Lipids in Health and Disease

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Lipid levels and multiple myeloma risk: insights from Meta-analysis and mendelian randomization

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Abstract

Background Lipid levels have been suggset to be correlated with multiple myeloma (MM) risk, though causality remains unconfirmed. To explore this further, a detailed study combining meta-analysis and Mendelian randomization (MR) was conducted.

Methods Literature searches were performed on PubMed and Embase; summary data for plasma lipid traits were extracted from the IEU and MM data from the FinnGen database. Meta-analysis and MR were utilized to analyze the link of lipids with MM risk, including mediator MR to identify potential mediators. The study was conducted in accordance with PRISMA and STROBE-MR guidelines.

Results Observational studies analyzed through meta-analysis showed that elevated levels of LDL, HDL, total cholesterol (TC), and triglycerides correlate with a lower risk of MM, with HRs of 0.73, 0.59, 0.60, and 0.84, respectively. MR analysis confirmed a potential causal link of triglyceride with a reduced MM risk (OR: 0.67, 95% CI: 0.46–0.98), independent of BMI. Mediation analysis pointed to X-11,423-O-sulfo-L-tyrosine and neuropilin-2 as potential mediators.

Conclusions The findings suggest that higher lipid levels (LDL, HDL, TC, and triglycerides) are linked with a reduced MM risk, and higher triglyceride levels are causally associated with a reduced MM risk. This suggests new avenues for therapeutic interventions targeting MM.

Keywords Meta-analysis, Mendelian randomization, Plasma lipids, Multiple myeloma

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Background

Multiple myeloma (MM) is an incurable blood cancer. Despite recent treatment advancements improving patient outcomes, identifying risk factors remains crucial for reducing MM incidence and enhancing prognosis [1, 2]. Among the various factors influencing MM development, lipid metabolism has garnered increasing attention in recent years [3, 4]. Adipose tissue, particularly adipocytes, has been recognized as a significant component of the MM tumor microenvironment and is intricately linked to MM development. Abnormal lipid metabolism is implicated in these biological processes,

suggesting its potential role in MM pathogenesis [5]. Preclinical research suggests that interventions targeting lipid metabolism could be a viable therapeutic strategy for MM [4, 6]. Recently, a large-scale epidemiological investigation involving over 3.5 million participants reported that higher plasma lipid levels were associated with lower MM risk [7]. Moreover, two meta-analyses have found that lipid-lowering medications might decrease the risk of MM [8, 9]. These studies collectively point to a vital role of lipid metabolism in MM development. Nonetheless, despite these insights, observational study results remain inconsistent, and causal link between plasma lipid levels and MM risk remains uncertain. Mendelian randomization (MR) overcomeing deficiencies of traditional epidemiologic investigation (e.g., confounding factors and reverse causation), enabling a more effective investigation of causal relationships [10]. MR can reduce the impact of confounding factors [11], and some studies have identified new risk factors and therapeutic targets for MM through MR analysis [12–14]. Therefore, MR has the potential to determine whether genetically predicted dyslipidemia constitutes a significant risk factor for MM. This study hypothesized that plasma lipid levels may be associated with MM risk and that the association may be causal. To this aim, this study explores the relationship between plasma lipid components (LDL, HDL, TC, and triglycerides) and MM risk via a combination of meta-analysis and MR methods. This study extends previous research by exploring potential mediating pathways using a two-step MR approach with blood metabolites and proteins, offering a unique perspective that expands upon the existing body of knowledge in the field. These findings may provide new insights into MM pathogenesis, identify potential biomarkers and therapeutic targets, and inform future preventive and treatment strategies.

Methods

Study design

Figure 1 illustrates the study workflow, which integrates meta-analysis and MR approaches. The study consists of three main stages: (1) Meta-analysis to explore the link of plasma lipid levels with MM risk; (2) Univariable and multivariable MR analyses to analysis the potential causal link of lipid levels with MM risk, along with MR and Summary-based MR (SMR) analyses to analysis the causal link of lipid-lowering target genes with MM risk; and (3) A two-step MR analysis to investigate potential mediators. The study was conducted in accordance with PRISMA and STROBE-MR guidelines.

Literature search and study selection

Two authors independently conducted a comprehensive literature search in Embase and PubMed, with the latest update on March 20, 2024 (see supplementary files for the detailed search strategy). Studies were included if they: (1) investigated the link between plasma lipid levels and MM risk; and (2) reported MM incidence according to plasma lipid levels. Studies excluded were (1) reviews, meeting abstracts, or letters without full text; (2) non-human studies; (3) duplicate publications; or (4) lacking usable data.

Data extraction and quality assessment

Data such as first author, publication year and hazard ratio for developing MM among groups from the included studies were extracted by two authors. Newcastle-Ottawa Scale was utilized to inspect the studies' quality [15]. Any disagreements were resolved through discussion.

Data sources of exposures, mediators, and outcomes

Summary data for lipid traits (HDL, LDL, TC and triglycerides) were extracted from the IEU OpenGWAS project, including data from the Global Lipids Genetics Consortium (GLGC) [16], the within-family GWAS consortium, and Barton et al. [17]. GLGC lipid traits were used for the primary analysis, while the remaining data were used for validation. Summary data for BMI (ieu-b-40) and mediators (human blood metabolites and proteins) were also obtained from the IEU OpenGWAS project. Summary data for MM were download from the FinnGen database R9 version, comprising 585 MM patients and 287,129 controls. Supplementary table S1 provides detailed information on the summary data.

