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# Causal Relationship between SLE and Chondromalacia patella-a two-sample Mendelian Randomisation Study

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**Abstract:** Systemic lupus erythematosus (systemic lupus erythematosus, SLE) may affect the development of chondromalacia patellae (CMP) through immune mechanism; in order to investigate the causal effect between SLE and chondromalacia patellae, genome-wide association study (GWAS) was conducted in a large European population. GWAS), mutually independent loci associated with SLE and chondromalacia patellae respectively were extracted as instrumental variables (SNPs), and three Mendelian randomisation (MR) analyses were applied to investigate the causal relationship, i.e., inverse variance weighting, weighted median and MR-Egger. To verify the robustness of the results, heterozygosity was used. To verify the robustness of the results, sensitivity analyses were performed using heterogeneity, multiplicity tests and the "leave-one-out" method. The results of the inverse variance weighting method showed that the OR (95% CI) between SLE and chondromalacia patella was 1.152 (1.063-1.248), P= 0.535E-03, indicating a causal relationship between SLE and chondromalacia patella. The results of this study all passed the heterogeneity and multiplicity tests and the sensitivity analysis results also showed reliable results. In this study, using two-sample MR analysis, SLE was found to be a risk factor for chondromalacia patella from a genetic point of view, and patients with SLE should be prevented or detected and treated early for chondromalacia patella. [Abbreviations] SLE = systemic lupus erythematosus; GWAS = genome-wide association study; IVW = inverse variance weighting; MR = Mendelian randomisation; SNP = single nucleotide polymorphism

**Keywords:** Systemic Lupus Erythematosus; Chondromalacia Patellae; Mendelian Randomization.

## 1. Introduction

Chondromalacia patella is one of the most common causes of knee pain and is characterised by softening and deterioration of the patellofemoral cartilage. The prevalence of the disease is as high as 36.2% in the general population, especially in middle-aged patients between 30 and 40 years of age (up to 50%), although the exact cause is still under investigation [1-3]. With the development of chondromalacia patellae, chondrocytes gradually become necrotic from the superficial layer to the deeper layer, resulting in softening, swelling, cracking, and even detachment of the patellofemoral interphalangeal joint cartilage, which leads to anterior knee pain and limited mobility [4-5]. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by the involvement of multiple tissues and internal organs, with a wide range of clinical manifestations, which has a serious negative impact on patients' quality of life and psychological well-being [6]. Zhu GQ et al [7] The authors have done A retrospective analysis found that SLE patients with a 5-year disease duration and younger patients had a relatively high risk of developing patellar infarctions, and in addition, studies have in addition, studies have shown that dysregulation of the immune microenvironment and the complex pathogenesis of SLE itself play an important role in the development of musculoskeletal disorders [8-9]. However, the exact etiological mechanisms need to be further investigated.

Mendelian randomisation (MR) is an epidemiological research design based on Mendelian laws of inheritance and instrumental variable estimation methods that enable causal effects to be inferred in the presence of unobserved confounders [10-11]. Through reviewing relevant literature and clinical observations, we found that SLE as an autoimmune disease has a major impact in the development of skeletal muscle diseases, and immune mechanisms have become one of the new directions in the current study of the etiology of chondromalacia patella. For this reason, we performed two-sample MR analysis of SLE and chondromalacia patella with the goal of discovering the causal relationship between SLE and chondromalacia patella.

