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IgD-CD38br lymphocyte affect myocardial infarction by regulating the glycerol to palmitoylcarnitine (C16) ratio

A Mendelian randomization study

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Abstract

Myocardial infarction, a type of coronary artery disease, results from various factors such as genetic predisposition, lifestyle choices, and immune system regulation. The exact causal links between immune cells, plasma metabolites, and myocardial infarction are currently unclear. Therefore, our study employed the Mendelian randomization approach to explore these potential causal relationships. To investigate the impact of immune cells on the risk of myocardial infarction mediated by alterations in plasma metabolite levels, we employed the Mendelian randomization (MR) framework. Our analysis utilized 5 distinct MR techniques (inverse variance weighted [IVW], weighted median, MR-Egger, simple mode, and weighted mode) to evaluate causal relationships among 731 immune cell types, 1400 plasma metabolites, and myocardial infarction. Genetic instruments for immune cells and metabolites were identified using data from a meta-analysis of genome-wide association studies. Furthermore, sensitivity analyses were performed to verify the robustness of our results, identify potential heterogeneity, and examine possible pleiotropic effects. IVW results indicated that IgD-CD38br lymphocytes was a risk factor for myocardial infarction, whereas IgD-CD38br lymphocytes also acted as a protective factor against myocardial infarction. Additionally, the glycerol to palmitoylcarnitine (C16) ratio was identified as a protective factor for myocardial infarction. IgD-CD38br lymphocytes could exert a detrimental effect on myocardial infarction by negatively regulating the glycerol to palmitoylcarnitine (C16) ratio, with the mediation effect ratio being 9%. IgD-CD38br lymphocytes potentially increase the risk of myocardial infarction by negatively affecting the glycerol to palmitoylcarnitine (C16) ratio. This finding opens avenues for developing early diagnostic tools and targeted therapies for myocardial infarction.

Abbreviations: GWAS = Genome-Wide Association Studies, IVs = instrumental variables, IVW = inverse variance weighted, MI = myocardial infarction, MR = Mendelian randomization, SNP = single nucleotide polymorphism.

Keywords: immune cells, Mendelian randomization (MR), myocardial infarction (MI), plasma metabolites

1. Introduction

Myocardial infarction (MI) is categorized under coronary artery diseases and remains a principal cause of morbidity and mortality globally, posing a significant challenge to the worldwide healthcare system. MI primarily results from the interruption of blood supply to parts of the heart, leading to cardiac cell damage or death.[1] The clinical manifestations of MI vary greatly, ranging from asymptomatic cases to severe conditions characterized by chest pain or discomfort that may radiate to the shoulders or back. Other symptoms may include shortness of breath, nausea, vomiting, palpitations, sweating, and anxiety, often culminating in acute, life-threatening medical emergencies.[2] Early identification and diagnosis through clinical assessment and biomarker evaluation are crucial for timely management and treatment of this condition. The occurrence of MI is closely associated with the accumulation of atherosclerotic plaques in coronary arteries, leading to coronary artery narrowing and subsequent blockage. This pathogenic process is influenced by various factors including genetics, age, sex, hypertension, diabetes, smoking, and lifestyle. Rupture of an atherosclerotic plaque can trigger an acute thrombotic event, ultimately resulting in coronary artery occlusion and myocardial ischemic injury.[3–5] Over the years, the range of therapeutic interventions for MI has significantly expanded, encompassing pharmacological measures such as thrombolytic agents, antiplatelet drugs, and β-blockers, as well as procedural

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The datasets generated during and/or analyzed during the current study are publicly available.

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interventions like percutaneous coronary intervention and coronary artery bypass grafting. The aim of these treatments is to restore coronary blood flow, reduce myocardial oxygen demand, and prevent further cardiac complications. Moreover, the focus of long-term management strategies is on reducing risk factors, promoting lifestyle changes beneficial to cardiac health, and regular monitoring for signs of cardiovascular event recurrence.[6–8]