Instrumental variable (IV) selection

The following steps were employed for the selection of IVs for exposures: (1) Single nucleotide polymorphisms (SNPs) strongly correlated with exposures ($P<5\times10^{8}$) were identified as potential IVs; (2) To ensure independence, SNPs were selected that were in linkage equilibrium over a 10,000 kb range, with $r^2<0.01$; (3) Palindromic SNPs, which may have bidirectional sequencing issues, were excluded from consideration; (4) SNPs that showed close association with potential confounders were also excluded to minimize the risk of residual confounding; (5) SNPs with an F-statistic < 10, indicating insufficient statistical power, were not included in the analysis.

IVs for lipid-lowering target genes were collected from a previous study [18]. These genes contain common lipid-lowering drug targets and novel therapeutic targets. In summary, seven genes (ABCG5, ABCG8, APOB, HMGCR, LDLR, NPC1L1, PCSK9) lower LDL, while four genes (ANGPTL3, APOC3, LPL and PPARA) lower triglycerides. Cis-expression quantitative trait loci variants (Cis-eQTL) genetic variants of lipid-lowering target

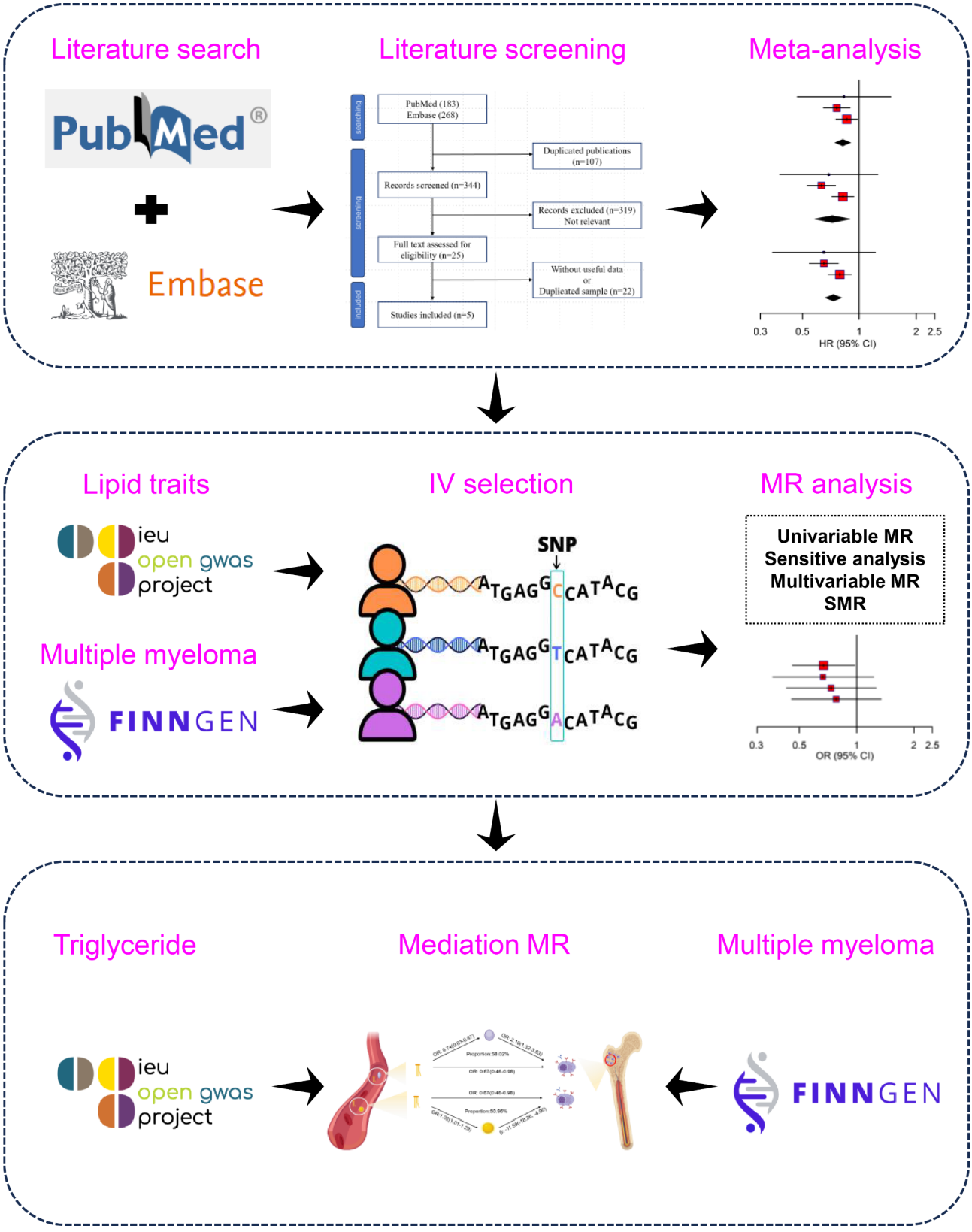

Fig. 1 Design of the study

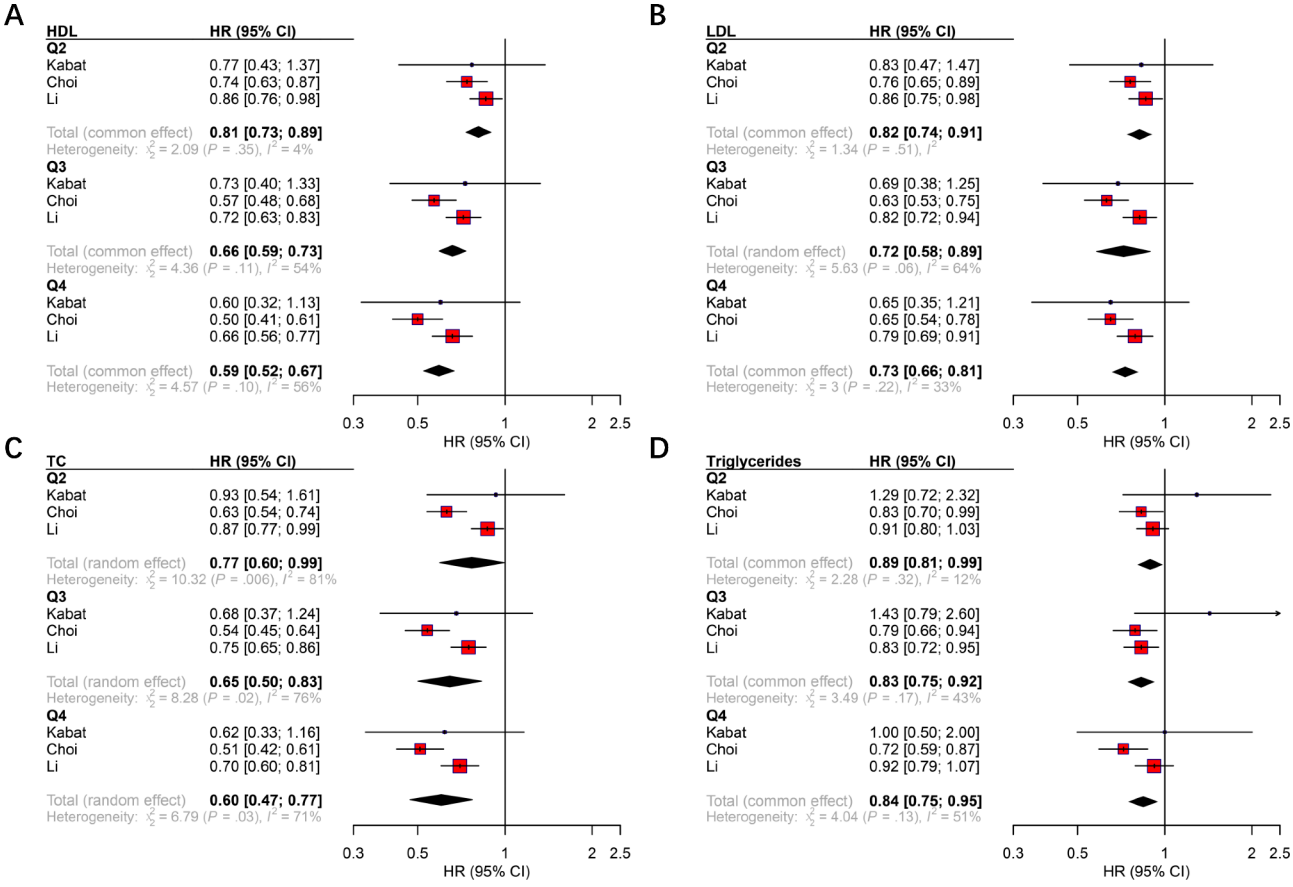

Fig. 2 Forest plot of association between plasma lipid levels and MM risk. **A**: HDL and MM; **B**: LDL and MM; **C**: TC and MM; **D**: triglyceride and MM. Q2: Q 2 vs. Q 1; Q3: Q3 vs. Q1; Q4: Q4 vs. Q1

genes obtained from eqtlGen Consortium were used as IVs for SMR analysis.

Statistical analysis

