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ORIGINAL RESEARCH

The Impact of Triglycerides on Rheumatoid Arthritis: Risk Factor and Mendelian Randomization Study

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Objective: This study investigates the association between triglycerides and Rheumatoid arthritis (RA) risk through risk factor analysis and Mendelian randomization (MR).

Methods: Data from the Dryad database were used for a case-control study with 455 participants (224 with RA and 231 controls), with a median age of 54 years (IQR: 45–62) and 34% male participants. Logistic regression analyses identified risk factors, and correlation coefficient analysis assessed associations between triglycerides and RA. A two-sample MR analysis was conducted using genetic variants associated with triglyceride levels as instrumental variables.

Results: Logistic regression identified higher triglyceride levels, a history of non-smoking, lower levels of C-reactive protein, and apolipoprotein A as significant risk factors for RA (all $P < 0.05$). MR analysis showed no significant causal relationship, with odds ratios (IVW OR = 0.944, P = 0.154) close to 1. Heterogeneity tests showed no significant variation in causal estimates, supporting the absence of a causal link between triglycerides and RA.

Conclusion: While elevated triglyceride levels are associated with an increased risk of RA, MR suggests that triglycerides do not play a direct causal role in its development. These findings indicate that triglyceride management may not be a primary focus in RA treatment, but further research into the mechanisms underlying RA progression is needed.

Keywords: Mendelian randomization, triglycerides, rheumatoid arthritis, causal relationship, risk factor

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by synovial inflammation, primarily affecting joints such as the hands, knees, and hips.[1] It can ultimately lead to joint destruction and disability.[2] The pathophysiology of RA is driven by abnormal immune system activation, resulting in sustained synovial inflammation and subsequent joint damage.[3] This is further exacerbated by the infiltration of immune cells, including lymphocytes and macrophages, and the overproduction of inflammatory mediators and cytokines, which amplify tissue damage.[4] Emerging evidence suggests that inflammation-related metabolic markers, particularly triglycerides, may play a significant role in the development and progression of RA.[5]

The prevalence of RA shows considerable geographical variation, with global estimates ranging between 0.5% and 1%, demonstrating a marked female predominance with a 3:1 female-to-male ratio.[6] Some studies indicating a potential link to dietary patterns.[7] A high-fat diet, for instance, can disrupt lipid metabolism and increase the risk of inflammatory responses.[8,9] While direct evidence establishing a causal relationship between lipid metabolism disturbances and RA remains limited, growing research suggests that lipid metabolism may contribute substantially to the disease's pathophysiology.[10–12]

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Triglycerides, a key metabolic product, have been found to be closely linked to inflammatory processes.[13] Elevated triglyceride levels have been associated with systemic inflammation and pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-12.[14] Elevated IL-6 levels can promote synovial cell proliferation and immune cell infiltration, further aggravating joint damage.[15] Additionally, lipid metabolism, including fatty acids stored as triglycerides, plays a critical role in the differentiation and function of T lymphocytes, including $CD4^+$ and $CD8^+$ T cells,[16] and may potentially influence inflammatory responses. In summary, triglycerides appear to play a dual role in the immune and inflammatory mechanisms of RA, warranting further investigation.

Traditional studies on RA risk factors have predominantly focused on obesity, inflammatory biomarkers, and antibodies,[17,18] but these methods often face challenges in disentangling correlation from causation due to the influence of confounding variables and reverse causation. Mendelian randomization (MR) is an emerging approach that utilizes single-nucleotide polymorphisms (SNPs) as instrumental variables to mitigate systematic bias and estimate the causal effects of risk factors on disease outcomes.[19] Compared to conventional clinical methods, MR offers a more robust approach to determining causal relationships, enhancing the reliability of study conclusions.

Although previous studies have indicated a link between lipid metabolism and systemic inflammation, direct causal evidence regarding the role of triglycerides in RA pathogenesis is still lacking. This represents a critical gap in our understanding, especially given the immunomodulatory potential of triglycerides via cytokine regulation and T-cell activation. Therefore, this study aims to assess both the association and potential causality between triglyceride levels and RA using risk factor analysis and MR. By clarifying this relationship, we hope to provide novel insights for risk assessment and potential preventive strategies in RA.

Materials and Methods

Study Design and Data Source

This study was a secondary analysis based on a publicly available dataset retrieved from the Dryad digital repository (https://doi.org/10.5061/dryad.hh3j7), which originated from a previously published cross-sectional study conducted in the Netherlands (van Breukelen-van der Stoep et al, 2015).[20] The dataset contains clinical and biochemical variables, including triglyceride levels, from patients with and without RA.

Participants were selected based on their RA diagnosis status and clinical eligibility as defined in the original study. Specifically, patients with RA were diagnosed according to the 1987 revised criteria by the American Rheumatism Association.[21] As this was a secondary analysis of a pre-existing dataset, the selection process was predetermined by the original study protocol[20] and was not under the control of the present investigators. No formal sample size calculation was performed, as all eligible participants from the original dataset were included. The sample therefore represents a convenience sample based on the full availability of data in the publicly released cohort.

All data were fully anonymized by the original authors prior to upload, and the original study had obtained ethical approval and informed consent. Since no personally identifiable information or commercial interests were involved, and no direct contact with human participants occurred in this secondary analysis, further ethical review was not required in accordance with Article 32(1) and 32(2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission of the People's Republic of China, 2023).

Notably, the dataset does not include detailed metadata on recruitment dates, exposure windows, follow-up periods, or data collection timelines.

Inclusion criteria were: 1) Patients diagnosed with RA based on the 1987 revised criteria by the American Rheumatism Association;[21] 2) Absence of other concurrent autoimmune diseases; 3) Complete clinical data with no missing values. Exclusion criteria included: 1) Presence of autoimmune diseases other than RA; 2) Significant missing clinical data.

Data Processing and Selection

The data collection process involved the removal of variables with a high proportion of missing values to enhance the completeness of the dataset. Subsequently, variables with minimal impact on the relationship between triglycerides and RA

were excluded, reducing the risk of model overfitting and improving the accuracy of the results. Finally, the dataset was filtered according to the predefined inclusion and exclusion criteria. A total of 455 patients were included, with 224 diagnosed with RA and 231 without. The clinical parameters collected for analysis included age, sex, smoking history, body mass index, systolic blood pressure, diastolic blood pressure, blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, C-reactive protein, apolipoprotein A, and apolipoprotein B.