The immune system is a complex network composed of cells, tissues, and organs. Immune cells are at the core of this defense mechanism, playing a pivotal role in both innate and adaptive immunity.[9] Studies indicated that immune cells play a crucial role during the MI process. Following an MI, the death of cardiac tissue triggers an inflammatory response, essential for clearing necrotic debris and facilitating repair.[10,11] However, if this inflammatory response is excessive or improperly regulated, it can exacerbate damage, leading to adverse cardiac remodeling and heart failure. Neutrophils are among the first immune cells to infiltrate the infarcted myocardium, typically appearing within hours after the MI. They play a vital role in clearing necrotic cells and matrix debris. Yet, their activation can also cause collateral damage through the release of proteases and reactive oxygen species.[12,13] Plasma metabolites are tiny molecules within the blood components, offering profound insights into physiological and pathological states through comprehensive analysis, reflecting the complex interplay between genetics, metabolism, and environmental influences.[14] Plasma, a crucial blood component, serves as an essential medium for the transport and exchange of metabolites, nutrients, hormones, and wastes between various organs and tissues. Plasma metabolites, comprising various small molecules from endogenous metabolic processes and exogenous sources, dynamically reflect an individual's metabolic status at any given time.[15] Research on plasma metabolites has gradually become a cornerstone in the fields of metabolomics and systems biology, identifying and quantifying numerous small molecules that play key roles in energy balance, cell signaling, and disease pathogenesis mechanisms.

Mendelian randomization (MR) is a well-established approach in epidemiology for identifying causal relationships. It utilizes genetic variants as instrumental variables (IVs) to explore the impact of specific exposures on outcomes.[16] The successful application of MR depends on 3 fundamental assumptions, which are that the selected genetic variants must have a strong association with the exposure, that they are independent of any confounding factors, and that their effect on the outcome is mediated solely through the exposure.[17] Research indicates that immune cells contribute to overall metabolic regulation by altering the types and levels of plasma metabolites. For example, they release cytokines and signaling molecules that modulate metabolic processes, thereby supporting systemic metabolic homeostasis.[18,19] Conversely, shifts in plasma metabolites, such as changes in amino acid levels or small molecule metabolic products, can also alter immune cell activity. This bidirectional interaction underscores the close relationship between immune cells and plasma metabolites.[20,21] Despite this understanding, it remains unclear whether immune cells can regulate plasma metabolites to impact MI. To explore this, we applied the MR method to examine the causal relationships between immune cells, plasma metabolites, and MI. This study seeks to uncover how immune cell regulation of plasma metabolites may contribute to MI development, offering fresh perspectives on potential strategies for immune and metabolic interventions in MI.

2. Materials and methods

2.1. Data sources

This study utilized Genome-Wide Association Studies (GWAS) summary statistics for MI, which were retrieved from the "Open GWAS" database. The dataset was identified by the GWAS ID ukb-d-I9_MI. This dataset encompasses data from 361,194 individuals of European ancestry, including 7018 MI patients and 354,176 control individuals. The GWAS catalog provides open access to the GWAS summary statistics for immunological traits (GCST90001391 to GCST90002121).[22,23] The GWAS analyses for immune traits were performed using datasets from 3757 European individuals, ensuring no overlap of samples between cohorts. A genetic study on 1400 metabolites was performed, which included whole-genome genotyping and circulating plasma metabolite assessments for 8299 individuals of European descent. In the GWAS process, following rigorous quality control and evaluation, around 15.4 million single nucleotide polymorphisms (SNPs) were retained for analysis. The metabolites were subsequently grouped into 8 primary categories: amino acids, carbohydrates, cofactors and vitamins, energy, lipids, nucleotides, peptides, and xenobiotic metabolism.[24] A flowchart of the study process is shown in Figure 1. As the data used in this study were obtained from publicly available databases, ethical approval from a committee was not required.

2.2. Selection of instrumental variables

In conducting the MR analysis, we initially selected SNPs closely associated with the exposure factor as IVs. These SNPs were chosen based on their meeting the Genome-Wide Association significance threshold, specifically a P value less than 5×10^{-8}. To ensure the independence of these SNPs, we conducted linkage disequilibrium tests and excluded SNPs that exhibited an r^2 value below 0.001 within a 10,000 base pair interval.[25] Furthermore, we calculated the F statistic for each IV to ensure sufficient association strength between the instrumental variables and the exposure factor, discarding any IVs with an F statistic <10.[26] Finally, to enhance the accuracy and reliability of the MR analysis, we eliminated any IVs that could influence the outcome through multiple pathways. This careful selection process ensures that the chosen IVs are valid for identifying the causal effects of the exposure on the outcome in the context of MR analysis.