## 2. Data and Methods

### 2.1. Data Sources

Firstly, GWAS data for SLE can be downloaded from the GWAS Catalog website (https://ftp.ebi.ac.uk/ pub/ databases/ gwas/summary_statistics/GCST003001-GCST004000/ GC ST003156/), in addition, twe would like to thank the authors of [12] such as Bentham J for completing the GWAS study on the SLE (https://ftp.ebi. ac.uk/pub/ databases/gwas/ summary_ statistics/GCST003001-GCST 004000/ GCST 003156/). We are also available from IEU OpenGWAS project (mr cieu.ac.uk) website The genome-wide association study (GWAS) data for this SLE (ebi-a- GCST003156) totalled 7,071,163 SNPs, with 5,201 individuals in the observer group and 9,066 individuals in the control group; in addition, we want to acknowledge the participants and investigators of the FinnGen study. GWAS data for chondromalacia patella were obtained from the FinnGen R5

database (https://www.finngen.fi/ en), which is available on the IEU OpenGWAS project (mr cieu.ac.uk) website with search ID: finn-b-M13_CHONDROMALACIA , with a total of 16,380,460 SNPs and a sample size of 215,767. This study was a re-analysis of publicly available GWAS data and therefore required no special ethical approval.

## 2.2. Selection Conditions for SNPs

We used the genome-wide significance threshold (p<5e-8) as a screening criterion to screen SNPs from the exposed GWAS data, and excluded SNPs that were directly associated with the outcome. In order to statistically measure the strength of the individual instrumental variables, the F statistics value was calculated for each SNP (F= [(n-k-1)/k] × [R2/1-R2]), and those with F value less than 10 were considered as weak instrumental variables and were excluded, where n represents the sample size, k represents the number of SNPs (F value was calculated for individual SNP, k=1), and R represents the variance explained by the SNPs, and R represents the variance explained by the SNP. considered as weak instrumental variables and were excluded, where n stands for sample size, k stands for number of SNPs (to calculate the F-value of a single SNP, k=1), and $R^2$ stands for variance explained by the SNP [13]. The instrumental variables used in this study were all strong instrumental variables (F>10), which showed a significant effect on the exposures, and could guarantee the reliability of MR results.

## 2.3. Screening and Processing of SNPs

Strongly correlated SNPs (p<5e-8) were filtered from the GWAS data from SLE, and to ensure SNPs independence, the data were clumped according to the European reference data from the 1000 Genomes Project [14] ($r^2$ <0.001 in a 10000-kb window). After screening the GWAS data of SLE for SNPs that met the conditions, the data were further coordinated in the GWAS data of chondromalacia patellae based on the same effector allele, and for the palindromic alleles, the allele frequency was checked in order to avoid potential strand-flipping problems; palindromic SNPs with a minor allele frequency of greater than 0.42 were excluded in order to avoid potential ambiguities [15].

## 2.4. Causality Verification Methods

The causal relationship between SLE and chondromalacia patellae was analysed primarily using the inverse variance weighting (IVW) method in order to reduce the impact of horizontal pleiotropy on the study results, we also included weighted median MR analysis and MR-Egger analysis to assess causal effects [16]. Weighted median MR analysis and MR-Egger analysis can compensate for the low tolerance of horizontal polyvalence bias in the inverse variance weighting (IVW) method, thus providing unbiased MR results.

## 2.5. Sensitivity Analysis

To assess the heterogeneity among SNPs, Cochran's Q test was performed using the IVW method. MR-egger intercept and MR-PRESSO global test can help to find out whether there is significant horizontal pleiotropy in this study [17] . If there is significant horizontal pleiotropy, the MR-PRESSO outlier test can identify and exclude the abnormal SNPs, and the causality analysis can be performed again with the remaining SNPs. In addition, leave one out analysis helped to detect the presence of specific SNPs driving the results of this study. Statistical analyses for this study were performed using the "TwoSampleMR" package in R software version 0.5.8.

# 3. Results

## 3.1. Instrumental Variables

We screened 45 SNPs from the GWAS data of SLE that were closely related (p < 5e-8) and did not have chain disequilibrium (r^2 < 0.001 in a 10,000-kb window), and showed that none of them were weak instrumental variables by calculating the F-value (for details, see Table 1). In reconciling exposure and ending data, Removing the following SNPs for being palindromic with intermediate allele frequencies: rs2736332, rs28834423, Removing the SNPs for incompatible alleles: rs28361029. the above SNPs will not be included in subsequent analyses.

