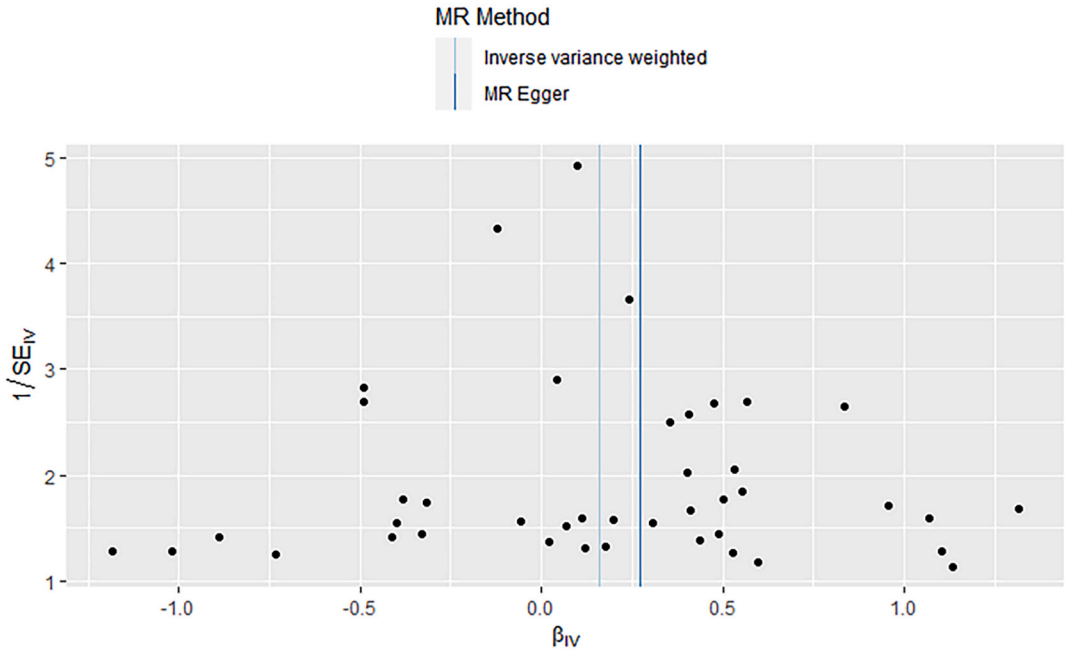

Fig. 4. The funnel plot of the causal effect of OM on SLE risk. It's almost symmetrical on both sides, which indicated no significant heterogeneity between the effect estimates of the IVs in both the IVW method and MR-Egger method.

deficiency has been recognized as a factor that increases vulnerability to bacterial infections [23,24] and triggers the onset of OM [25]. Moreover, SLE is characterized by defects in cellular and humoral immune function, including impaired neutrophil phagocytosis and chemotaxis, lymphocyte deficiency, and reduced levels of IL-2. In our study, we employed a set of 40 SNPs to comprehensively explore the genetic relationship between SLE and OM. Of significance is the association identified between the R77H (rs1143679) polymorphism of the ITGAM gene and SLE susceptibility. This polymorphism has been attributed to the encoding of cell-surface receptors expressed on monocytes and neutrophils, which influence various leukocyte processes [26]. Moreover, mutations in the NADPHO gene