Meta-analysis Heterogeneity was evaluated using the I^2 statistic and the Cochran Q test. When significant heterogeneity exist (Cochran Q test *P*-value < 0.10), random-effects models were applied to account for the variability between studies. Otherwise, fixed-effects models were utilized. The potential impact of publication bias on the findings was assessed by constructing Begg's funnel plots and conducting Egger's regression test. Subgroup analysis was performed base on population.

MR analysis Firstly, the MR analysis employed univariable MR methods, including inverse-variance weighted (IVW), weighted median, MR-Egger regression, and MR-PRESSO. The IVW results were considered the primary findings. IVW results were considered as main results. MR-Egger regression model was used to test for horizontal pleiotropy and utilized the MR-PRESSO method was used to identify and adjust for outlying estimates that may be influenced by pleiotropy. If pleiotropic outliers were identified, the main and sensitivity analyses were repeated after excluding these outliers. Heterogeneity was evaluated using Cochran's Q-test. It is notable that, when multiple datasets were available for a specific lipid trait, a meta-analysis was performed to combine the IVW results of univariable MR.

Secondly, multivariable MR assessed the link of lipid levels with MM risk independently of BMI, and SMR analysis investigated the link between lipid-lowering target genes and MM, complementing MR analysis. Finally, a two-step MR analysis assessed whether human blood metabolites and proteins mediate the relationship between triglycerides and MM.

