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Causal relationships between rheumatism and dyslipidemia: A two-sample Mendelian randomization study

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Background: Dyslipidemia is often observed in rheumatic diseases, such as ankylosing spondylitis (AS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), yet it remains to be detected whether rheumatic diseases have a causal effect on dyslipidemia.

Methods: Significant ($P < 5 \times 10^{-8}$) and independent ($r^2 < 0.1$) single-nucleotide polymorphisms in genome-wide association studies were selected as instrumental variables to conduct Mendelian randomization (MR) analysis. Inverse variance weighted, weighted median, and MR–Egger regression were adopted for the causal inference. Subsequently, sensitivity analysis was conducted to assess the stability and reliability of MR.

Results: The MR results revealed positive causal relationships of AS with total cholesterol (TC) (β = 0.089, 95% CI = 0.050 to 0.128, $P = 6.07 \times 10^{-6}$), low-density lipoprotein (LDL) (β = 0.087, 95% CI = 0.047 to 0.127, $P = 1.91 \times 10^{-5}$), and high-density lipoprotein (HDL) (β = 0.043, 95% CI = 0.001 to 0.074, $P = 0.009$). There was no causal effect of RA on TC (β = 0.008, 95% CI = 4.86×10^{-4} to 0.017, $P = 0.064$), LDL (β = 6.4×10^{-4}, 95% CI = -0.008 to 0.007, $P = 0.871$), or HDL (β = 0.005, 95% CI = -0.003 to 0.013, $P = 0.200$). Additionally, SLE had negative causal links for TC (β = -0.025, 95% CI = -0.036 to -0.015, $P = 4.42 \times 10^{-6}$), LDL (β = -0.015, 95% CI = -0.025 to -0.005, $P = 0.003$), and HDL (β = -0.013, 95% CI = -0.021 to -0.004, $P = 0.004$). The results were stable and reliable.

Conclusion: This study suggested positive causal effects of AS on TC, LDL, and HDL and negative causal effects of SLE on these cholesterol levels, which could provide much help for the pathogenesis and treatment of rheumatic disease patients with dyslipidemia.

KEYWORDS

ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, dyslipidemia, Mendelian randomization

Introduction

Rheumatic diseases are rare heterogeneous disorders associated with substantial morbidity and mortality, and these include ankylosing spondylitis (AS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (1). AS is a chronic inflammatory disease that mainly influences the sacroiliac joints and spine and covers people with both non-radiographic and radiographic axial spondyloarthritis. This disease usually attacks individuals over 20 years old with a male-to-female ratio of 2:1 (2). Nearly 0.32%–1.4% of the population is affected by AS, which has higher mortality rates than normal individuals (3, 4). RA is one of the most common forms of chronic arthritis, affecting nearly 1% of the world's population and placing a substantial burden on both the individual and society (5). SLE is an autoimmune disease in which healthy cells or tissues are attacked by the immune system, causing inflammation of multiple organs, including the kidneys, skin, cardiovascular system, and central nervous system (6). The standardized mortality for SLE is estimated at 2.4%–5.9% despite advances in treatment (7). All three of these rheumatic diseases have burdened both individuals and society.

Dyslipidemia refers to the abnormality of lipid metabolism, one of the most important risk factors for atherosclerosis in these rheumatic diseases, contributing to the increased mortality of AS, RA, and SLE (8, 9). High-density lipoprotein (HDL) provides a protective effect against atherosclerosis, while low-density lipoprotein (LDL) and total cholesterol (TC) have an adverse influence (10). Some scholars found that lower HDL was surprisingly associated with an increased risk of complications in patients with AS (11, 12). Furthermore, Kucuk et al. (13) indicated that the LDL/HDL ratio was higher in AS patients. Regarding RA, Boyer et al. (14) indicated that lower HDL cholesterol levels were more prevalent in RA patients and could cause increased morbidity and mortality. However, the cholesterol levels in RA may be controversial. According to a previous comparative study, individuals with RA had lower TC and LDL but higher HDL levels than those of the general population (15). Regarding dyslipidemia in SLE, it was indicated that 73.4% of SLE patients have dyslipidemia (16). Similarly, a cohort study determined that 36.3% of participants had dyslipidemia (higher TC and LDL, lower HDL) at the time of SLE diagnosis, while it rose to over 60% 3 years later (17). Nevertheless, it is uncertain whether AS, RA, and SLE have causal effects on abnormal lipid metabolism, meaning that more research is needed to determine their potential relationships.