2.3. Statistical analysis

To ensure the robustness and accuracy of the results, we utilized multiple MR analysis approaches to evaluate the causal relationship between the exposure factor and the outcome. In our analysis, the inverse-variance weighted (IVW) approach was applied to synthesize data from different genetic variants, based on the presumption that these variants exert their effects solely through the exposure being studied, ensuring their relevance, independence, and instrumentality. For individual genetic variants identified, the

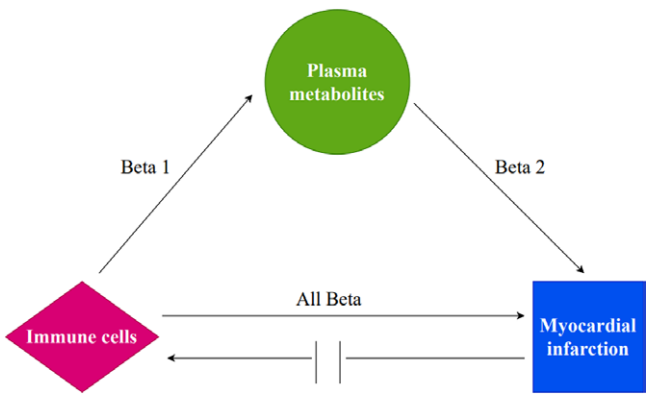

Figure 1. Flowchart of this study.

Wald estimator was utilized for effect size estimation. Given the numerous tests conducted in this study, we identified significant associations between plasma metabolites, immune cells, and MI, applying the Bonferroni correction to account for multiple testing.[27] To confirm these associations, we employed various MR methods, such as MR-Egger, the weighted median, and mode-based estimates, alongside analyses to address heterogeneity and potential pleiotropy. Given the variability in study designs, analytical methods, and populations, we assessed heterogeneity's impact on our causal inferences using Cochran's *Q* test.[28] In our IVW-based causal analysis, we were particularly vigilant about the possible biases due to genetic heterogeneity. To evaluate pleiotropy, we utilized the IVW method and the MR-Egger intercept, with an intercept close to zero (<0.1) and a nonsignificant *P* value (>.05) indicating minimal pleiotropy concerns.[29] Moreover, we examined horizontal pleiotropy and potential outliers using MR-Egger regression and the MR-PRESSO global test.[30] A leave-one-out analysis was conducted to verify that no single SNP disproportionately influenced our findings. To visually inspect for bias and estimate consistency, funnel plots and scatter plots were employed.

3. Results

3.1. Causal relationship of immune cells to myocardial infarction

Considering immune cells as the exposure factors and MI as the outcome, the IVW results demonstrated significant causal relationships between 3 types of immune cells and MI. Specifically, IgD– CD27– B cells, IgD-CD38br lymphocytes, and CM DN (CD4–CD8–) DN cells are identified as risk factors for MI (Supplementary File 1, Supplemental Digital Content, http://links.lww.com/MD/O131). Subsequently, to delve deeper, we conducted a reverse MR analysis, considering MI as the exposure factor and the aforementioned immune cells as the outcomes. The IVW results indicated that MI does not exhibit a causal relationship with these 3 types of immune cells (Supplementary File 1, Supplemental Digital Content, http://links.lww.com/MD/O131). The MR results files for all immune cells' causal relationships to MI were available in Supplementary File 2, Supplemental Digital Content, http://links.lww.com/MD/O131.

3.2. Causal relationships of plasma metabolites to myocardial infarction

The IVW results identified 21 plasma metabolites as having significant causal relationships with MI. These include the levels of indoleacetoylcarnitine, 1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6), 1-oleoyl-2-arachidonoyl-GPE (18:1/20:4), methylsuccinoylcarnitine, 1-stearoyl-2-arachidonoyl-GPE (18:0/20:4), 1-stearoyl-2-docosahexaenoyl-GPE (18:0/22:6), 1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4), 1-palmitoyl-2-oleoyl-GPE (16:0/18:1), oleoyl-linoleoyl-glycerol (18:1/18:2) [2], myristoleate (14:1n5), myristate (14:0), linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1], and alpha-ketobutyrate levels as risk factors for MI. Conversely, the glycerol to palmitoylcarnitine (C16) ratio, gamma-glutamylisoleucine levels, X-11847 levels, sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2) levels, retinol (vitamin A) to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [1] ratio, S-adenosylhomocysteine to leucine ratio, chiro-inositol levels, and phosphate to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio were identified as protective factors against MI (Supplementary File 3, Supplemental Digital Content, http://links.lww.com/MD/O131). The MR results files detailing the causal relationships of all plasma metabolites to MI can be found in Supplementary File 4, Supplemental Digital Content, http://links.lww.com/MD/O131.