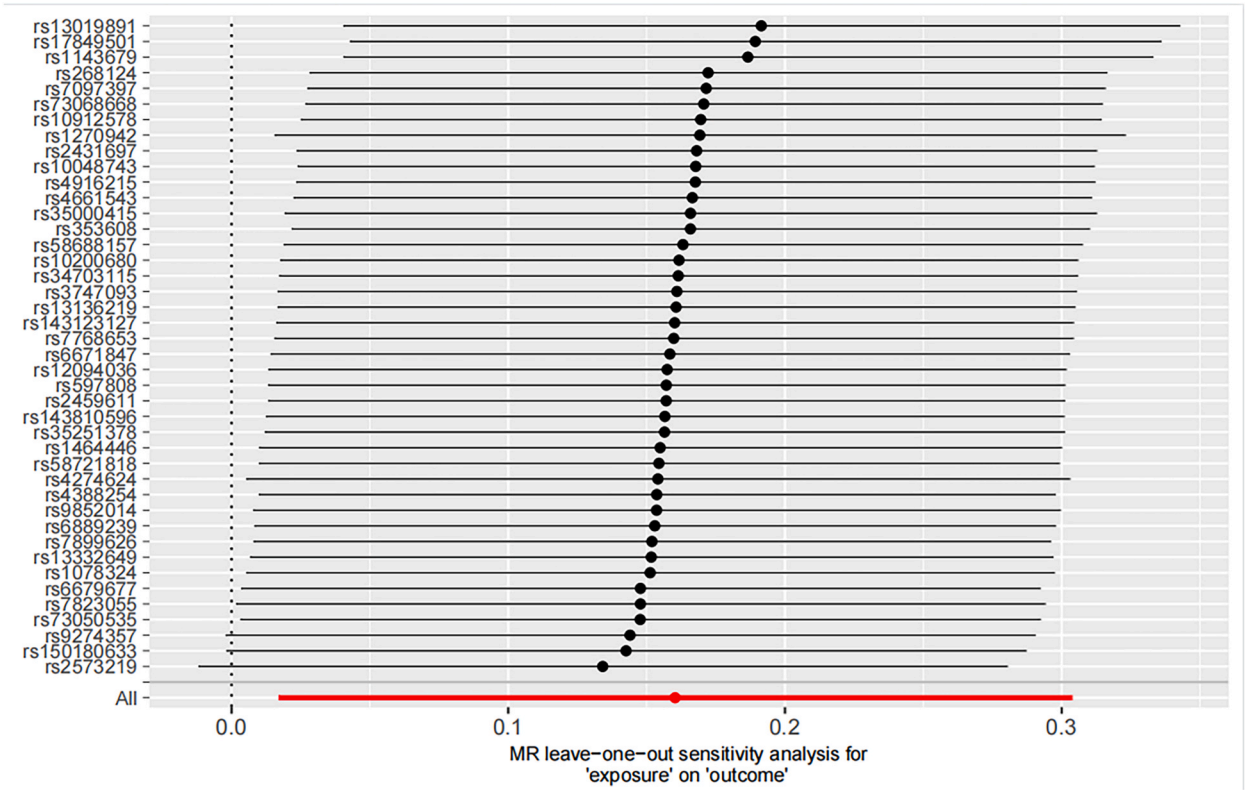

Fig. 5. Leave-one-out analysis of the causal association between systemic lupus erythematosus and Osteomyelitis. The exclusion of individual SNPs did not result in substantial differences in the combined effect estimates between the remaining SNPs and the overall results.

Table 2
MR analysis for OM with the risk of SLE.

Methods	*P*	*OR*	*Se*	95%*Cl*	*Q*(*P*)	intercept(*P*)	Global test *P*
MR-Egger	0.07	1.384	0.125	0.9824–1.9506	36.0511 (0.5598)	−0.065 (0.282)	0.522
Inverse variance weighted	0.049	1.167	0.079	1.0001–1.3631	37.239 (0.5503)		
Weighted median	0.063	1.245	0.118	0.9881–1.5690			

OR: odds ratio; *Se*: Standard error; *Cl*: Confidence level.

(rs17849502) impede the production of reactive oxygen species (ROS), crucial regulators of inflammation, acquired immunity, intracellular signaling, chemoattraction, and autophagy. These mutations predispose SLE patients to neutrophil dysfunction, accentuating immune aberrations [27]. These immune deviations, especially during active disease phases when serum complement levels are depleted due to immune complex consumption, heighten susceptibility to infections in SLE patients. The complement system, pivotal in host defense against microorganisms, including *Salmonella typhi* and Streptococcus pneumoniae [28,29], might contribute to this heightened susceptibility. The rs1143679 variant of ITGAM stands out as a potent genetic susceptibility factor in human SLE. This variant encodes the R77H variant, which compromises various complement receptor effectors in human monocytes, leading to impaired phagocytosis [30]. Consequently, hypocomplementemia resulting from complement deficiency in SLE might contribute to the heightened susceptibility to OM. A retrospective study with a small sample size reported that all episodes of OM occurred during the active phase of SLE (SLEDAI score ≥4) [31]. Additionally, deficiencies in immunoglobulin quantity and quality, particularly low serum levels of IgG subtypes and IgM, have been observed in approximately one-quarter of SLE patients [32]. Deficiencies in IgG subclasses have been associated with an increased risk of OM [33]. However, a study by Ibrahim Almaghlouth et al. found that low levels of IgA were associated with an increased risk of infection in adult SLE patients, whereas IgG and IgM did not demonstrate a similar effect [34]. While our Mendelian randomization study highlights the presence of susceptibility genes in SLE patients that elevate their risk of OM, it's imperative to recognize the potential influence of acquired behaviors. The utilization of immunosuppressive drugs and hormones in SLE treatment can heighten infection chances and consequently induce OM. These drugs modulate cellular and humoral immunity to control SLE by dampening overactive T cells, B cells, and other immune components. However, this suppressive effect on protective immunity concurrently raises infection susceptibility [35]. Furthermore, the use of immunosuppressive drugs in SLE may contribute to secondary immunodeficiency and further increase the risk of developing OM. An observational