Statistical Analysis

The Shapiro–Wilk test was used to assess the normality of continuous variables, revealing that none of the variables met the normality assumption. Consequently, continuous variables were reported as medians and interquartile ranges (IQR; PR25, PR75). Comparisons between patients with and without RA were performed using the Mann–Whitney *U*-test. Categorical variables were expressed as counts and percentages and analyzed using the Chi-square test.

Univariate and multivariate logistic regression analyses were conducted to identify independent variables associated with RA. Variables with a p-value < 0.10 in the univariate analysis were included in the multivariate logistic regression model. Variables that remained significant in the multivariate model were considered risk factors for RA.

Correlation coefficient analysis, including point-biserial and phi correlation, was performed to assess the strength of associations between risk factors and RA. Correlation analysis was performed to visualize pairwise associations among variables as a complementary exploratory step, in addition to regression modeling.

All statistical analyses were conducted using IBM SPSS (Version 27, IBM Corporation, Somers, NY). A two-tailed p-value < 0.05 was considered statistically significant.

Two-Sample MR Analysis

A two-sample MR analysis was conducted using the "TwoSampleMR" package in R (version 4.3.2). This analysis aimed to evaluate the causal relationship between triglyceride levels and RA using the odds ratio (OR) and 95% confidence interval (CI). Methods employed included inverse variance weighted (IVW), MR-Egger regression, simple mode, weighted median estimator (WME), and weighted mode.

IVW is a statistical method for causal inference typically used in studies examining the effect of genetic variants on specific traits or diseases. Causality can be assessed only when all SNPs are valid instrumental variables. MR-Egger regression disregards the validity of SNPs by evaluating the exposure's effect on outcomes through the intercept and slope. WME evaluates the exposure-outcome relationship by assessing the effect of each SNP and weighting them accordingly. A p-value < 0.05 indicates a causal relationship between triglyceride levels and RA.

Data from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/) were used for the analysis. The triglyceride sample (GWAS ID: ebi-a-GCST90025957) included individuals from the European population, comprising 437,532 cases and 4,231,999 SNPs. SNPs significantly associated with triglyceride levels were selected using a threshold of P < 5 x 10^-8. To ensure the independence of SNPs, a linkage disequilibrium coefficient (r^2) of 0.001 was applied, and a region width of 10,000 kb was defined. SNPs with an F-statistic > 10 were included, resulting in 287 SNPs.

The RA sample (GWAS ID: ebi-a-GCST90018910) was also sourced from the IEU OpenGWAS project, consisting of 417,256 individuals and 24,175,266 SNPs.

The Cochran Q test was used to assess heterogeneity in the individual effects of each genetic variant on the outcome. If $p \geq 0.05$, no heterogeneity was assumed; otherwise, the IVW results were considered valid. Horizontal pleiotropy, where genetic variations affect outcomes through mechanisms other than the risk factor of interest, was detected using the MR-Egger intercept. A significant intercept indicates the presence of horizontal pleiotropy. The leave-one-out analysis involved sequentially removing each SNP and recalculating the meta-effect of the remaining SNPs to check for the influence of specific SNPs on the results. Leave-one-out analysis is commonly used for sensitivity testing.

Results

The Clinical Characteristics of the Dryad Cohort

Table 1 summarizes the clinical characteristics of 455 patients retrieved from the Dryad database, including 231 patients without RA and 224 patients with RA. Among the cohort, 156 (34.29%) were male, and 299 (65.71%) were female. The median age of the patients was 54 years (IQR: 45–62).

A comparison of clinical characteristics between patients with and without RA is also presented in Table 1. Patients with RA were significantly older and had a lower prevalence of smoking history, higher triglyceride levels, and lower levels of C-reactive protein (CRP) and apolipoprotein A (ApoA) compared to those without RA (all $p < 0.05$). Other parameters, such as body mass index (BMI), blood pressure, glucose levels, and cholesterol levels, did not show significant differences between the two groups.

The Risk Factors for RA of the Dryad Cohort

Table 2 presents the results of univariate and multivariate logistic regression analyses identifying factors associated with RA in the Dryad cohort. Four variables consistently showed significant associations with RA risk. Specifically, a history of non-smoking, lower levels of CRP and ApoA, and higher triglyceride levels were identified as significant risk factors for RA.

Correlation coefficient analysis further supported these findings (Figure 1, Table 3). Negative correlations were observed between CRP, ApoA, and smoking history and the occurrence of RA, whereas triglyceride levels exhibited a positive correlation with RA risk. Notably, triglycerides demonstrated the strongest association with RA among all variables, with a correlation coefficient of $r=0.20$ ($P < 0.001$).

Two-Sample MR Analysis

Data on triglycerides and RA were obtained from the IEU OpenGWAS project. The MR analysis was then conducted using the "TwoSampleMR" package in R (version 4.3.2). Detailed descriptions of the datasets are provided in Table 4,

Table 1 Clinical Characteristics of Patients with and without RA

Parameters	Non-RA (n=231)	RA (n=224)	All (n=455)	χ^2/Z	P
Sex				0.69	0.407
Female	156 (67.53%)	143 (63.84%)	299 (65.71%)		
Male	75 (32.47%)	81 (36.16%)	156 (34.29%)		
Age, year	53 (44 to 61)	55.50 (47 to 62)	54 (45 to 62)	2.06	**0.039**
BMI, kg/m2	25.40 (23.12 to 28.27)	25.58 (22.97 to 28.38)	25.54 (23.05 to 28.34)	0.02	0.985
SBP, mmHg	130 (120 to 140)	130 (120 to 140)	130 (120 to 140)	0.75	0.452
DBP, mmHg	80 (70 to 84)	80 (70 to 85)	80 (70 to 85)	0.70	0.482
Smoking				4.08	**0.043**
No	180 (77.92%)	191 (85.27%)	371 (81.54%)		
Yes	51 (22.08%)	33 (14.73%)	84 (18.46%)		
Glucose, mmol/L	5.30 (5 to 5.70)	5.30 (4.90 to 5.90)	5.30 (5 to 5.80)	0.03	0.973
Cholesterol, mmol/L	5.40 (4.60 to 6.10)	5.40 (4.60 to 6)	5.40 (4.60 to 6)	0.04	0.971
HDL-C, mmol/L	1.50 (1.20 to 1.80)	1.50 (1.20 to 1.80)	1.50 (1.20 to 1.80)	0.55	0.584
LDL-C, mmol/L	3.30 (2.60 to 4.10)	3.20 (2.60 to 3.90)	3.30 (2.60 to 4)	1.04	0.298
Triglyceride, mmol/L	1.01 (0.72 to 1.36)	1.18 (0.82 to 1.66)	1.07 (0.76 to 1.57)	3.47	**0.001**
CRP, mg/L	2 (1 to 5)	1.50 (1 to 3)	2 (1 to 5)	3.65	**<0.001**
ApoA, g/L	1.66 (1.47 to 1.93)	1.61 (1.42 to 1.83)	1.63 (1.44 to 1.87)	2.50	**0.012**
ApoB, g/L	0.97 (0.79 to 1.16)	0.99 (0.83 to 1.18)	0.99 (0.81 to 1.17)	0.92	0.358

Notes: Significant results are indicated in bold P-values.