3.3. Causal relationships of immune cells to plasma metabolites (beta 1)

In our analysis, we utilized the aforementioned 3 types of immune cells as exposure factors and twelve plasma metabolites as outcomes to calculate beta 1 using MR analysis. The IVW results indicated significant causal relationships where 2 immune cells were related to 4 plasma metabolites. Specifically, IgD– CD27– B cells were identified as a risk factor for sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2) levels. Conversely, IgD– CD27– B cells were protective against 1-stearoyl-2-docosahexaenoyl-GPE (18:0/22:6) levels and 1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6) levels. Additionally, HLA DR on CD14– CD16– cells showed a protective effect on pregnenolone sulfate levels, and IgD-CD38br lymphocytes had a protective impact on the glycerol to palmitoylcarnitine (C16) ratio (Supplementary File 5, Supplemental Digital Content, http://links.lww.com/MD/O131). Finally, IVW showed the smallest *P* value for IgD-CD38br lymphocyte and glycerol to palmitoylcarnitine (C16) ratio ($P = .040$). Therefore, we used IgD-CD38br lymphocyte and glycerol to palmitoylcarnitine (C16) ratio for subsequent analysis. Moreover, leave-one-out analysis, along with scatter plots, forest plots, and funnel plots, were performed for IgD-CD38br lymphocytes and the glycerol to palmitoylcarnitine (C16) ratio, revealing no outliers (Fig. 2). The utilized SNPs are listed in Supplementary File 6, Supplemental Digital Content, http://links.lww.com/MD/O131.

3.4. Causal relationship of the glycerol to palmitoylcarnitine (C16) ratio to myocardial infarction (beta 2)

In this analysis, we designated the glycerol to palmitoylcarnitine (C16) ratio as the exposure factor and MI as the outcome. We excluded the SNPs used in the beta 1 calculation (Supplementary File 6, Supplemental Digital Content, http://links.lww.com/MD/O131) and conducted an MR analysis to compute beta 2. The IVW results demonstrated that the glycerol to palmitoylcarnitine (C16) ratio acts as a protective factor against MI ($P < .01$). These findings were presented in Figure 3 and Supplementary File 7, Supplemental Digital Content, http://links.lww.com/MD/O131.

3.5. Causal relationship of IgD-CD38br lymphocytes to myocardial infarction (all beta)

In this study, we identified IgD-CD38br lymphocytes as the exposure and MI as the outcome and employed the MR method to calculate the total beta. The IVW results indicated that IgD-CD38br lymphocytes were a risk factor for MI. These findings were depicted in Figure 4 and detailed in Supplementary File 8, Supplemental Digital Content, http://links.lww.com/MD/O131. Integrating all the analyses, we determined that the immune cell IgD-CD38br lymphocytes could influence MI by modulating the plasma metabolite glycerol to palmitoylcarnitine (C16) ratio, as illustrated in Figure 5. Additionally, we calculated the mediation effect, defined by the formula: mediation effect = beta 1 * beta 2. Thus, the proportion of the mediation effect through which IgD-CD38br lymphocytes impacted MI by regulating the glycerol to palmitoylcarnitine (C16) ratio was estimated at 9% (Supplementary File 9, Supplemental Digital Content, http://links.lww.com/MD/O131).

4. Discussion

In this MR study, we explored the potential causal roles of immune cells and plasma metabolites in MI. Our findings suggest that IgD-CD38br lymphocytes negatively regulate the