Evidence for a causal effect was established when: (i) the Bonferroni correction for multiple testing was applied, with an adjusted *P*-value threshold of $P<0.0125$ for the four lipid traits assessed by IVW, and $P<0.0055$ for the nine lipid-lowering target genes assessed by IVW; (ii) the results of other MR methods were consistent with the direction of the IVW results; and (iii) there were no horizontal pleiotropy. Additionally, when the IVW analysis yielded a *P*-value between the adjusted threshold and $P<0.05$, the association was considered indicative of

probable causality. Analyses were performed in R (v4.2.1) with "meta", "TwoSampleMR", and "MVMR" packages.

Results

Meta-analysis of lipid and MM risk

Published data have shown inconsistent link between abnormal lipid levels and MM risk [7, 19]. A meta-analysis was performed to address this issue. As shown in Figure S1, PubMed and Embase databases identified 451 relevant studies, of which 5 studies [7, 19–22] involving 4,634,465 participants were included. The detailed information on the included studies is listed in supplementary Table 2. The study populations originated from diverse geographical locations, including the United States [20], Korea [7], the United Kingdom [19], Denmark [22], Austria, Norway, and Sweden [21]. The meta-analysis included data from four studies on HDL [7, 19, 20, 22], three on LDL [7, 19, 20], four on TC [7, 19–21], and four on triglycerides [7, 19–21]. For HDL, three studies categorized HDL levels into quartiles [7, 19, 20], while one study treated it as a continuous variable [22]. All studies concerning LDL categorized the levels into quartiles. Similarly, three studies on TC categorized levels into quartiles [7, 19, 20], and one treated TC as a continuous variable [21]. Triglyceride levels were categorised into quartiles in three studies [7, 19, 20], while one treated triglyceride levels as a continuous variable [21]. Consequently, two meta-analysis approaches were employed: one combining HRs from identical quartile groups across various studies, while the other entailed merging HRs from the highest quartile (Q4) with those from studies that treated the variables on a continuous scale. The models in different studies were adjusted for sex, BMI, age, diabetes, alcohol consumption, smoking, and lipid-lowering medication. All included studies had Newcastle-Ottawa Scale scores > 7.

As shown in Fig. 2, Q4 of baseline HDL (Fig. 2A), LDL (Fig. 2B), TC (Fig. 2C) and triglyceride (Fig. 2D) levels were significantly associated with a reduced MM risk compared to Q1 group (HR and 95% CI for Q4 vs. Q1: (0.73, 0.66–0.81, $P<0.001$) for LDL; (0.59, 0.52–0.67, $P<0.001$) for HDL; (0.60, 0.47–0.77, $P<0.001$) for TC; (0.84, 0.75–0.95, $P=0.004$) for triglyceride). Another meta-analysis for continuous scale also found that higher HDL, TC, and triglyceride levels were significantly associated with a reduced MM risk (Figure S2A). To mitigate confounding factors, subgroup analysis was performed base on population demographics, the results also indicated higher HDL and TC were significantly associated with a reduced MM risk. However, triglyceride levels were only significantly associated with a reduced MM risk in Q3 level. The results of subgroup analyses for Caucasians are shown in supplementary Tables 3, and the results of subgroup analyses for Asians are not shown because there was only one study. No publication bias was found in any of the above results. In summary, the meta-analysis results indicated that higher lipid levels were associated with a reduced MM risk.

MR analysis of lipid and MM risk

Figure 3A shows univariable MR results, that HDL, LDL, and TC were not associated with MM risk, while triglyceride levels had a potential causal link with MM risk (OR: 0.67, 95% CI: 0.46–0.98, $P=0.038$). Figure 3B shows multivariable MR analysis that adjusted for BMI as a potential confounder, triglyceride levels remained associated with MM risk (OR: 0.64, 95% CI: 0.41–0.99, $P=0.048$), suggesting that the observed relationship is robust and potentially independent of BMI.

There were no individual overlap between exposure and outcome. The robustness of these findings was further validated by additional analysis using GWAS data from multiple sources. As shown in Figure S2B, while HDL, LDL, and TC showed no association with MM risk in both individual and meta-analyses, triglyceride levels exhibited a significant relationship in the meta-analysis (OR: 0.81, 95% CI: 0.67–0.98, $P=0.048$). Importantly, there was no horizontal pleiotropy or heterogeneity in any of the analyses, supporting the validity of above MR findings.

MR analysis of lipid-lowering genes and MM risk

The potential association of lipid-lowering medication with a lower MM risk [8, 9] led to an investigation of whether genes targeted by these drugs are causally associated with MM risk. Both MR and SMR approaches were utilized for this analysis. The MR analysis found no evidence to suggest that lipid-lowering target genes were associated with MM risk (Fig. 4A). PPARA, LDLR, LPL, and HMGCR were available for SMR analysis, which also showed no association between these genes and MM risk (Fig. 4B). This indicates that, at a genetic level, these lipid-lowering target genes may not influence MM risk. There was no horizontal pleiotropy or heterogeneity in any of the analyses.

Mediation MR

The above results suggest a causal association of triglyceride levels with MM risk, but the mediating pathways through which triglycerides influence MM development remain unclear. Previous research has highlighted abnormalities in metabolite and protein metabolism as potential risk factors for MM [13, 23, 24]. Given the known associations between triglycerides and various metabolites and proteins [25, 26], these could form complex networks influencing MM risk. To explore these interactions, it was hypothesized that triglycerides might affect MM risk through specific metabolites and proteins.