Abbreviations: AS, ankylosing spondylitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MR, Mendelian randomization; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IVs, instrumental variables; SNPs, single-nucleotide polymorphisms; GWAS, genome-wide association study; IVW, inverse variance weighted; β, beta.

Mendelian randomization (MR) is a powerful method that is widely used in causal inference by taking genetic variants as instrumental variables (IVs) and abiding by the law of independent assortment (18, 19). The MR method could minimize the confounders to a large extent and avoid reverse causality because genotypes appear before the occurrence of disease and are largely unrelated to lifestyle or environmental factors after birth (20). Hence, this study took single-nucleotide polymorphisms (SNPs) as IVs to perform a two-sample MR analysis to estimate the causal effect of rheumatic diseases (AS, RA, and SLE) on dyslipidemia (TC, LDL, and HDL).

Materials and methods

Study design

The design of this study is displayed in Figure 1. A two-sample MR analysis was conducted to explore the causal effect of rheumatic diseases on dyslipidemia. Three assumptions need to be met when performing MR analysis. First, the SNPs should be closely related to exposures. Second, the IVs selected are supposed to be independent of confounders. Third, SNPs should influence the outcomes just through exposure (19). In this study, additional ethical approval or informed consent was not required because the data used came from publicly published data.

Data sources

The summary-level genetic data used in this two-sample MR analysis originated from genome-wide association study (GWAS) datasets. Genetic variants for AS were obtained from a GWAS including 22,647 individuals (9,069 AS patients and 13,578 controls) and 99,962 SNPs of European ancestry (21). The selection of RA-associated genetic predictors was based on a GWAS of 58,284 objects (14,361 RA cases and 43,923 controls) and 8,747,963 SNPs of European descent (22). Additionally, there were 5,201 SLE patients and 9,066 controls (altogether 14,267 individuals) of European ancestry with 7,071,163 SNPs selected as the genetic variants from another GWAS (23). Moreover, one GWAS with 94,595 subjects of European descent from 23 studies was used to identify IVs for TC, LDL, and HDL levels, the details of which have been elucidated by previous research (24). All of the data adopted in this current study are publicly available at the GWAS summary datasets (https://gwas.mrcieu.ac.uk).

Selection of instrumental variables

This two-sample MR analysis took the genome-wide significant ($P < 5 \times 10^{-8}$) SNPs as IVs to assess the causal effects of AS, RA, and SLE on TC, LDL, and HDL. The clumping process

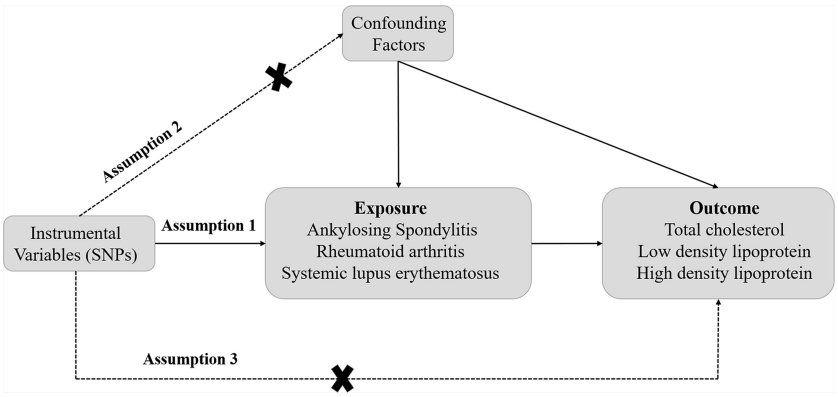

FIGURE 1
The schematic diagram of Mendelian randomization (MR). Three assumptions should be met, as follows: Assumption 1: The SNPs should be closely related to exposures; Assumption 2: The IVs selected are supposed to be independent of confounders; Assumption 3: SNPs should influence the outcomes just through the exposure. (IVs, instrumental variables; SNPs, single-nucleotide polymorphisms).