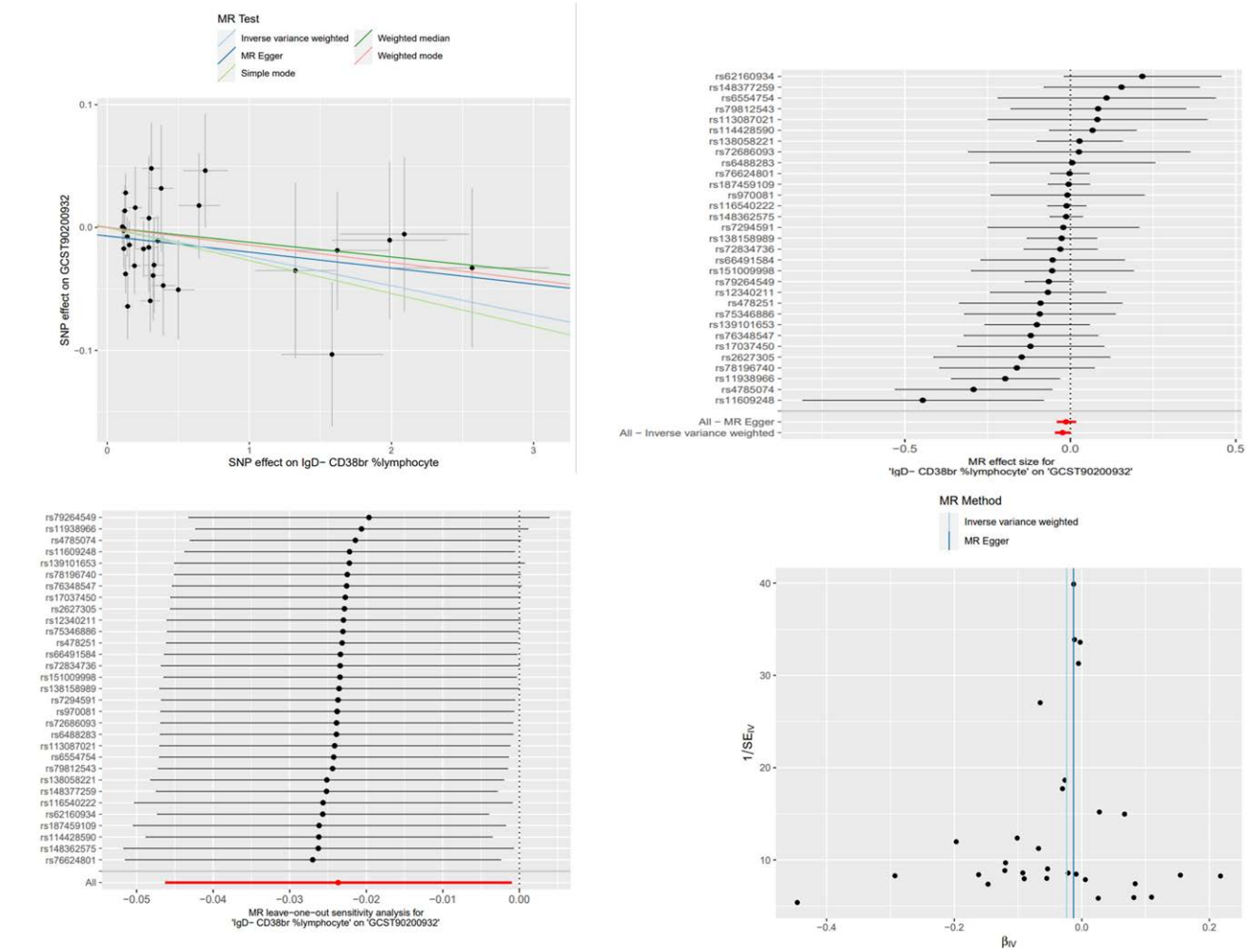

Figure 2. Mendelian randomization (MR) results for the association of IgD-CD38br lymphocyte with the glycerol to palmitoylcarnitine (C16) ratio. (A) MR scatter plot for the association of IgD-CD38br lymphocyte with the glycerol to palmitoylcarnitine (C16) ratio. (B) MR forest plot for the association of IgD-CD38br lymphocyte with the glycerol to palmitoylcarnitine (C16) ratio. (C) Leave-one-out analysis for the MR study of IgD-CD38br lymphocyte with the glycerol to palmitoylcarnitine (C16) ratio. (D) MR funnel plot for the association of IgD-CD38br lymphocyte with the glycerol to palmitoylcarnitine (C16) ratio. IgD = immunoglobulin D, MR = Mendelian randomization.

glycerol to palmitoylcarnitine (C16) ratio, which, in turn, negatively influences MI. Specifically, IgD-CD38br lymphocytes posed a risk for myocardial infarction. Hence, it can be inferred that IgD-CD38br lymphocytes exert a deleterious effect on MI by negatively modulating the glycerol to palmitoylcarnitine (C16) ratio. This relationship underscores the intricate interplay between immune cells and metabolic processes in the context of MI, offering insights that could inform future research and potential therapeutic strategies.