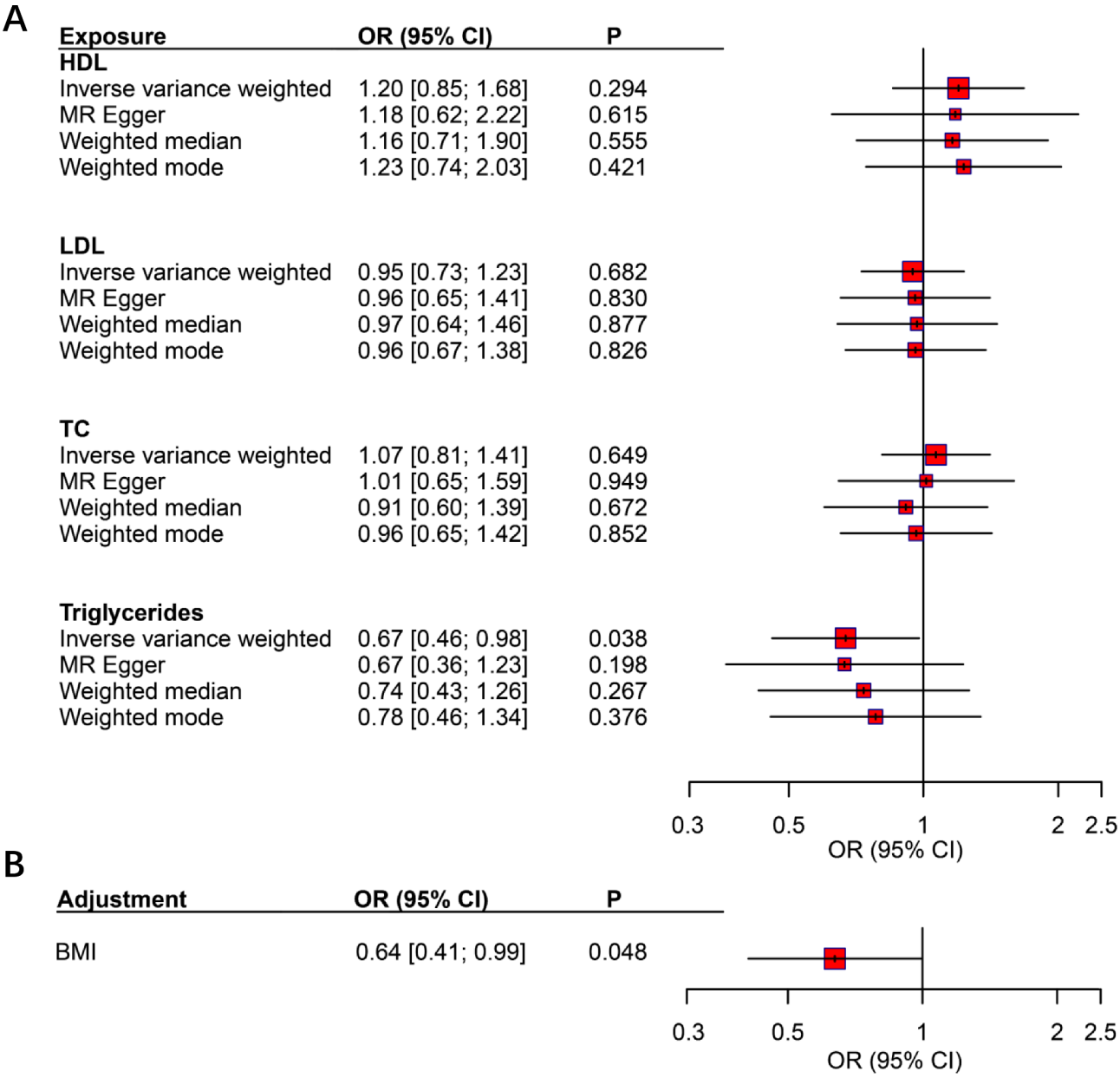

Fig. 3 Forest plot of association of plasma lipid levels with MM risk. **A**: univariable MR results for lipid levels and the MM risk; **B**: multivariable MR results for triglyceride levels and MM risk

A two-step MR approach was employed to seek potential mediating effects between triglycerides and MM. As shown in Fig. 5, X-11,423-O-sulfo-L-tyrosine metabolite (mediating effect: 51%, $P=0.002$) and neuropilin-2 protein (mediating effect: 58%, $P=0.019$) were identified as potential mediators between triglycerides and MM. Notably, neuropilin-2 is a therapeutic target of Efzofitimod, a selective modulator investigated in clinical trials [27]. Based on these results, this drug may have therapeutic potential for MM.