## 3.2. Causal Relationship between SLE and Chondromalacia Patella

The results obtained by MR analysis showed a causal relationship between SLE and chondromalacia patella (IVW OR = 1.152, 95% CI = 1.063-1.248, P = 0.535E-03), see Table 2. in addition, the results of the scatterplot (Fig. 1) and the forest plot (Fig. 2) demonstrated that SLE increases the risk of developing chondromalacia patella.

## 3.3. Sensitivity Analysis

To test for heterogeneity across SNPs, we performed a Cochran Q-test (p=0.649).

The results showed that no significant heterogeneity was found, and the results of the test for heterogeneity can be observed through a funnel plot, as shown in Figure 3. Horizontal pleiotropy was detected using MR-egger intercept (P=0.971) test and MR-PRESSO's global test (0.648), the results indicated that there was no significant horizontal pleiotropy, and the MR-PRESSO outlier test did not find any SNPs that could lead to horizontal pleiotropy, and the Leave one out analysis test also showed that the individual instrumental variables used in this study were stable, which indicates the robustness of the results of this study.

# 4. Discussion

Chondromalacia patellae This diagnostic term was first proposed in 1917 and is still used today. Early symptoms include knee joint tenderness, weakness and pain when bearing weight or walking up and down stairs, which is relieved by rest and aggravated by exercise, and as the disease progresses, it will be accompanied by inflammation of the osteoarthritic joints, and obvious pain will occur when squatting or walking up and down stairs, and the patient can't stop sharply, jumping, or limiting the flexion of the knee joints because of the pain. Knee joint similar to strangulation symptoms [18-19]. SLE is a chronic autoimmune disease that involves multiple tissues and organs, and it also has a significant impact on the skeletal system, SLE combined with osteoporosis, osteoarthritis, osteochondritis dissecans, osteonecrosis cases are common in the clinic, the orthopaedic diseases concomitant with SLE bring great pain to the patients, and the serious ones even suffer from disability [20-21]. The aim of our study was to find a causal relationship between SLE and chondromalacia patella by MR analysis, and the results of our two-sample MR analysis showed an OR (95 % CI) of 1.152 (1.063-1.248), P=0.535E-03, suggesting that SLE and chondromalacia patellae are causally related, and

that patients with SLE have 1.152 times the risk of developing chondromalacia patellae as compared with the general population.