(r^2 < 0.1, window size = 10,000 kb) was performed with the European samples from the 1000 Genomes Project to wipe off the influence of linkage disequilibrium. Then, the Steiger test was also adopted to remove those SNPs that explain more of the variance in the dyslipidemia than in rheumatic diseases. Moreover, the F-statistics were calculated, and the sensitive SNPs were extracted for further analysis based on F-statistics ≥10.

Statistical analyses

This study adopted the inverse variance weighted (IVW), weighted median, and MR–Egger methods to explore the causal relationships between AS, RA, and SLE and TC, LDL, and HDL. The IVW method analyzes each Wald ratio and provides a consistent estimate of the causal effect when all IVs are valid, which is primarily used in the results with no heterogeneity or directional pleiotropy (25). The weighted median method gives unbiased estimates even when up to 50% of the information comes from invalid IVs (26). It would provide a more accurate estimation than IVW and MR–Egger when heterogeneity exists in the results. MR–Egger regression was conducted to test horizontal pleiotropy. However, the effect size rather than the statistical significance of MR–Egger was concentrated because the statistical power is low (27).

Sensitivity analyses

Additionally, heterogeneity was assessed by Cochran's Q test and I^2 statistics. Generally, there was no heterogeneity in the results when I^2 < 50%. MR–Egger regression was used to detect pleiotropy. Moreover, this study conducted a sensitivity analysis using the "leave-one-out" sensitivity test to evaluate the reliability and stability of MR results. All statistical analyses were performed with the "Two-Sample MR" package in R (version 4.1.2) software. The results were statistically significant when $P < 0.05$.

Results

The single-nucleotide polymorphisms selected for this study

This study chose rheumatic disease (AS, RA, and SLE) as exposures to conduct a two-sample MR analysis for dyslipidemia. Significant and independent ($P < 5 \times 10^{-8}$, $r^2 < 0.1$) SNPs were extracted, and the remaining SNPs were chosen for further MR analysis after excluding the weak IVs (F < 10). Supplementary Tables S1–S9 show the basic information of the selected SNPs for MR analysis. For AS exposure, there were 63 AS-related SNPs with a mean value of F = 178.32 for TC, 63 SNPs with a mean of F = 178.32 for LDL, and 62 SNPs with a mean value of F = 177.85 for HDL selected for MR analysis. For RA exposure, 78, 79, and 79 SNPs were selected for analysis, with mean F values of 160.65, 159.74, and 159.74 for TC, LDL, and HDL, respectively. For SLE exposure, 49 SNPs for TC, LDL, and HDL with the same mean of F = 83.89 were selected for MR analysis.

Causal effect of ankylosing spondylitis on dyslipidemia

The MR results of AS on TC are listed in Table 1, Figure 2A, and Supplementary Figure S1, which were reported as beta (β). According to Cochran's Q, I^2, and MR–Egger regression tests, there was heterogeneity (Q = 375.20, $P = 9.49 \times 10^{-47}$; I^2 = 83.74%) but no

TABLE 1 The Mendelian randomization (MR) analysis results with regard to causal effect of AS on TC, LDL, and HDL levels.