IgD-CD38br lymphocytes represent a distinct immune cell subset that has garnered attention due to their unique features and functions within the immune system. Characterized by the bright expression of CD38 molecules and immunoglobulin D (IgD) on their surfaces, these cells stand apart from other lymphocyte subsets. In human immunology, these markers are not merely surface identifiers but also represent the potential functions and activation states of the cells.[31,32] IgD-CD38br lymphocytes were primarily considered an important B cell subset involved in immune responses. Their high levels of CD38 expression indicate a state of heightened activation or reactivity, which may play a pivotal role in immune processes. Compared to IgM and IgG, IgD is a less understood immunoglobulin, but it is crucial for antigen recognition and the initiation of immune responses.[33] The co-expression of IgD and CD38 suggests that these cells may play a significant role in the early and immediate responses to pathogens or injury. In the context of MI, a robust immune response is triggered, with various immune cells migrating to the injured cardiac tissue to aid in debris clearance and promote repair. Besides neutrophils and macrophages, the involvement of IgD-CD38br lymphocytes may be equally crucial.[13,34] Through their immunomodulatory functions, these cells can influence the healing process post-MI, potentially affecting the resolution of inflammation and the quality of tissue repair. Moreover, the role of IgDrCD38br lymphocytes in MI might extend beyond the acute phase, impacting long-term outcomes and the risk of subsequent cardiovascular events. The regulatory function of lymphocytes in immune responses could influence scar formation, ventricular remodeling, and even susceptibility to recurrent ischemic events.[35,36] Understanding these dynamic changes is vital for comprehending the complexity of post-MI immune interactions and could offer insights into new therapeutic strategies or prognostic markers.

The glycerol to palmitoylcarnitine (C16) ratio is an index that reflects the relative concentrations of these 2 molecules within the body. Glycerol, a simple 3-carbon compound, is a key intermediate in lipid metabolism and can serve as a substrate for gluconeogenesis or be converted into triglycerides for storage.[37] Palmitoylcarnitine, on the other hand, is a long-chain fatty acylcarnitine involved in the transport of fatty acids into the mitochondria for beta-oxidation, providing a crucial