**Table 1.** Information on SNPs ultimately screened from GWAS data of SLE (n=45).

| ID | SNP | Effect_Allele | Other_Allele | β | SE | P | F |
|---|---|---|---|---|---|---|---|
| 1 | rs6679677 | A | C | 0.336472 | 0.0464854 | 4.55E-13 | 52.39196829 |
| 2 | rs4661543 | G | T | 0.274437 | 0.0423755 | 9.40E-11 | 41.94262961 |
| 3 | rs10912578 | G | A | -0.24686 | 0.0309918 | 1.65E-15 | 63.44652606 |
| 4 | rs17849501 | T | C | 0.81093 | 0.0498642 | 1.81E-59 | 264.4776777 |
| 5 | rs6671847 | A | G | 0.198851 | 0.0289651 | 6.64E-12 | 47.13087409 |
| 6 | rs4916215 | T | C | 0.223144 | 0.0339693 | 5.07E-11 | 43.15163271 |
| 7 | rs12094036 | C | T | -0.328504 | 0.0578595 | 1.37E-08 | 32.23531894 |
| 8 | rs13019891 | T | G | -0.562119 | 0.0290336 | 1.65E-83 | 374.8476147 |
| 9 | rs2573219 | C | A | 0.587787 | 0.0429292 | 1.13E-42 | 187.4711151 |
| 10 | rs10200680 | T | C | -0.248461 | 0.0424835 | 4.96E-09 | 34.20391984 |
| 11 | rs268124 | T | C | 0.18633 | 0.0323703 | 8.60E-09 | 33.13386659 |
| 12 | rs2459611 | T | C | 0.261365 | 0.045245 | 7.62E-09 | 33.36980543 |
| 13 | rs4274624 | T | C | -0.559616 | 0.0326791 | 9.73E-66 | 293.2513845 |
| 14 | rs10048743 | T | G | -0.231112 | 0.0412056 | 2.04E-08 | 31.45810134 |
| 15 | rs34703115 | C | T | -0.616186 | 0.104778 | 4.08E-09 | 34.58465476 |
| 16 | rs1464446 | T | G | -0.328504 | 0.0401497 | 2.79E-16 | 66.94477944 |
| 17 | rs9852014 | G | A | 0.620577 | 0.0492727 | 2.26E-36 | 158.6275546 |
| 18 | rs13136219 | T | C | -0.174353 | 0.027787 | 3.50E-10 | 39.37091669 |
| 19 | rs1078324 | A | C | -0.71335 | 0.0781665 | 7.11E-20 | 83.28446466 |
| 20 | rs4388254 | T | C | 0.378436 | 0.0603977 | 3.71E-10 | 39.25943866 |
| 21 | rs2431697 | C | T | -0.223144 | 0.0292964 | 2.60E-14 | 58.01521611 |
| 22 | rs6889239 | C | T | 0.277632 | 0.03174 | 2.19E-18 | 76.51123259 |
| 23 | rs389884 | G | A | 0.928219 | 0.0432319 | 2.92E-102 | 460.9908042 |
| 24 | rs9274357 | T | C | 0.457425 | 0.0351961 | 1.28E-38 | 168.9081898 |
| 25 | rs7768653 | T | C | -0.207014 | 0.0296891 | 3.11E-12 | 48.6189269 |
| 26 | rs12524498 | T | G | -0.673345 | 0.120793 | 2.48E-08 | 31.0736124 |
| 27 | rs58721818 | T | C | 0.65752 | 0.0755941 | 3.38E-18 | 75.6557835 |
| 28 | rs150180633 | T | C | 0.928219 | 0.0689573 | 2.66E-41 | 181.1925808 |
| 29 | rs28361029 | A | G | -0.385662 | 0.0613604 | 3.27E-10 | 39.50365995 |
| 30 | rs35000415 | T | C | 0.587787 | 0.041539 | 1.86E-45 | 200.2294151 |
| 31 | rs2736332 | C | G | 0.277632 | 0.0320694 | 4.83E-18 | 74.94753854 |
| 32 | rs7823055 | T | G | -0.350657 | 0.0286208 | 1.64E-34 | 150.1071876 |
| 33 | rs7899626 | T | C | 0.182322 | 0.0332532 | 4.19E-08 | 30.06154268 |
| 34 | rs7097397 | A | G | -0.18633 | 0.0287118 | 8.60E-11 | 42.11576829 |
| 35 | rs58688157 | G | A | -0.223144 | 0.0335647 | 2.97E-11 | 44.19823106 |
| 36 | rs353608 | G | A | 0.18633 | 0.0280198 | 2.93E-11 | 44.22170731 |
| 37 | rs73050535 | T | C | -0.71335 | 0.124134 | 9.11E-09 | 33.02355559 |
| 38 | rs597808 | G | A | -0.162519 | 0.0294736 | 3.51E-08 | 30.40478329 |
| 39 | rs1143679 | A | G | 0.582216 | 0.0399866 | 5.03E-48 | 212.0016865 |
| 40 | rs28834423 | C | G | 0.457425 | 0.0365295 | 5.65E-36 | 156.8022672 |
| 41 | rs13332649 | G | A | -0.314711 | 0.0375683 | 5.43E-17 | 70.17473145 |
| 42 | rs143123127 | A | G | 0.470004 | 0.0840342 | 2.23E-08 | 31.28174476 |
| 43 | rs35251378 | A | G | -0.235722 | 0.0324266 | 3.61E-13 | 52.84420952 |
| 44 | rs73068668 | A | G | -0.314711 | 0.0574903 | 4.40E-08 | 29.96640854 |
| 45 | rs3747093 | A | G | 0.262364 | 0.0345055 | 2.88E-14 | 57.8138428 |