Abbreviations: χ^2, chi-square statistic; Z, Z-score; P, P-value; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; ApoA, apolipoprotein A; ApoB, apolipoprotein B.

Table 2 Logistic Regression Analysis of Independent Variables Associated with RA

Parameters	Univariate		Multivariate	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Sex				
Female	1 [reference]	–		
Male	1.18 (0.80 to 1.74)	0.407		
Age, year	1.02 (1.00 to 1.03)	0.051	1.02 (1.00 to 1.03)	0.087
BMI, kg/m2	1.01 (0.96 to 1.05)	0.808		
SBP, mmHg	1.01 (0.99 to 1.02)	0.307		
DBP, mmHg	1.01 (0.99 to 1.03)	0.208		
Smoking				
No	1 [reference]	–	1 [reference]	–
Yes	0.61 (0.38 to 0.99)	0.045	0.55 (0.33 to 0.91)	**0.019**
Glucose, mmol/L	1.05 (0.82 to 1.36)	0.690		
Cholesterol, mmol/L	0.99 (0.83 to 1.16)	0.863		
HDL-C, mmol/L	0.77 (0.51 to 1.14)	0.190		
LDL-C, mmol/L	0.92 (0.76 to 1.11)	0.369		
Triglyceride, mmol/L	1.93 (1.41 to 2.65)	<0.001	1.94 (1.39 to 2.70)	**<0.001**
CRP, mg/L	0.94 (0.90 to 0.98)	0.003	0.93 (0.89 to 0.97)	**0.001**
ApoA, g/L	0.45 (0.25 to 0.79)	0.006	0.42 (0.23 to 0.76)	**0.004**
ApoB, g/L	1.41 (0.70 to 2.83)	0.332		

Notes: Significant results are indicated in bold P-values.
Abbreviations: OR, odds ratio; CI, confidence interval; P, P-value; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; ApoA, apolipoprotein A; ApoB, apolipoprotein B.

and the characteristics of the SNPs for both the exposure (triglycerides) and the outcome (RA) variables are presented in Supplementary Table S1.

Selection of Instrumental Variables

In this study, triglycerides were considered the exposure factor. To ensure that the genetic variants used in the analysis were independent of one another, we excluded SNPs located within a 10,000 kb range that had an r^2 value greater than 0.001 (a measure of genetic correlation between variants). Additionally, all selected SNPs had an F-statistic greater than 10, which helps ensure that the instrumental variables are strong and reduces potential bias from weak genetic instruments. After applying these criteria, we identified 287 genome-wide SNPs that were significantly associated with triglyceride levels and used them as instrumental variables.

To visualize the relationship between the SNPs and their effect on triglycerides, we created a forest plot (Figure 2A), which shows each instrumental variable on the y-axis and their corresponding effect sizes on the x-axis. A second forest plot (Figure 2B) presents the results of the MR analysis itself.

MR Analysis Results

The MR analysis produced the following results for the causal relationship between triglycerides and RA:

IVW: OR = 0.944 (95% CI: 0.872–1.022, P = 0.154)
WME: OR = 0.965 (95% CI: 0.871–1.068, P = 0.488)
MR-Egger: OR = 0.946 (95% CI: 0.848–1.056, P = 0.323)
Simple Mode: OR = 1.001 (95% CI: 0.783–1.280, P = 0.993)
Weighted Mode: OR = 0.979 (95% CI: 0.911–1.051, P = 0.553)

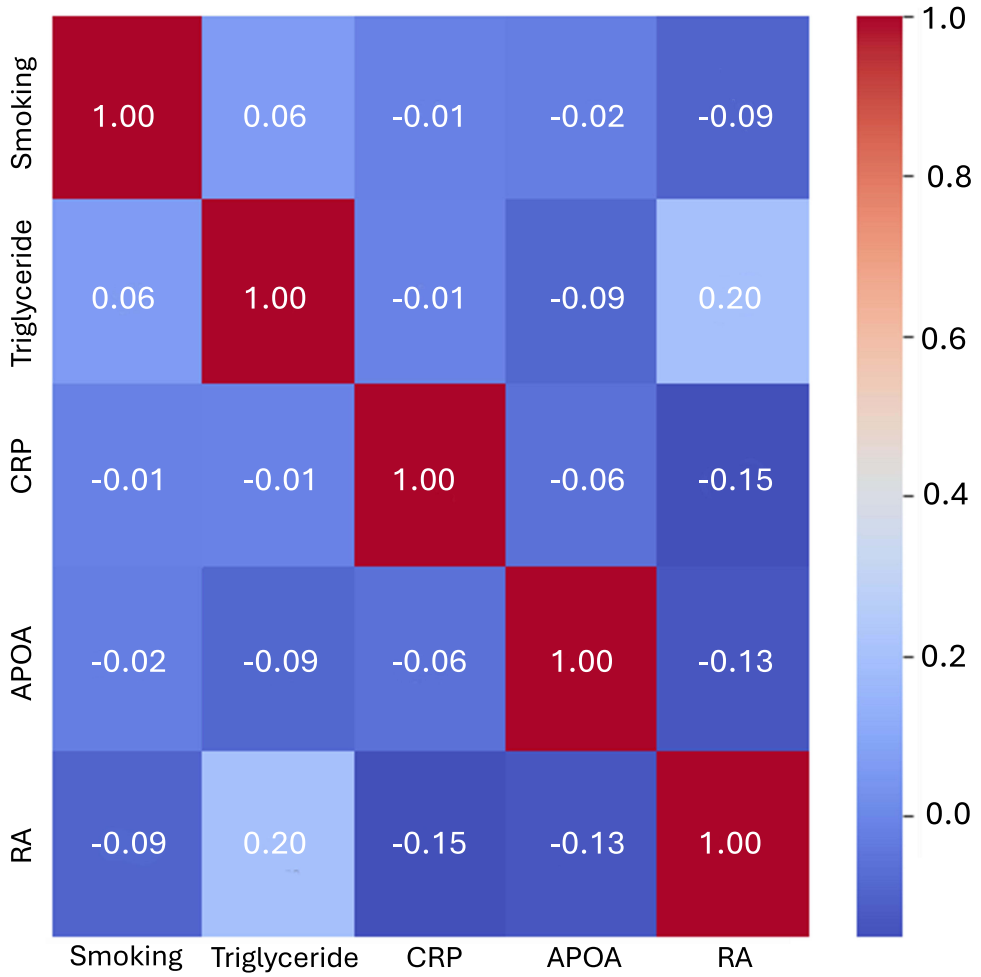

Figure 1 Heatmap showing the correlation coefficients between risk factors and RA in the multivariate model. The strongest correlation is observed between triglycerides and RA, with a correlation coefficient of 0.20 ($P < 0.001$).
Abbreviations: ApoA, apolipoprotein A; CRP, C-reactive protein; RA, Rheumatoid Arthritis.