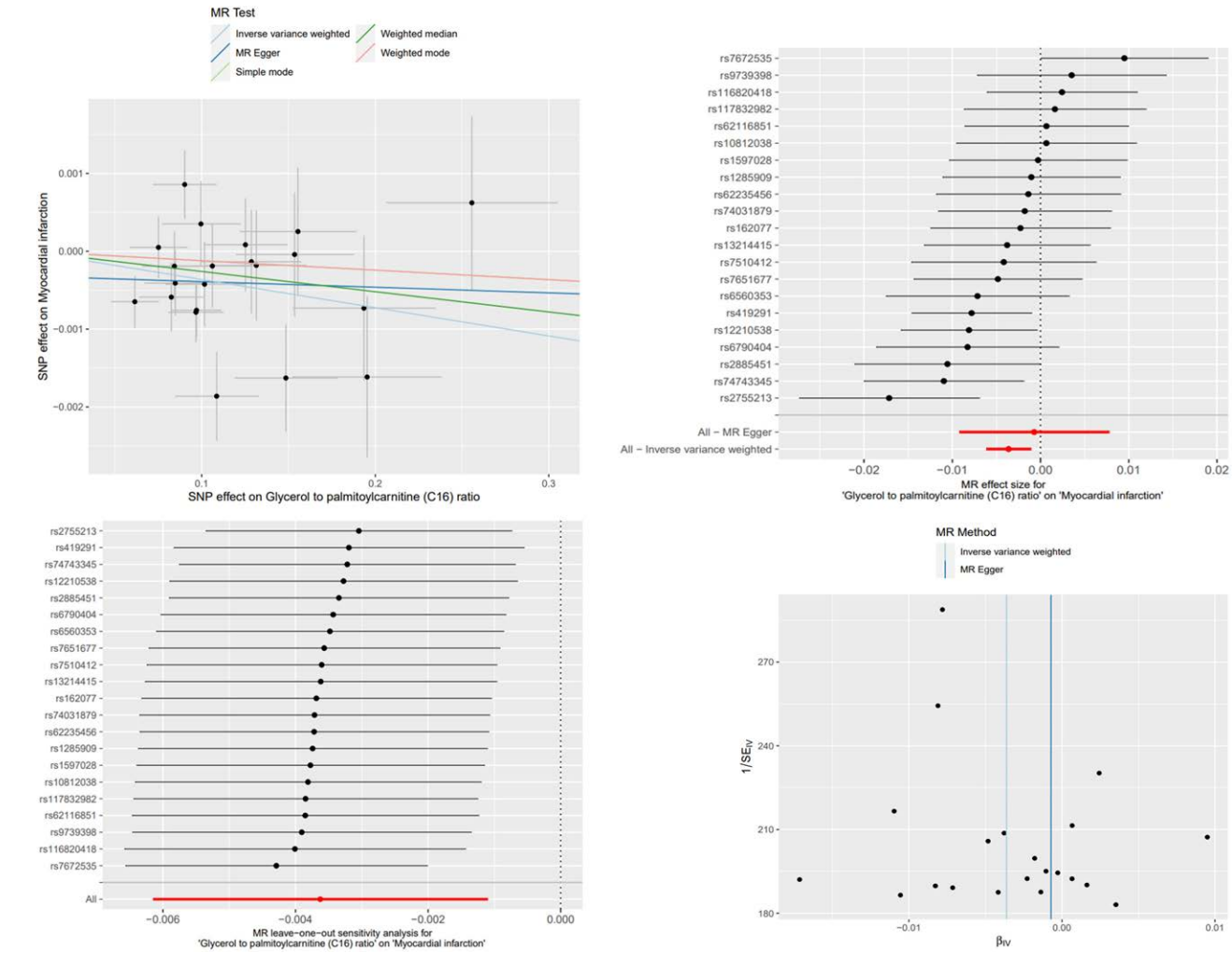

Figure 3. Mendelian randomization (MR) results for the effect of the glycerol to palmitoylcarnitine (C16) ratio on myocardial infarction (MI). (A) MR scatter plot for the glycerol to palmitoylcarnitine (C16) ratio's effect on MI. (B) MR forest plot for the glycerol to palmitoylcarnitine (C16) ratio's effect on MI. (C) Leave-one-out analysis for the MR study of the glycerol to palmitoylcarnitine (C16) ratio on MI. (D) MR funnel plot for the effect of the glycerol to palmitoylcarnitine (C16) ratio on MI. MI = myocardial infarction, MR = Mendelian randomization.

energy source, particularly for cardiac muscle. In the context of MI, energy metabolism within heart tissue becomes critically important.[38] During an MI, the affected cardiac tissue experiences ischemia, leading to a rapid depletion of its primary energy reserves. The heart predominantly relies on fatty acid oxidation under normal physiological conditions. However, during an ischemic event, the availability of oxygen and thus the efficiency of fatty acid oxidation is significantly compromised, forcing the heart to depend more on anaerobic glycolysis.[39] The glycerol to palmitoylcarnitine ratio can serve as an indicator of this metabolic shift. An increase in glycerol levels relative to palmitoylcarnitine could indicate a heightened reliance on glycolysis or a block in fatty acid transport or oxidation. Conversely, a lower ratio might suggest a maintained or increased capacity for fatty acid oxidation, which could be beneficial in the context of limited oxygen availability. Moreover, this ratio might also reflect broader metabolic disturbances in the context of MI, such as insulin resistance or altered lipid metabolism, which are common in cardiovascular disease.[40]

Currently, there is limited research on the relationship between IgD-CD38br lymphocytes and the glycerol to palmitoylcarnitine (C16) ratio in the context of MI. Based on the results of this study, we hypothesized that IgD-CD38br lymphocytes may indirectly regulate metabolic pathways through their modulatory effects on inflammation and direct interactions with metabolic processes. The glycerol to palmitoylcarnitine (C16) ratio, as a metabolic indicator, reflects the balance between glycerol availability and the capacity for fatty acid oxidation, represented by the level of palmitoylcarnitine. This ratio is particularly important for cardiac energy metabolism, as the heart predominantly relies on fatty acid oxidation for energy under normal physiological conditions. Alterations in the glycerol to palmitoylcarnitine (C16) ratio influenced by IgD-CD38br lymphocytes may indicate a shift in this metabolic balance, potentially compromising cardiac energy efficiency and increasing vulnerability to ischemic damage. In the context of MI, the negative regulation of this ratio by IgD-CD38br lymphocytes could adversely affect myocardial tissue, especially under ischemic stress. This could manifest as the myocardium being unable to optimally utilize fatty acids, forcing a shift to less efficient energy substrates and thereby stressing cardiac function during ischemia. Thus, modulating the activity of IgD-CD38br lymphocytes or influencing the glycerol to palmitoylcarnitine (C16) ratio could have implications for MI outcomes. Our study highlighted the complexity of MI, involving intricate interactions among immune cells, metabolic states, and cardiac tissue. Understanding these complex relationships opens new research directions and may pave the way for managing and preventing MI, emphasizing the importance of an integrated perspective on immune and metabolic considerations in MI disease.