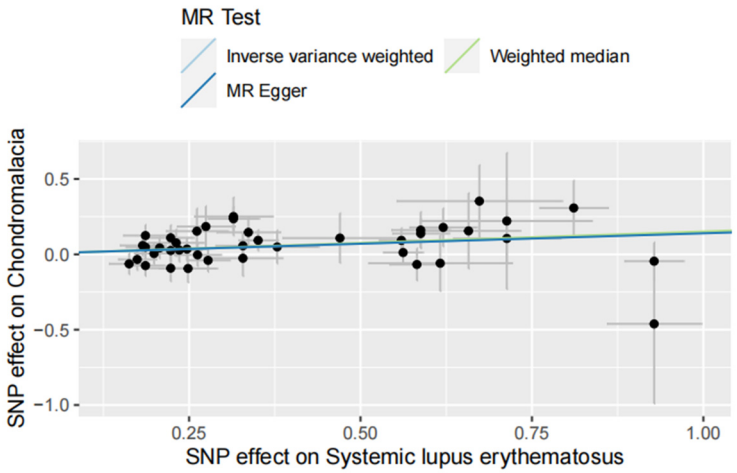


**Figure 1.** Scatter plot of SLE and Chondromalacia. SLE= systemic lupus erythematosus.

**Table 2.** MR regression results of the 3 methods.

| Method | β | SE | OR(95%CI) | P |
|---|---|---|---|---|
| Inverse variance weighted | 0.141 | 0.041 | 1.152 (1.063-1.248) | 0.535E-03 |
| Weighted median | 0.152 | 0.060 | 1.164 (1.034-1.310) | 0.012 |
| MR Egger | 0.138 | 0.088 | 1.148 (0.967-1.364) | 0.122 |