The results from all five methods consistently indicated that there is no significant causal relationship between triglyceride levels and the risk of RA. Specifically, an odds ratio close to 1 suggests that changes in triglyceride levels do not have a strong effect on the likelihood of developing RA.

Heterogeneity Test

Heterogeneity refers to differences in the causal effects of genetic variants across different locations in the genome. We conducted a heterogeneity test to examine whether such differences were present. The Cochran's Q statistic for the IVW

Table 3 Correlation Coefficient Analysis of Risk Factors Associated with RA

Parameters	Correlation type	r (95% CI)	P
Triglyceride, mmol/L	Point-biserial correlation	0.20 (0.11 to 0.28)	**<0.001**
CRP, mg/L	Point-biserial correlation	−0.15 (−0.24 to −0.06)	**0.001**
ApoA, g/L	Point-biserial correlation	−0.13 (−0.22 to −0.04)	**0.005**
Smoking	Phi correlation	−0.09 (−0.19 to 0.00)	**0.044**
Age, year	Point-biserial correlation	0.09 (0.00 to 0.18)	0.0501

Notes: Significant results are indicated in bold P-values. Variables were sorted by the magnitude of the correlation coefficient from largest to smallest.
Abbreviations: r, correlation coefficient; CI, confidence interval; P, P-value; CRP, C-reactive protein; ApoA, apolipoprotein A.

Table 4 Sources of Data for Two-Sample MR Analysis

Exposure/Outcome	Source	Sample Size	Number of SNP	Author	Year	Population
Triglycerides	gwas.mrcieu.ac.uk	437532	4231999	Barton AR	2021	European
RA	gwas.mrcieu.ac.uk	417256	24175266	Sakaue S	2021	European

analysis was 585.28 (P < 0.001), and for the MR-Egger analysis, it was 585.29 (P < 0.001), indicating significant heterogeneity. This suggests that the causal effects may vary across different genetic variants. The presence of heterogeneity is not unusual and may be attributed to factors like the large sample size or variability in the genetic variants themselves. Previous research indicates that heterogeneity does not necessarily undermine the validity of MR results when using instrumental variables.[22]

Sensitivity Analysis

To ensure the robustness of our findings, we performed several sensitivity analyses. The MR-Egger intercept test showed no evidence of horizontal pleiotropy, a phenomenon where genetic variants affect multiple traits, which could bias the results (Intercept = −0.0001, P = 0.952).

This conclusion was further supported by the scatter plot analysis (Figure 3), which showed no evidence of systematic bias in the genetic variants used.

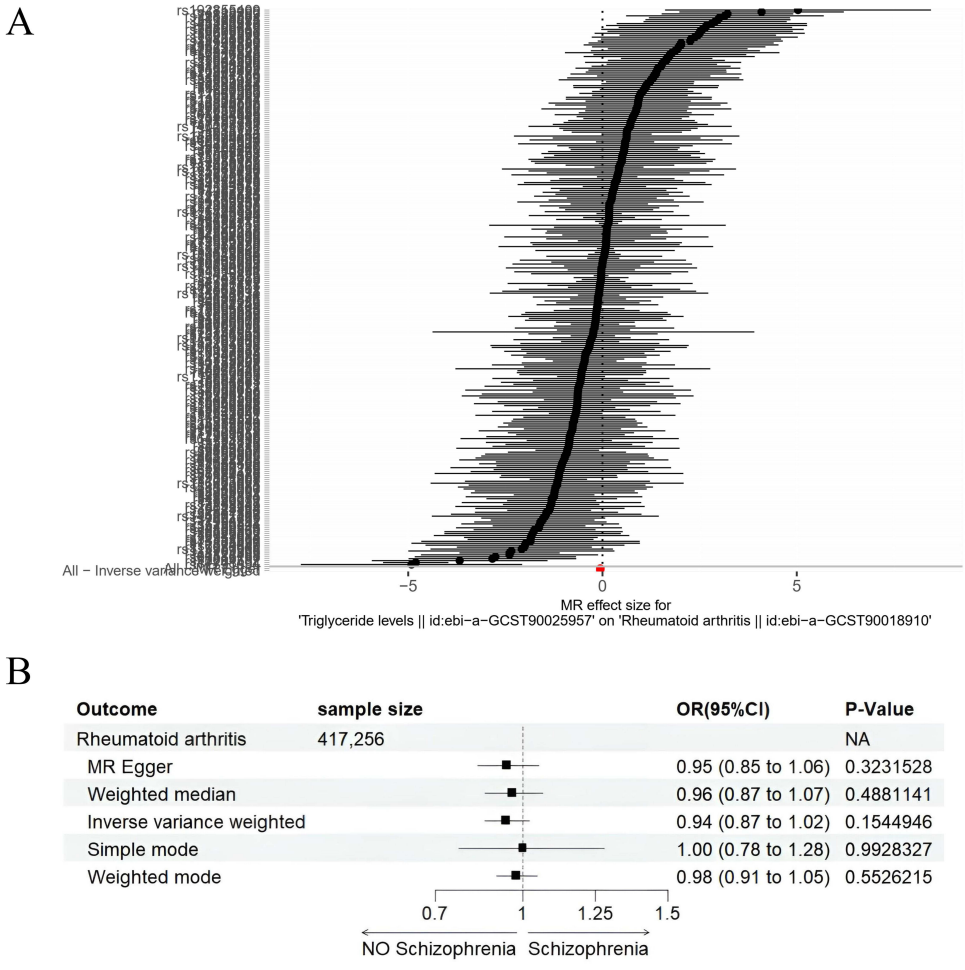

Figure 2 (**A**) Forest plot of SNPs associated with triglycerides and RA. Black dots represent the effect of individual SNPs on RA, red dots indicate the combined causal estimate using all SNPs as a single instrument, and horizontal lines represent the 95% confidence intervals. (**B**) Forest plot illustrating the MR analysis results.
Abbreviations: OR, odds ratio; CI, confidence interval; MR, Mendelian Randomization.