study by Wu et al. highlighted the association between immunosuppressive drug use and susceptibility to OM in patients with SLE [36]. Nevertheless, further experimental investigations are required to elucidate the potential mechanisms underlying SLE-induced OM.

This study offers several strengths. Firstly, Firstly, this study is the first to employ the MR method to investigate the causal association between SLE and OM. Secondly, in contrast to previous observational studies, our study design reduces the impact of confounding factors, thus enhancing the internal validity of our findings. Lastly, our study utilized a large sample size and instrumental variables derived from genome-wide association studies (GWAS) data, ensuring statistical robustness for estimating causal associations and bolstering the credibility of our study. However, several limitations should be acknowledged. In our investigation, the computed power value (0.68) is notably below the conventional threshold of 0.8. This observation implies that our study might have limited statistical power to accurately identify a causal effect. However, it is noteworthy that our sensitivity analysis outcomes remained consistent, and there was an absence of weak IVs. The power values in our Mendelian randomization study, although below the conventional threshold of 0.8, are likely influenced by the constraints imposed by our limited sample size. Considering the nature of the genetic data and the constraints we encountered, we will thoroughly assess the feasibility of recruiting a larger sample size in the future. Our dataset predominantly consisted of individuals of European origin, and there may be an overlap in participants between the two datasets, potentially leading to an overestimation of our findings. Additionally, it remains uncertain whether studies conducted in other ethnic populations would yield consistent results regarding the causal relationship between SLE and OM. Moreover, clinically, SLE is more likely to occur in female individuals between the ages of 20–40 years of age. Confounding factors such as age, gender, and other environmental variables also exert a certain influence on MR analysis. Finally, like all MR studies, we were unable to address unobserved pleiotropy, which may introduce bias into our findings.

5. Conclusion

In conclusion, our two-sample MR analysis provided evidence supporting a causal relationship between SLE and OM. We found that SLE significantly increases the relative risk of developing OM in individuals of European ancestry. These findings emphasize the importance of effectively managing SLE to mitigate the risk of osteomyelitis in affected patients. Implementing aggressive control strategies and appropriate interventions targeting SLE may contribute to reducing the incidence of OM in this population. Further research is warranted to investigate the underlying mechanisms and explore preventive measures to minimize the burden of osteomyelitis in individuals with SLE.

Data availability statement

The datasets presented in this study come from GWAS Catalog (https://www.ebi.ac.uk/gwas/) and Fast GWA data portal (https://yanglab.westlake.edu.cn/data/ukb_fastgwa/imp/). The data associated with our study has not been deposited into a publicly available repository. The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

Not applicable.

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CRediT authorship contribution statement

Minhua Hu: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Investigation, Methodology, Software, Visualization. **Zhizhong Sun:** Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. **Xintao Tang:** Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. **Wenxing Zeng:** Data curation, Formal analysis, Writing – original draft. **Hongsong Yan:** Formal analysis, Investigation, Methodology, Software, Visualization. **Ziwei Jiang:** Data curation, Formal analysis, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. **Feng Huang:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

List of abbreviations

SLE	Systemic lupus erythematosus
OM	Osteomyelitis
MR	Mendelian randomization
IVs	Instrumental variables
GWAS	genome-wide association study
IVW	Inverse Variance Weighted
WM	Weighted Median
PRESSO	Pleiotropy Residual Sum and Outlier
RCTs	Randomized controlled trials
SNPs	single nucleotide polymorphisms
LD	Linkage disequilibrium

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