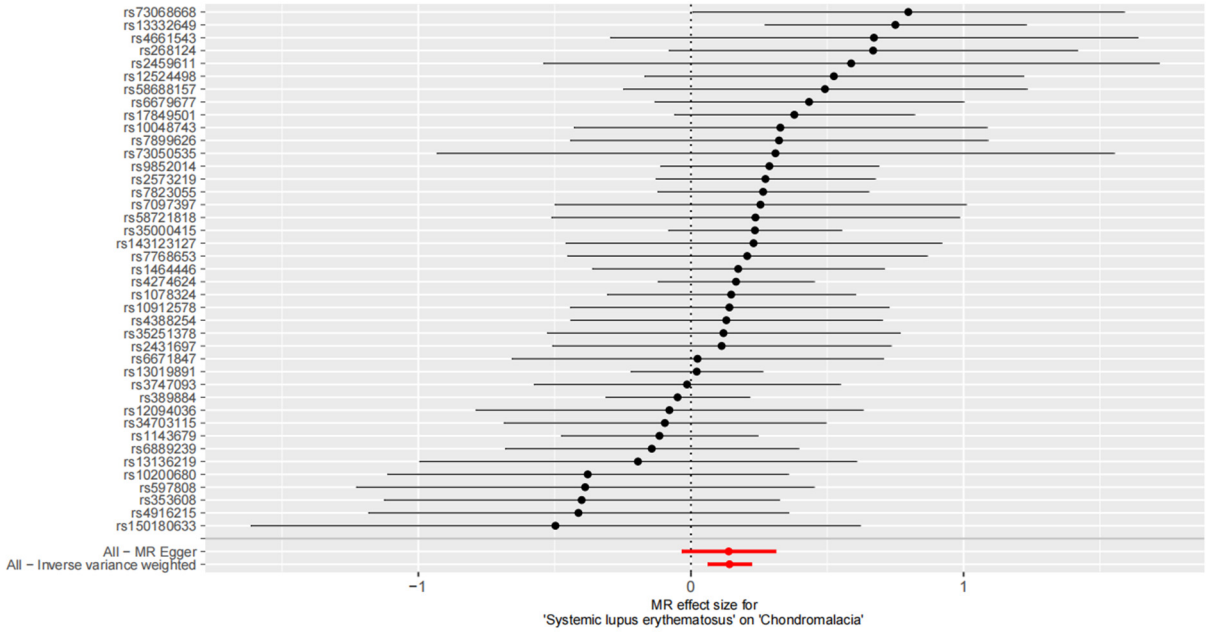


**Figure 2.** Forest plot of SLE and Chondromalacia. SLE= systemic lupus erythematosus.

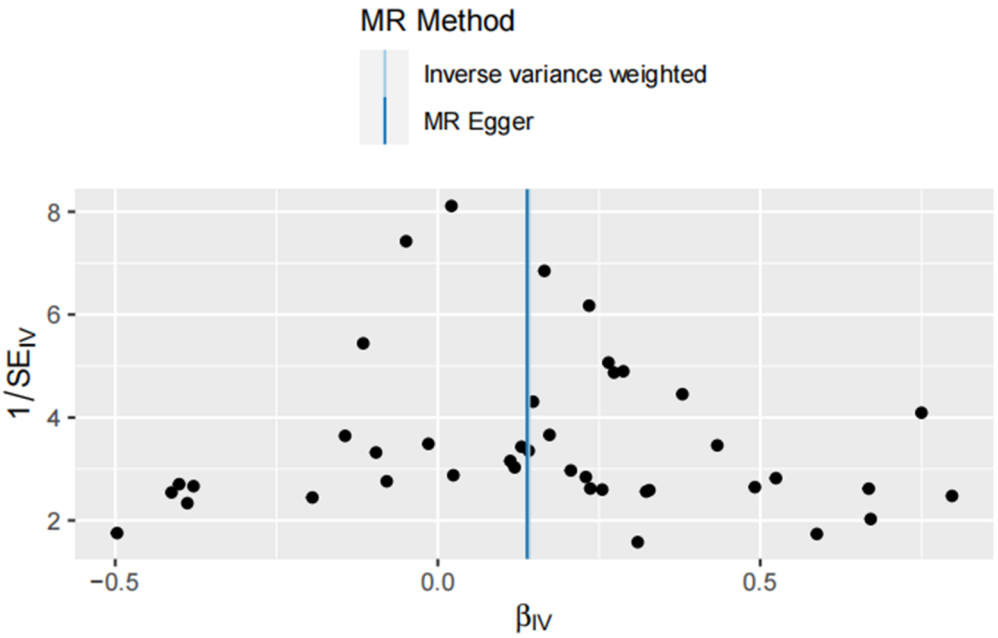


**Figure 3.** Funnel plot of SLE and Chondromalacia. SLE= systemic lupus erythematosus

The risk of chondromalacia patella in SLE patients is 1.152 times higher than in the general population. The hyaline cartilage in the patellofemoral joint, which provides almost frictionless joint movement under physiological conditions, is the physiological basis for its ability to withstand the enormous loads placed on the body [22]. Continued development of chondromalacia patella leads to and exacerbates the progression of arthritis, which may ultimately lead to a disabling outcome. SLE is an autoimmune disease that involves multiple organs, with autoantibody-mediated mechanisms of injury that also encompasses the musculoskeletal disorders. While previous studies on the etiology of chondromalacia patella have included trauma, chondrolysis, and patellofemoral instability, in recent years, autoimmunity has emerged as a major factor in the etiology of chondromalacia patella. In recent years, the autoimmune theory has gradually become one of the hotspots for the etiological study of chondromalacia patella, which suggests

that there is a complex and close link between chondromalacia patella and SLE.