Outcome	Method	SNP (n)	β	95% CI	*P*-value
TC	Weighted median	63	0.089	0.050, 0.128	6.07×10^{-6}
	Inverse variance weighted	63	0.048	0.003, 0.092	0.035
	MR Egger	63	0.028	-0.056, 0.112	0.515
LDL	Weighted median	63	0.087	0.047, 0.127	1.91×10^{-5}
	Inverse variance weighted	63	0.041	0.003, 0.079	0.035
	MR Egger	63	0.024	-0.048, 0.096	0.522
HDL	Weighted median	62	0.043	0.011, 0.074	0.009
	Inverse variance weighted	62	0.032	0.004, 0.060	0.023
	MR Egger	62	-0.002	-0.053, 0.050	0.998

beta (β), a ratio of changes in standard deviations; AS, ankylosing spondylitis; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SNP, single-nucleotide polymorphism; CI, confidence interval.

pleiotropy (intercept = 0.002, $P = 0.589$) in the results. Therefore, the weighted median method was adopted for the causal relationship between AS and dyslipidemia (28). The weighted median method showed that AS had a positive causal effect on TC (β = 0.089, 95% CI = 0.050 to 0.128, $P = 6.07 \times 10^{-6}$), and a similar result was obtained from IVW (β = 0.048, 95% CI = 0.003 to 0.092, $P = 0.035$). Then, the "leave-one-out" sensitivity indicated that the causal relationship between AS and TC was not affected by individual SNPs (Supplementary Figure S1D), meaning that the result was stable and reliable. Additionally, Table 1, Figure 2B, and Supplementary Figure S2 show the MR results of AS on LDL. According to the weighted median method, AS was positively associated with higher LDL levels (β = 0.087, 95% CI = 0.047 to 0.127, $P = 1.91 \times 10^{-5}$). The IVW method showed a similar result (β = 0.041, 95% CI = 0.003 to 0.079, $P = 0.035$). Cochran's Q and I^2 statistics indicated the existence of heterogeneity (Q = 258.74, $P = 3.49 \times 10^{-26}$; $I^2 = 76.42\%$). There was no evidence for directional pleiotropy in the MR–Egger regression analysis (intercept = 0.002, $P = 0.581$). In the "leave-one-out" analysis, no single SNP strongly drove the overall effect of AS on LDL (Supplementary Figure S2D). For the HDL outcome, the MR results are listed in Table 1, Figure 2C, and Supplementary Figure S3. There was a positive causal effect of AS on HDL (β = 0.043, 95% CI = 0.001 to 0.074, $P = 0.009$) according to the weighted median method. The association was consistent with the IVW method (β = 0.032, 95% CI = 0.004 to 0.060, $P = 0.023$). Heterogeneity (Q = 156.09, $P = 1.71 \times 10^{-10}$; $I^2 = 61.56\%$) but not directional pleiotropy (intercept = 0.003, $P = 0.130$) existed in the MR results, meaning that it was more appropriate to adopt the weighted median method to analyze the results. Then, the "leave-one-out" sensitivity indicated that the causal effect of AS on HDL was not affected by individual SNPs (Supplementary Figure S3D).

Causal effect of rheumatoid arthritis on dyslipidemia

In terms of the relationships of RA with TC, LDL, and HDL, the results provided sufficient statistical power for causal analysis between them according to the results in Supplementary Table S10 and Supplementary Figures S4–S6. Nevertheless, none of the three methods provided evidence for a causal relationship between RA and TC (weighted median: β = 0.008, 95% CI = 4.86×10^{-4} to 0.017, $P = 0.064$; IVW: β = 0.004, 95% CI = -0.005 to 0.014, $P = 0.386$; MR–Egger: β = -0.003, 95% CI = -0.009 to 0.014, $P = 0.764$) based on the results in Supplementary Table S10. The MR analysis with regard to the causal effect of RA on LDL also showed that there was a null effect between them (weighted median: $\beta = 6.4 \times 10^{-4}$, 95% CI = -0.008 to 0.007, $P = 0.871$; IVW: β = 0.002, 95% CI = -0.006 to 0.009, $P = 0.635$; MR–Egger: β = -0.004, 95% CI = -0.017 to 0.009, $P = 0.547$). Similarly, there was no evidence for the causal effect of RA on HDL according to the weighted median method (β = 0.005, 95% CI = -0.003 to 0.013, $P = 0.200$), IVW (β = 0.006, 95% CI = -7.5×10^{-4} to 0.013, $P = 0.081$), and MR–Egger (β = 0.009, 95% CI = -0.002 to 0.021, $P = 0.124$). Hence, there was no causal effect of RA on TC, LDL, and HDL.