Discussion

This study assessed the association between lipid levels and MM using meta-analysis and MR analysis and showed that higher lipid levels (LDL, HDL, TC, and triglycerides) are linked with a reduced risk of MM, and triglyceride levels are causally associated with MM risk. However, lipid-lowering target genes may not influence MM risk. By integrating blood metabolites and proteins, the results indicated that X-11,423-O-sulfo-L-tyrosine and neuropilin-2 could be potential mediating pathways between triglycerides and MM. This study sheds light on

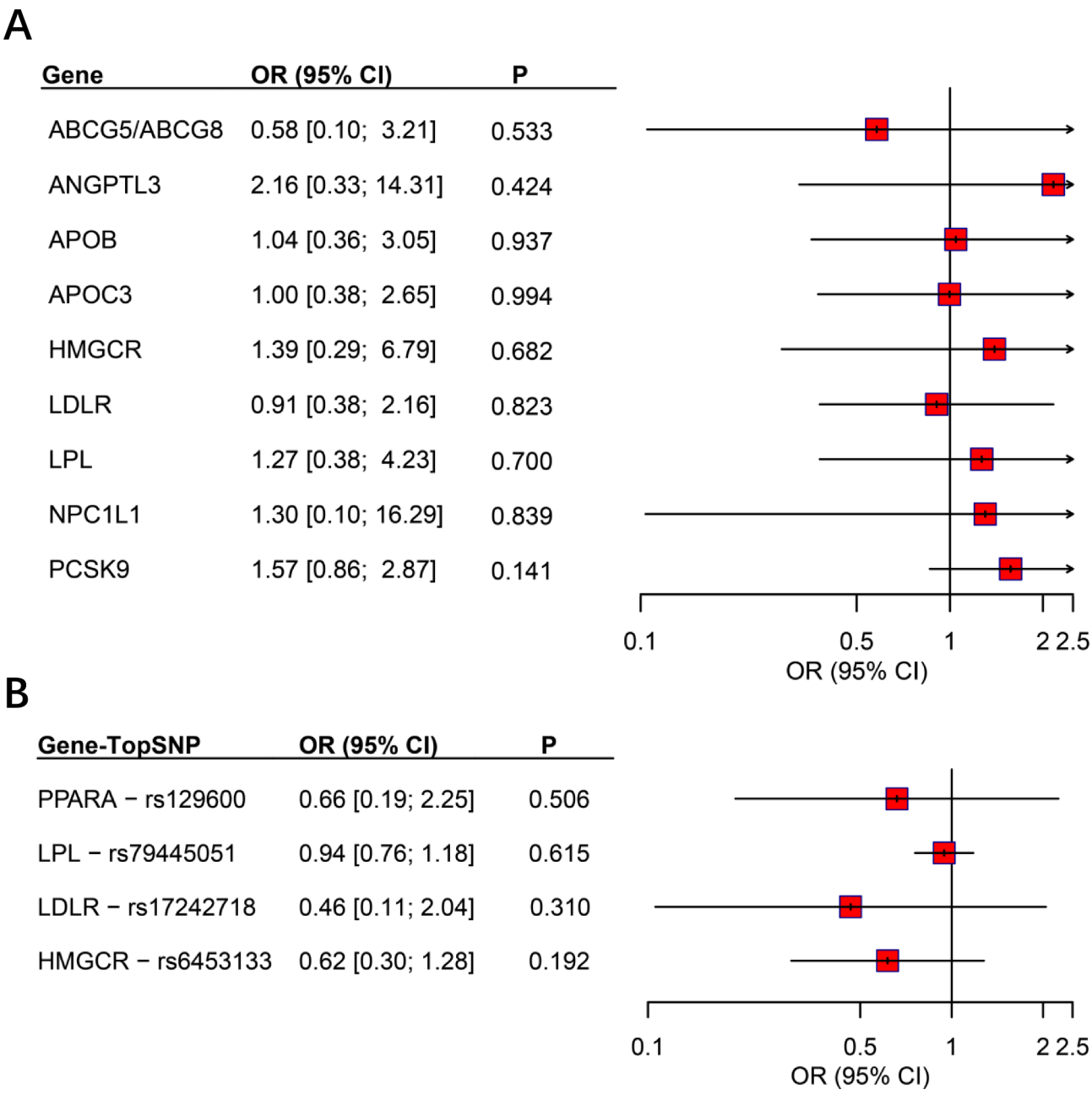

Fig. 4 Forest plot of association of lipid-lowering target genes with MM risk. A: MR results for lipid-lowering target genes and the MM risk; B: SMR results for lipid-lowering target genes and MM risk

the underlying mechanisms of MM and highlights potential avenues for innovative treatments.

Growing evidence suggests that dysregulated lipid metabolism plays a pivotal role in various malignancies, including MM [3, 28]. Various studies have compared plasma lipid levels between MM patients and healthy donors, revealing significant differences and suggesting that plasma lipid levels could serve as diagnostic and prognostic markers [29–31]. Based on the published data to date, lipid metabolism may contribute to onset of MM; however, it remains unclear whether aberrant lipid metabolism causes MM or MM causes aberrant lipid metabolism. Epidemiological studies have explored the potential link between MM risk and lipid levels [7, 19–22], but results have been inconsistent among different populations. The meta-analysis in this study shows that higher LDL, TC, HDL, and triglyceride levels associated with a lower MM risk. The included studies in the meta-analysis were adjusted for similar variables, making the results more prospective and robust. However, the possibility of residual confounding, particularly related to socioeconomic status, dietary habits, and comorbidities,