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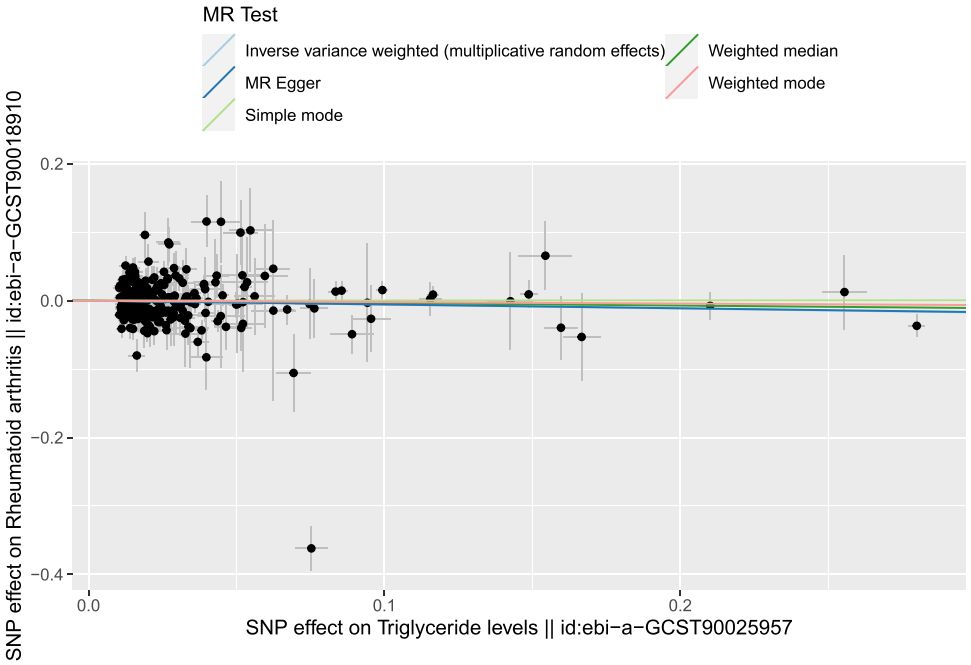

Figure 3 Scatter plot depicting the association between triglycerides and RA. The plot shows the effect sizes of SNP-triglycerides and SNP-RA with 95% confidence intervals. The regression slope of the line corresponds to the causal estimates from five MR methods (IVW, weighted median estimator, MR-Egger, simple mode, and weighted mode).
Abbreviations: SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization.

A leave-one-out analysis, where we systematically excluded one SNP at a time, demonstrated that no single SNP had a significant impact on the observed relationship between triglycerides and RA (Figure 4).

Finally, a funnel plot (Figure 5) revealed a symmetrical distribution of all SNPs, suggesting that the results were not significantly influenced by biases or confounding factors.

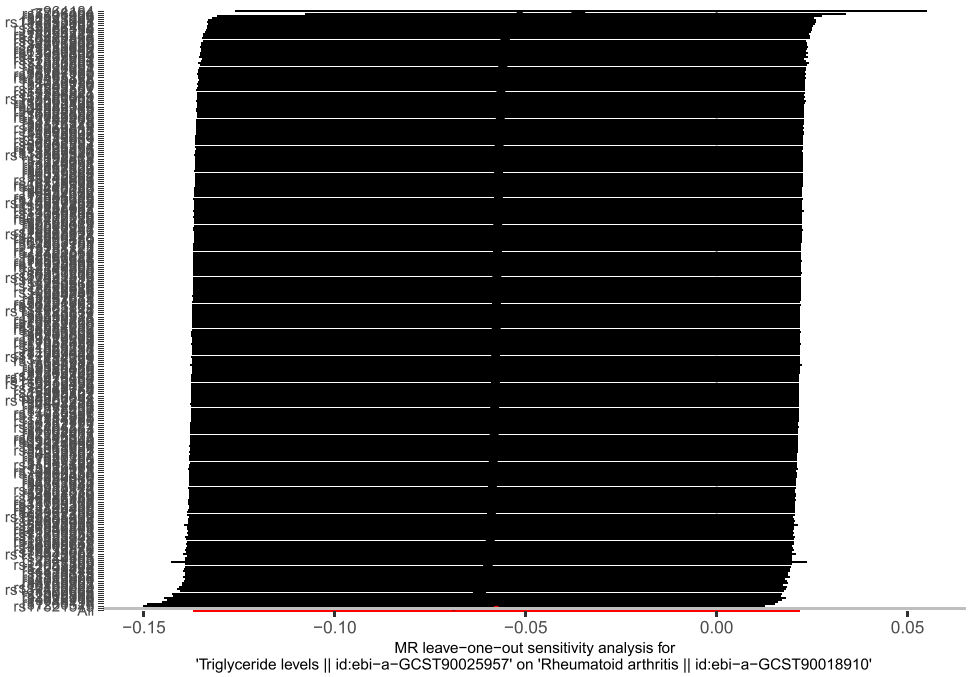

Figure 4 Leave-one-out analysis plot for the relationship between triglycerides and RA. No single SNP significantly influences the overall results.
Abbreviations: SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization.

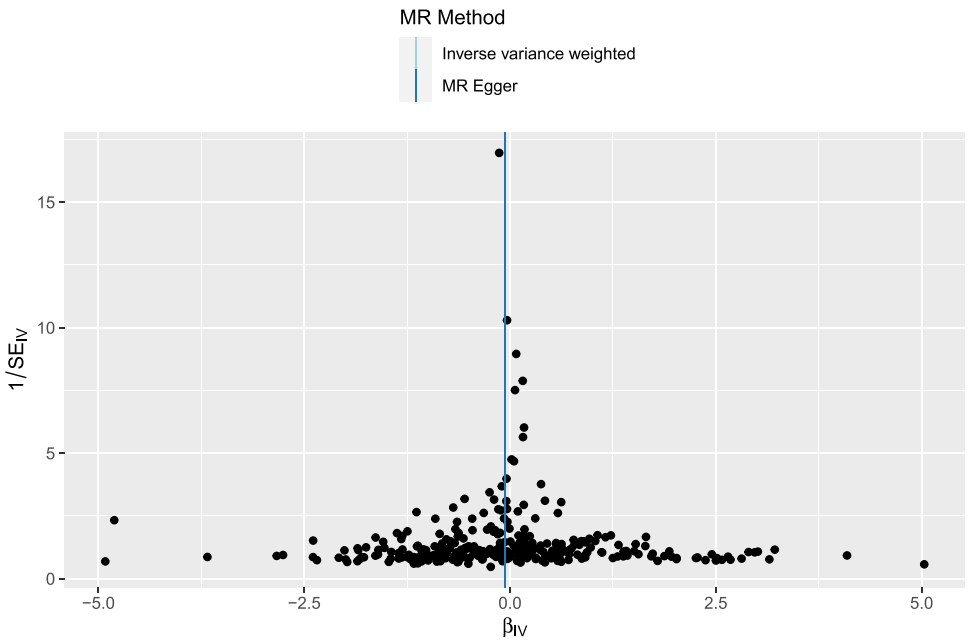

Figure 5 MR-Egger regression funnel plot. The distribution of all SNPs is essentially symmetrical, indicating no significant bias in the analysis.
Abbreviations: SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization.