Causal effect of systemic lupus erythematosus on dyslipidemia

Table 2, Figures 2D–F, and Supplementary Figures S7–S9 show the MR results of SLE on TC, LDL, and HDL. According to the weighted median method, SLE was negatively associated with LDL (β = 0.025, 95% CI = -0.036 to -0.015, $P = 4.42 \times 10^{-6}$). The association was consistent with the IVW method (β = -0.028, 95% CI = -0.039 to -0.018, $P = 2.16 \times 10^{-7}$). According to Cochran's Q, I^2, and MR–Egger regression, there was heterogeneity (Q = 153.30, $P = 7.09 \times 10^{-15}$; $I^2 = 73.26\%$) but no pleiotropy (intercept = -0.006, $P = 0.200$) in the results, which means that the weighted median method was more appropriate for analysis of the results. The "leave-one-out" sensitivity showed that the causal effect of SLE on TC was not affected by individual SNPs (Supplementary Figure S7D). For the LDL outcome, the weighted median (β = -0.015, 95% CI = -0.025 to -0.005, $P = 0.003$) and IVW (β = -0.018, 95% CI = -0.027 to -0.009, $P = 1.39 \times 10^{-4}$) methods indicated a negative causal effect of SLE on LDL. Heterogeneity (Q = 108.19, $P = 5.72 \times 10^{-8}$; $I^2 = 62.11\%$) but not pleiotropy (intercept = -0.005, $P = 0.201$)

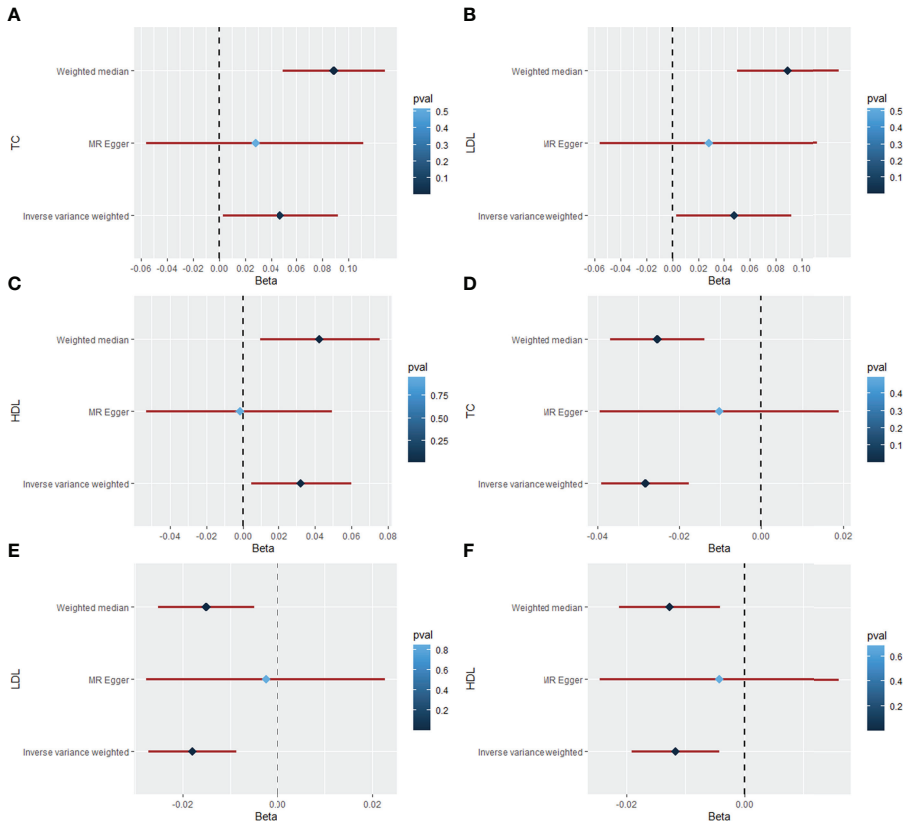

FIGURE 2
The forest plot for causal effects of rheumatic diseases on dyslipidemia. **(A)** Forest plot of the casual effect of AS on TC. **(B)** Forest plot of the casual effect of AS on LDL. **(C)** Forest plot of the casual effect of AS on HDL. **(D)** Forest plot of the casual effect of SLE on TC. **(E)** Forest plot of the casual effect of SLE on LDL. **(F)** Forest plot of the casual effect of SLE on HDL. (AS, ankylosing spondylitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; beta (β), a ratio of changes in standard deviations).