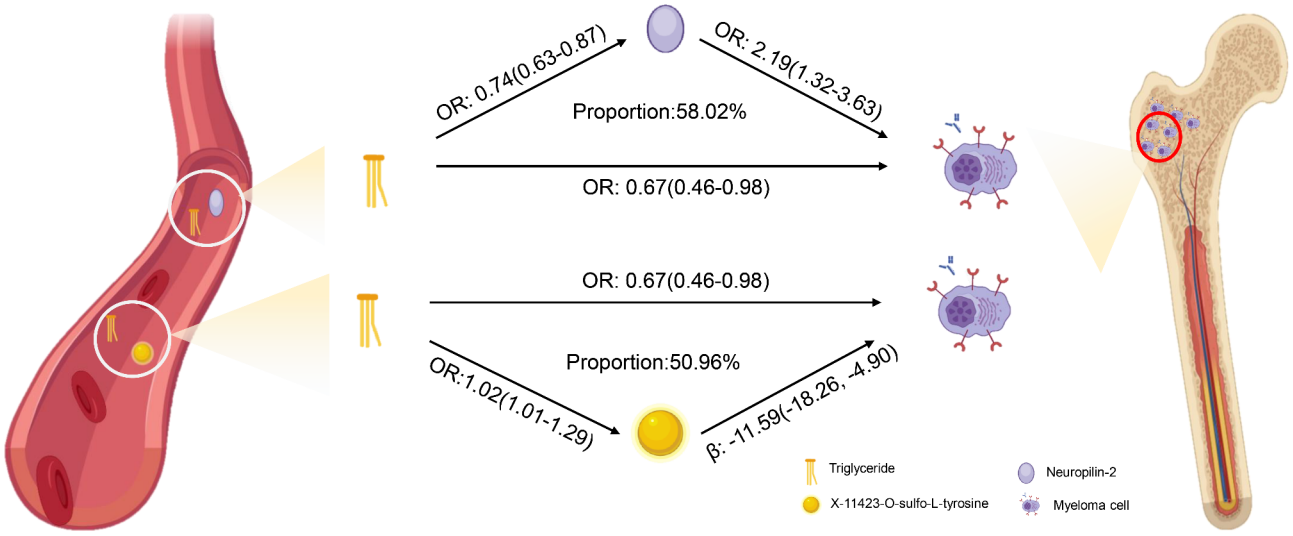

Fig. 5 Mediation analysis between triglycerides and MM

cannot be entirely dismissed. Due to there are differences in dietary habits and living habits among different populations, subgroup analysis was performed base on population. However, given the limited number of studies included in the meta-analysis, and with only one study specifically focusing on the Asian population, the findings from the subgroup analysis should be interpreted with caution. Future investigation with a larger and more diverse dataset should mitigate these confounders and confirm these preliminary findings. Nevertheless, these findings providing a rationale for further investigating the potential causal association of lipid levels with MM risk.

MR results suggest that triglyceride levels have a potential causal impact on MM risk. However, the MR results did not generate consistent results with different methods, and *P*value in the Bonferroni correction method did not exihabit significantly. It could be biased by weak IV or other confounding, and this may affect the stability of the results. But it's worth noting that, this finding remains significant even after adjusting for BMI in the multivariate MR analysis. The robustness of the findings, as demonstrated by the concordance of results obtained through various MR approaches and the use of multiple lipid GWAS datasets, provides compelling support for a potential causal link of triglyceride levels with MM risk. The above results suggest that triglycerides are the core component of plasma lipids related to MM. Xu et al. [4] reported a similar result; they investigated the lipid metabolic processes in MM cells prior to and following treatment with proteasome inhibitors and found that triglycerides were the main change after proteasome inhibition, indicating the critical role of triglycerides in MM development. The causal association between triglyceride levels and MM risk indicate that triglycerides could serve as a biomarker for MM risk assessment, potentially enhancing the predictive capabilities of existing risk assessment tools. Incorporating triglyceride measurements into clinical guidelines may facilitate the identification of at-risk populations, thereby enabling earlier detection and more timely intervention strategies for MM.

Lipid-lowering drugs have been proposed to reduce the risk of MM [8, 9]. However, the MR and SMR analyses did not provide evidence for a causal association of lipid-lowering target genes with MM risk. This finding suggests that the observed reduction in MM risk associated with the use of lipid-lowering medications in previous studies may be due to mechanisms other than their direct effects on lipid metabolism. Indeed, in addition to regulating lipids, statins have been reported to induce cell cycle arrest by regulating the Chk1-Cdc25A-Cyclin A/CDK2 pathway [32] and to regulate pro-apoptotic and anti-apoptotic proteins in myeloma cells [33, 34]. It is crucial to recognize that the genetic variants analyzed in these studies represent the impact of long-term alterations in lipid levels on the MM risk, representing a cumulative exposure over time. The lifelong changes in lipid levels associated with genetic variants may have different implications for MM compared to the short-term effects of lipid-lowering medications, which are usually prescribed later in life. Therefore, the impact of genetic variants on the likelihood of developing MM might not be directly analogous to the potential effectiveness of lipid-lowering treatments in altering disease risk.

X-11,423-O-sulfo-L-tyrosine and neuropilin-2 were identified as potential mediating pathways between triglycerides and MM, suggesting a complex interaction network between triglycerides, metabolites, and proteins. MM patients exhibited a distinct serum metabolomic profile different from healthy donors, with