These sensitivity analyses confirmed the robustness of our findings, indicating that the relationship between triglycerides and RA is not driven by individual genetic variants or biases in the data.

Reverse Mendelian Randomization Analysis (RA → Triglycerides)

To explore the possibility of reverse causality, we conducted a reverse MR analysis with RA as the exposure and triglyceride levels as the outcome. The IVW method yielded an OR of 0.984 (95% CI: 0.965–1.022, p = 0.089), indicating no significant causal effect. Similar results were observed using the MR-Egger method (OR = 0.978, 95% CI: 0.934–1.018, p = 0.298), simple mode (OR = 0.979, 95% CI: 0.953–1.008, p = 0.179), and weighted mode (OR = 0.976, 95% CI: 0.959–0.993, p = 0.016). Although the weighted median estimator showed a nominally significant result (OR = 0.979, 95% CI: 0.964–0.996, p = 0.016), the effect size was small and not consistent across all methods (Figure 6).

Sensitivity analyses supported the robustness of the findings. Heterogeneity tests indicated no evidence of heterogeneity (IVW Q-test p > 0.05; MR-Egger Q-test p > 0.05). The MR-Egger intercept was not significantly different from zero (intercept = 0.001, p = 0.744), suggesting no horizontal pleiotropy. Scatter plots (Figure 7) and leave-one-out analysis (Figure 8) confirmed the stability of the results. The funnel plot (Figure 9) demonstrated symmetry, indicating minimal influence from potential confounding due to unbalanced pleiotropy.

These findings suggest that RA is unlikely to have a causal effect on TG levels, providing further support against reverse causality in the RA–TG relationship.

Discussion

This study is the first to integrate public data and GWAS information using two-sample MR to investigate the potential causal relationship between triglycerides and RA. The results of multivariate regression analysis identified smoking, apolipoprotein A, and C-reactive protein as significant risk factors for RA. However, no independent causal relationship between triglyceride levels and RA was found in the MR analysis.

Currently, research on the molecular mechanisms by which elevated triglycerides increase the risk of RA is limited, but several plausible pathways have been suggested. One key mechanism involves the elevation of lipoprotein concentrations due to hypertriglyceridemia,[23] particularly oxidized low-density lipoprotein (ox-LDL), which is absorbed by macrophages and endothelial cells, leading to intracellular lipid accumulation and subsequent inflammation.[24] This

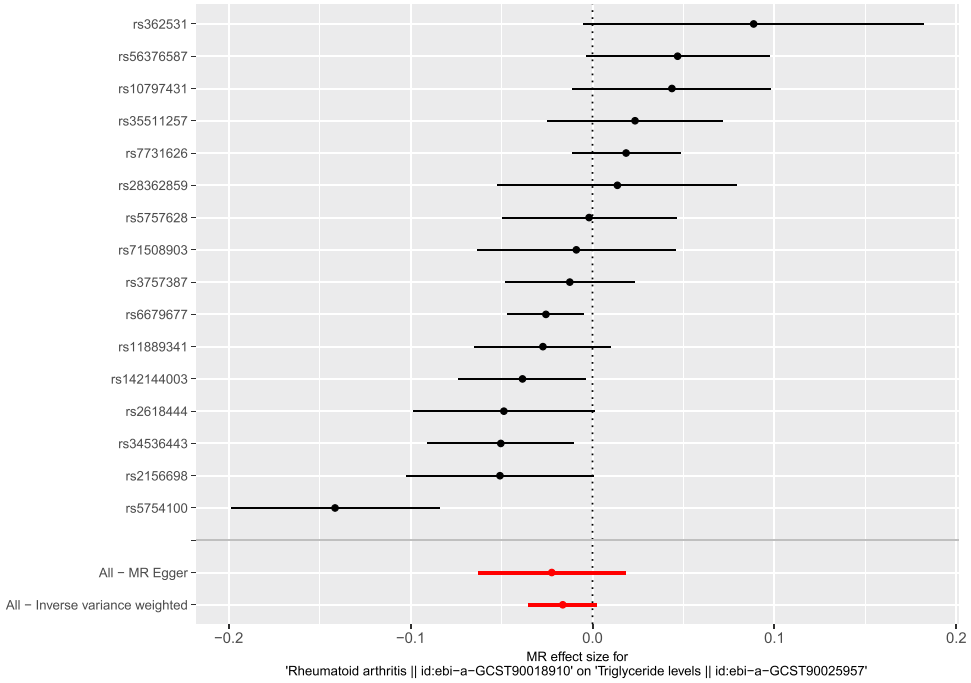

Figure 6 Forest plot of the reverse MR analysis evaluating the causal effect of RA on triglyceride levels. Each black dot represents the causal estimate of an individual SNP on triglycerides levels. The red diamond represents the combined causal estimate using all SNPs as a single instrument. Horizontal lines indicate 95% CIs.
Abbreviations: SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization.