existed in the results. The "leave-one-out" analysis showed that the result was reliable and stable (Supplementary Figure S8D). Additionally, there was a negative causal effect of SLE on HDL by the weighted median method (β = 0.013, 95% CI = -0.021 to -0.004, $P = 0.004$). The IVW showed a similar result regarding the causal effect of SLE on HDL (β = -0.012, 95% CI = -0.019 to -0.004, $P = 0.002$). There was heterogeneity (Q = 82.86, $P = 1.18 \times 10^{-4}$; I^2 = 50.52%) but no pleiotropy (intercept = -0.003, $P = 0.446$) in the

TABLE 2 The Mendelian randomization (MR) analysis results with regard to causal effect of SLE on TC, LDL, and HDL levels.

Outcome	Method	SNP (n)	β	95% CI	*P*-value
TC	Weighted median	49	-0.025	-0.036, -0.015	4.42×10^{-6}
	Inverse variance weighted	49	-0.028	-0.039, -0.018	2.16×10^{-7}
	MR Egger	49	-0.010	-0.039, -0.019	0.494
LDL	Weighted median	49	-0.015	-0.025, -0.005	0.003
	Inverse variance weighted	49	-0.018	-0.027, -0.009	1.39×10^{-4}
	MR Egger	49	-0.002	-0.028, 0.023	0.848
HDL	Weighted median	49	-0.013	-0.021, -0.004	0.004
	Inverse variance weighted	49	-0.012	-0.019, -0.004	0.002
	MR Egger	49	-0.004	-0.025, 0.016	0.683

beta (β), a ratio of changes in standard deviations; SLE, systemic lupus erythematosus; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SNP, single-nucleotide polymorphism; CI, confidence interval.

results according to Cochran's Q, I^2, and MR–Egger regression. The result was not affected by a single SNP according to "leave-one-out" analysis (Supplementary Figure S9D).

Discussion

The aim of this study was to explore the relationship between autoimmune rheumatic diseases and dyslipidemia using MR. To the best of our knowledge, this was the first study to assay the causal effect of AS, RA, and SLE on TC, LDL, and HDL based on GWAS datasets. According to the MR results, this study provided strong genetic evidence that AS had a positive causal effect on TC, LDL, and HDL, while SLE had a negative causal effect on TC, LDL, and HDL. However, there were no causal effects of RA on TC, LDL, and HDL according to the MR results. These findings would contribute greatly to research on the mechanism and treatment of dyslipidemia in different kinds of rheumatic diseases.

AS is an inflammatory disease associated with dyslipidemia that involves the spine, peripheral joints, and entheses (29). García-Gómez et al. (30) reported that 20.7% (95% CI: 16.91 to 24.82) of patients with AS had hyperlipidemia in a 10-year prospective study. Additionally, another study found that the LDL/HDL ratio was higher in AS patients than that in controls (13). The conclusions of these observational studies were consistent with our results that AS could increase the levels of LDL. However, low HDL cholesterol levels were also observed in AS individuals (31). It was elucidated that increased disease activity and inflammatory indicators, such as erythrocyte sedimentation rate and C-reactive protein, in patients with AS were related to a decrease in lipids (32). Moreover, AS-related inflammation could increase the levels of HDL-associated serum amyloid A and reduce plasma paraoxonase-1 activity in patients with active AS, which would greatly affect the levels and function of HDL (33). These observational studies could determine the associations but not the causal relationship between HDL and AS due to the existence of confounding factors and reverse causality. Our study indicated a positive causal effect of AS on TC, LDL, and HDL, providing much help for the mechanism and treatment of dyslipidemia in AS patients to prevent complications due to lipid abnormalities. More studies are needed to reveal the potential pathogenesis for the causal relationships between AS and dyslipidemia.