X-11,423-O-sulfo-L-tyrosine, a sulfated tyrosine derivative, is a product of the enzymatic reactions involved in breaking down phenylalanine and tyrosine [35]. MM patients at diagnosis have been reported to exhibit higher levels of phenylalanine and tyrosine [36]. Similarly, Huang et al. observed that the metabolic irregularities in MM were related to the processing of phenylalanine [37]. Despite the identification of X-11,423-O-sulfo-L-tyrosine's involvement in MM, the precise biological processes by which it influences the disease remain elusive, necessitating additional investigative efforts to elucidate its role. Neuropilin-2, a transmembrane protein with a limited intracellular domain, relies on interactions with other cell surface molecules, such as VEGF receptors, to facilitate intracellular signaling cascades [38]. Neuropilin-2 is highly expressed in various cancers, including colon cancer [39] and prostate cancer [40], and promotes cancer progression and induces epithelial-mesenchymal transition via VEGF. Although limited evidence focuses on neuropilin-2 and MM, BM endothelial cells isolated from MM patients have shown higher levels of VEGF compared to normal controls [41, 42], hinting at a potential involvement of neuropilin-2 in MM progression. Further experimental exploration is needed. The identification of X-11,423-O-sulfo-L-tyrosine and neuropilin-2 as potential mediators in the association between triglyceride levels and MM risk opens new frontiers for targeted therapeutics. Specially, drugs targeting neuropilin-2, such as Efzofitimod currently in clinical trials, may represent promising therapeutic strategies for preventing or treating MM. And the biological pathways through which triglycerides may influence MM development, as hinted by our mediation analysis, offer novel insights into the disease's etiology. Understanding these mechanisms could lead to the discovery of new therapeutic targets and the development of precision medicine approaches tailored to the lipid metabolism characteristics of individual patients.

Strengths

This study has several strengths and potential clinical implications. This study investigate the link between lipids and MM using both meta-analysis and MR analysis. This makes it a fairly complete and organized review of the lipids related to MM. The identified causal relationship between triglyceride levels and MM risk suggests that triglyceride could serve as biomarkers for MM risk assessment. Adding triglyceride measurements to risk assessment tools could assist in pinpointing people more likely to develop MM, allowing for earlier detection and intervention. Moreover, the findings are novel, and the mediation MR results provide insights into the potential mechanisms linking triglycerides and MM development. The identification of X-11,423-O-sulfo-L-tyrosine and neuropilin-2 as potential mediators between triglycerides and MM risk opens up new avenues for therapeutic intervention. Targeting these specific metabolites and proteins could provide a more targeted approach to MM prevention and treatment. For instance, developing drugs that modulate the levels or activity of X-11,423-O-sulfo-L-tyrosine and neuropilin-2 may have therapeutic potential in MM. Notably, neuropilin-2 is already a therapeutic target of Efzofitimod, a selective modulator investigated in clinical trials. These findings further support exploring this drug for MM treatment.

Limitations

This study has several limitations that may affect the generalizability and applicability of the findings. Firstly, the observational studies included in the meta-analysis may be subject to residual confounding factors such as socioeconomic status, dietary habits, and comorbidities, which could influence the observed associations. Although adjustments for potential confounders were made, the possibility of unmeasured or inadequately controlled variables cannot be entirely ruled out. Secondly, the MR analysis, while robust, relies on several key assumptions, including the exclusion of influence from other traits and the robustness of the genetic markers used. Despite additional approaches to confirm the reliability of the analysis, the possibility of undetected pleiotropy cannot be completely excluded. Thirdly, the MR analysis was primarily conducted in individuals of European descent, which may limit the applicability of the results to other racial and ethnic populations. Given the known differences in MM incidence and lipid profiles across populations, further studies in diverse ethnic groups are essential to confirm the findings. Fourthly, while the mediation MR analysis identified potential mediators between triglycerides and MM risk, the underlying biological mechanisms require further elucidation. Future research should aim to explore these pathways and their implications for MM development.

Conclusions

This study provides strong evidence supporting a causal association between higher triglyceride levels and a reduced risk of MM. The identification of X-11,423-O-sulfo-L-tyrosine and neuropilin-2 as potential mediators in this relationship sheds new light on the biological mechanisms linking lipid metabolism to MM pathogenesis. The findings suggest that triglyceride levels could serve as a novel biomarker for MM screening, with the potential to facilitate earlier detection and intervention. Furthermore, the implication of neuropilin-2 as a therapeutic target is bolstered by the ongoing clinical trials for drugs like Efzofitimod, which may offer promising strategies for the prevention or treatment of MM. In the future,

further investigation into the detailed mechanisms connecting triglycerides and MM is warranted. Additionally, well-designed clinical trials should be conducted to confirm the therapeutic potential of neuropilin-2 targeting drugs in MM.

Abbreviations

GWAS	Genome wide association studies
Cis-eQTL	Cis expression quantitative trait loci
GLGC	Global Lipids Genetics Consortium
HDL	High Density Lipoprotein Cholesterol
BMI	Body Mass Index
MR	Mendelian randomization
MM	Multiple myeloma
LDL	Low-Density Lipoprotein Cholesterol
IV	Instrumental variable
TC	Total Cholesterol
IVW	Inverse-variance weighted
SNPs	Single nucleotide polymorphisms
SMR	Summary-based Mendelian randomization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02289-5.

Supplementary Material 1: Figure S1. Flowchart depicting the study selection process for meta-analysis.

Supplementary Material 2: Figure S2. The correlation between plasma lipid levels and MM risk. A: forest plot of meta-analysis results for lipid levels and MM risk. B: forest plot of univariable MR results for plasma lipid levels from different sources and the risk of MM.

Supplementary Material 3

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Not applicable.

Author contributions
Formal analyses were performed by WWZ. WWZ , AC, QL, LHH and LFP collected and interpreted the data. LHH conceptualized and designed the study. Supervision and manuscript editing were performed by AC, ZMZ and LFP.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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