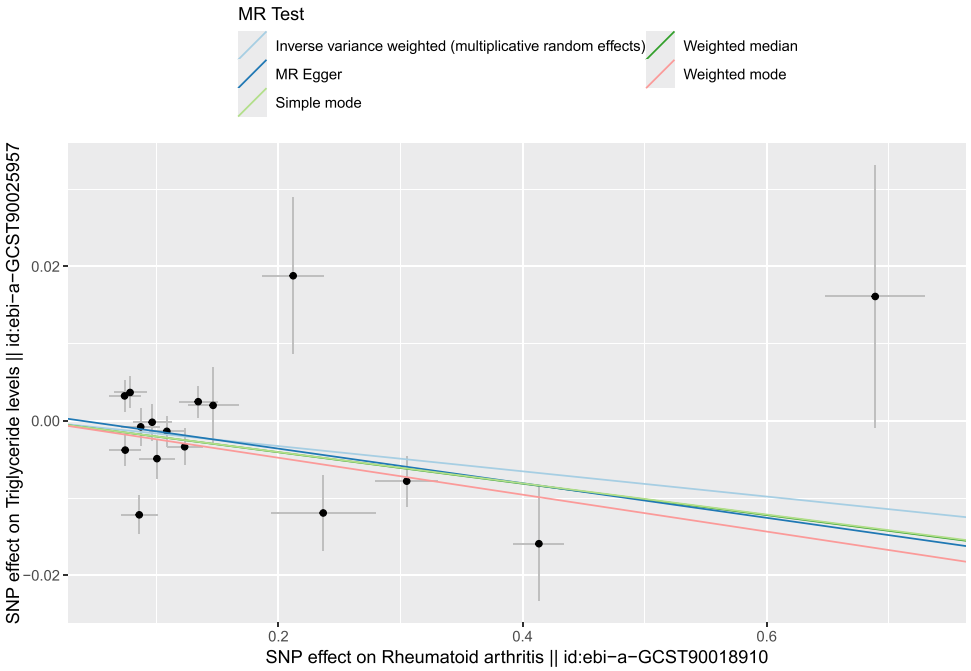

Figure 7 Scatter plot illustrating the associations between SNPs related to RA and their effects on TG levels. Each dot represents a single SNP, with error bars indicating 95% CIs for SNP-RA (x-axis) and SNP-TG (y-axis) effects. The slope of each line corresponds to the causal estimate derived from five MR methods: inverse variance weighted (IVW), weighted median estimator (WME), MR-Egger, simple mode, and weighted mode.
Abbreviations: SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization.

process can activate the NF-κB signaling pathway, which is associated with elevated CRP levels and systemic inflammation,[25,26] and may further stimulate the release of TNF-α and IL-6, both of which have been implicated in RA progression.[27,28] In parallel, triglyceride metabolism may influence immune cell function, particularly the activation

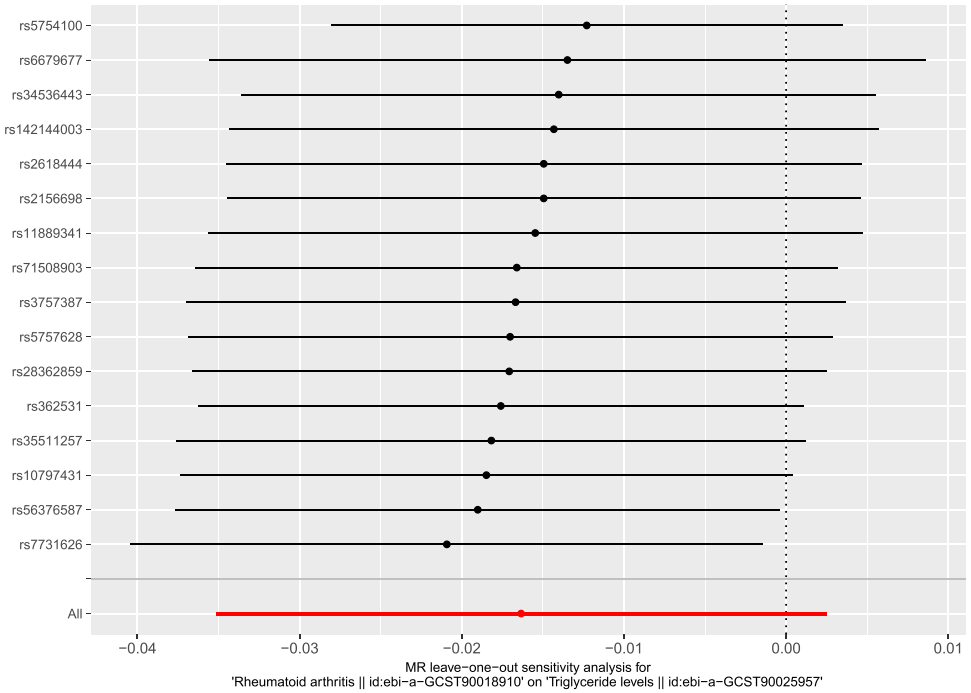

Figure 8 Leave-one-out sensitivity analysis for the reverse MR analysis. Each point shows the overall IVW estimate after removing one SNP at a time. The dashed red line represents the pooled estimate using all SNPs. The analysis demonstrates that no single SNP had a disproportionate influence on the overall result, supporting the robustness of the findings.
Abbreviation: MR, Mendelian Randomization.

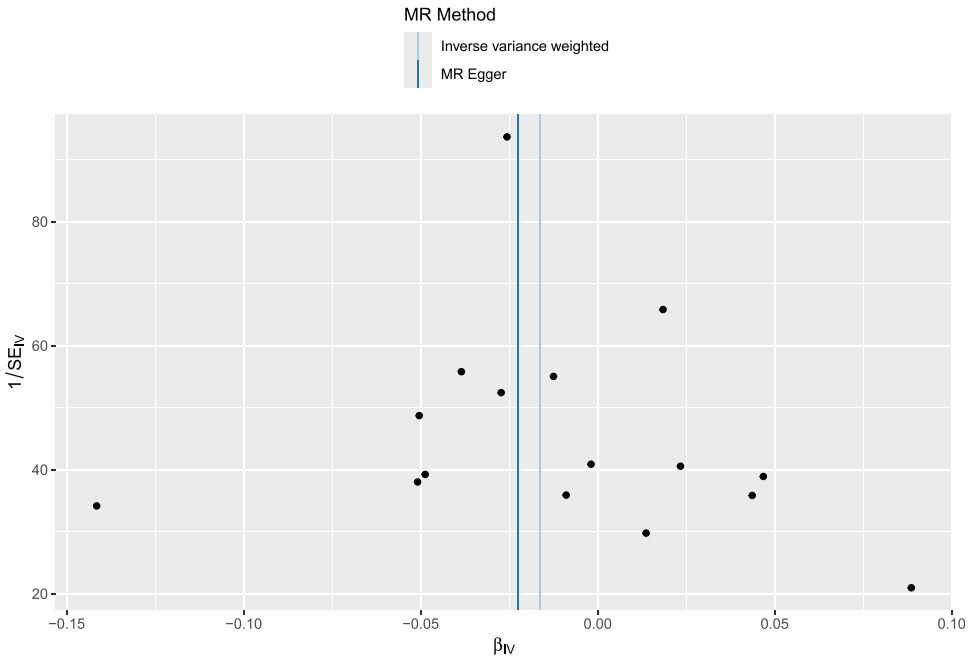

Figure 9 Funnel plot assessing the symmetry of SNP effects in the reverse MR analysis. The vertical line indicates the pooled IVW estimate. Symmetrical distribution of SNPs around this line suggests minimal bias due to directional pleiotropy or unbalanced heterogeneity.
Abbreviations: SNPs, Single Nucleotide Polymorphisms; MR, Mendelian Randomization.