RA is the most common form of chronic arthritis and is associated with abnormal levels of cholesterol (34). Boyer et al. (14) indicated that lower HDL cholesterol levels appeared more prevalent in RA patients and could contribute to the increased morbidity and mortality of RA. In a retrospective study, 79 patients who later developed RA had higher TC and lower HDL cholesterol levels than those in controls (35). However, a 10-year cohort study found that lipid changes commenced prior to RA diagnosis (36). In another retrospective study, RA patients displayed lower mean TC (by 10%) and LDL (by 17%) but no significant difference in HDL levels when compared with those in non-RA controls in the 5 years preceding diagnosis (34), revealing that dyslipidemia and RA might have a similar pathogenesis. RA-related inflammation plays a crucial role in lipid metabolism alterations, which could affect the levels of cholesterol (37). Semb et al. (38) found that lipid levels were initially low and then increased after disease activity was controlled in RA patients with a high inflammatory burden. In our study, the conclusion that RA had no causal effect on TC, LDL, and HDL was different from the results of observational studies, which might be explained by the fact that severe inflammation in RA could change the function and serum levels of lipids (39). The sample sizes, different races, confounders not yet considered and treatment effects might also affect the results regarding the relationship between RA and dyslipidemia. As a result, it remains to be explored whether treatment of RA would improve the abnormal lipid levels in RA patients, as the relationship between them is unclear.

SLE is a chronic autoimmune disease associated with dyslipidemia (40). A previous study reported that prior to treatment with rituximab, 69% of SLE patients had dyslipidemia, among which the major abnormalities were LDL and HDL (41). Elfving et al. (42) showed that 90% of patients with SLE used drugs at the onset of the disease to control the major comorbidities of dyslipidemia, which implied that dyslipidemia in SLE is not caused by medications. Another study also illustrated that the levels of HDL decreased in SLE patients (43), which was consistent with our results. Autoimmunity, inflammation, and oxidative stress in the process of SLE could alter lipid and lipoprotein metabolism (44). Resolvin D1 is a product of the metabolism of the omega-3 polyunsaturated fatty acid docosahexaenoic acid and can improve homeostasis in inflamed tissues. It was found that the levels of resolvin D1 decreased significantly in SLE patients (45). Moreover, Atta et al. (16) showed a positive correlation between Interleukin-6 (IL-6) and C-reaction protein (CRP) levels in a group of patients with dyslipidemia. As a result, it was hypothesized that SLE might cause dyslipidemia by decreasing the levels of resolvin D1 to increase the levels of inflammatory biomarkers such as IL-6 and CRP. This study revealed that it was important to treat SLE when curing dyslipidemia in SLE patients. However, more work is needed to determine the potential mechanism of the causal effect of SLE on dyslipidemia.

Regarding the associations between autoimmune diseases and dyslipidemia, this was the first study to explore their causal relationships with MR analysis, which minimized the unmeasured confounders and reverse causality biases and detected the causality with high precision. Nevertheless, limitations existed in this study. First, whether similar results could be obtained in other ancestries is unknown because this MR analysis focused on individuals of

European ancestry. Second, this MR analysis mainly concentrated on the levels of TC, LDL, and HDL and could not explore the functions of the lipoproteins.

In conclusion, this study suggested positive causal effects of AS on TC, LDL, and HDL and negative causal effects of SLE on these cholesterol levels. No causal relationship was identified between RA and TC, LDL, and HDL. This study could be important for further exploration of the pathogenesis and management of rheumatic disease patients with a high risk of dyslipidemia, subsequently decreasing the long-term complications of these autoimmune diseases.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://gwas.mrcieu.ac.uk/.

Author contributions

GZ, YC and JL designed and performed the study. JZ, ZJ, LL, JS and RZ collected and analyzed the data. QS and XD interpreted the results. GZ wrote this paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.961505/full#supplementary-material

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