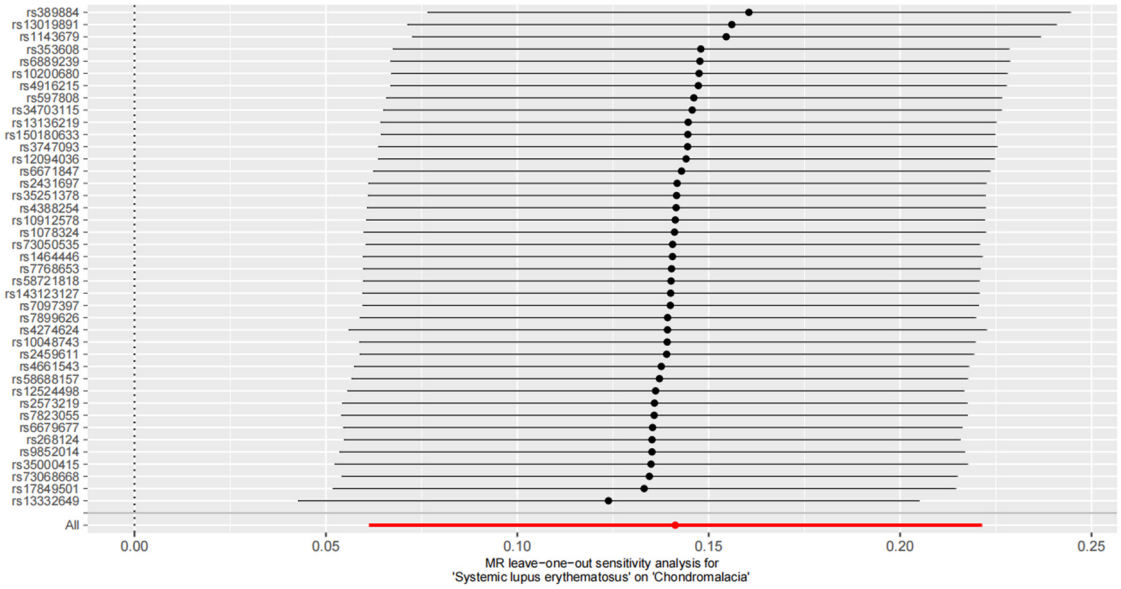


**Figure 4.** Analysis of SLE and Chondromalacia by the leave-one-out method. SLE= systemic lupus erythematosus

The causality analysis of SLE and chondromalacia patellae from a genetic perspective in our study showed a positive correlation between SLE and the development of chondromalacia patellae. Sensitivity analyses also demonstrated the robustness of the findings. Therefore, early screening for chondromalacia patella in patients with SLE is necessary for early intervention and treatment to improve the prognosis of the disease. In response to the fact that SLE increases the risk of chondromalacia patella, the following recommendations can be made: firstly, patients with SLE should maintain good knee postural habits, avoid overloading, and reasonably schedule their activities and rest periods. Secondly, a healthy dietary plan is necessary to ensure adequate intake of vitamins, minerals and proteins, which help to maintain joint health. In addition, in order to achieve early treatment to ensure a good prognosis, SLE patients should have regular medical checkups to effectively control the development of the disease. Finally, there are still many gaps in the understanding of the molecular and cellular mechanisms that cause chondromalacia patella, and effective interventions need to be guided by the exact etiological mechanism of the disease.

Finally, there are some limitations to this study. Firstly, the population subjects we studied were of European origin and therefore not truly representative of a randomised population sample. Second, although the global tests of MR-egger intercept and MR-PRESSO did not find significant horizontal pleiotropy, complete exclusion of horizontal pleiotropy is still difficult to achieve. Finally, the current GWAS data sample size is not large enough, and more GWAS data need to be included for more in-depth studies in the future.

## 5. Conclusion

In summary, this study analyzed GWAS data using two-sample MR analysis to reveal SLE as a risk factor for the development of chondromalacia patella from a genetic perspective.

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