and differentiation of T lymphocytes (CD4+ and CD8+), which play a central role in RA pathogenesis.[29] Adipose tissue, especially in individuals with elevated BMI, also contributes to this pro-inflammatory state by secreting adipokines and other immune-modulatory molecules.[30,31] These interconnected mechanisms support the hypothesis that elevated

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triglycerides may indirectly exacerbate immune dysregulation and chronic inflammation, thereby contributing to the development or progression of RA. Furthermore, some studies have reported that higher triglyceride levels are associated with faster increases in immune cell proportions and inflammatory cytokine levels, which may correlate with poorer treatment outcomes in RA patients.[32] Collectively, these findings support the notion that systemic inflammation triggered by elevated triglycerides may be closely associated with the onset and progression of RA, potentially influencing patient prognosis through enhanced cytokine production and immune cell activation.

Our findings should also be considered in the context of prior literature. For example, Yan et al (2024)[33] identified remnant cholesterol (RC) as an independent risk factor for RA using a large NHANES cohort. In contrast to our MR-based approach, their study was cross-sectional in nature and evaluated RC[33]—a marker reflecting cholesterol in triglyceride-rich lipoproteins—rather than triglycerides directly. While both studies highlight the importance of lipid metabolism in RA, the biomarkers and methodologies differ. Notably, both studies found limited associations between traditional lipid markers (eg, LDL-C, HDL-C) and RA risk, suggesting these may lack specificity for RA pathogenesis. Yan et al[33] further reported stronger associations in participants without diabetes and those not on statins, highlighting how metabolic comorbidities and medications may influence lipid-related risk. Although such subgroup stratification was not possible in our analysis due to dataset limitations, our MR results suggest that TG may influence RA risk indirectly via immune-inflammatory pathways, rather than through direct causality.

To our knowledge, no previous study has specifically explored the potential causal relationship between triglycerides and RA using Mendelian randomization. Unlike the original study from which our dataset was derived,[20] which focused on subclinical atherosclerosis (cIMT), our analysis investigated RA risk using both observational and genetic approaches. We included all participants with complete data on triglycerides, CRP, and ApoA. No additional exclusions were applied based on CRP thresholds or medication use, as such metadata were not available. Interestingly, we observed lower ApoA and CRP levels in RA patients compared to controls, in contrast to earlier findings.[20] These differences likely reflect variation in sample composition, data completeness, and lack of medication-related exclusion, and should be considered when interpreting biomarker distributions across studies. Taken together, our study complements and extends prior work by applying MR to assess causality, and by focusing specifically on triglycerides as a potentially modifiable metabolic marker in RA. Future studies may benefit from examining multiple lipid components—including RC, TG, and apolipoproteins—while accounting for comorbid conditions, medication use, and genetic background.

Luo et al[34] conducted a prospective cohort study involving 369,065 participants, exploring the relationship between metabolic syndrome and RA risk, and found that factors such as triglycerides and hyperglycemia were associated with an increased RA risk. In contrast, VanEvery et al[35] analyzed 97,411 participants and found that low-density lipoprotein cholesterol (LDL-C) was a risk factor for RA, while triglycerides did not significantly affect RA incidence. Several factors may explain these inconsistent findings: (1) many studies employed single-method approaches, failing to assess the combined impact of multiple risk factors on RA; (2) clinical cohort studies are often subject to confounding factors, such as lifestyle and socioeconomic status, which can affect the accuracy of the results; and (3) biological differences in RA across individuals or populations could lead to conflicting conclusions.

MR, an emerging epidemiological method, addresses some limitations of traditional studies.[36] The advantages of MR include: (1) genetic variation is highly stable and unaffected by external factors, minimizing confounding bias; (2) genetic variation precedes both exposure factors and disease outcomes, eliminating the possibility of reverse causality; and (3) MR utilizes publicly available, stable data, enhancing the reliability of its conclusions. This study integrated traditional risk factor analysis with MR to explore the relationship between triglycerides and RA from multiple perspectives. By employing this approach, we comprehensively analyzed the impact of triglycerides on RA and directly identified the independent causal relationship between the two at the genetic level. Our findings provide new insights into the etiology of RA and suggest that triglycerides may play a critical role in RA risk management. Future studies could explore whether triglycerides could serve as screening and monitoring markers for RA or even as potential therapeutic targets.

However, there are several limitations to this study. First, the data primarily come from European populations, which may limit the generalizability of the findings to other populations, particularly in Asia, where genetic differences may exist. Second, the clinical public databases used in this study lacked detailed information on cytokines and immune cells, restricting our understanding of the specific mechanisms through which triglycerides influence RA. Additionally, there

may be potential measurement bias in the triglyceride data, and the effect of genetic drift on SNP selection in the MR analysis requires further validation. Future research should focus on collecting genetic data from diverse populations and conducting both in vivo and in vitro studies to validate key molecular targets and mechanisms associated with triglycerides, thereby improving the generalizability and reliability of the findings.

Conclusion

This study integrated traditional risk factor analysis with MR methods to investigate whether triglyceride levels are associated with an increased risk of RA and whether this association is causal. Logistic regression identified higher triglyceride levels, lower CRP and ApoA levels, and non-smoking status as significant risk factors for RA, suggesting a potential association between triglycerides and RA risk. However, the MR analysis found no evidence for a causal relationship, indicating that elevated triglyceride levels may be a correlate rather than a direct driver of RA pathogenesis. Taken together, these findings suggest that while triglycerides may contribute to RA risk through immune and inflammatory pathways, they are unlikely to be an independent causal factor. Therefore, triglyceride management alone may not be a primary target in RA diagnosis or treatment. Further research is needed to elucidate the underlying mechanisms and to explore whether triglycerides might serve as markers for disease monitoring or therapeutic response.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The data were obtained from the Dryad database. Since no personally identifiable information or commercial interests were involved, and no direct contact with human participants occurred in this secondary analysis, further ethical review was not required in accordance with Article 32(1) and 32(2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (National Health Commission of the People's Republic of China, 2023).

Consent for Publication

Consent for publication is not required since data were obtained from the Dryad database.

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Disclosure

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