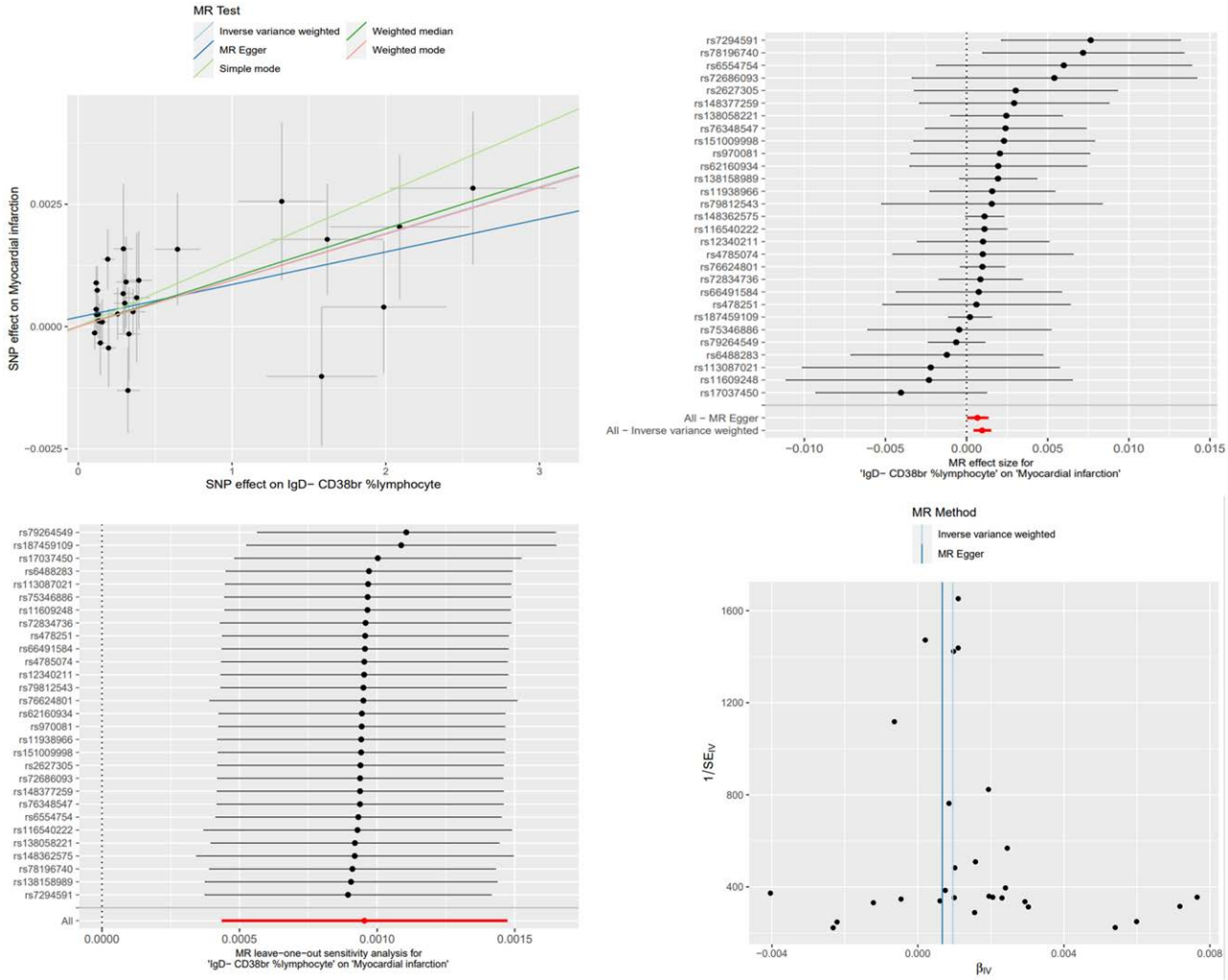

Figure 4. Mendelian randomization (MR) results for IgD-CD38br lymphocyte's impact on myocardial infarction (MI). (A) MR scatter plot showing the association between IgD-CD38br lymphocyte and MI. (B) MR forest plot for IgD-CD38br lymphocyte's effect on MI. (C) Leave-one-out analysis for the MR assessment of IgD-CD38br lymphocyte on MI. (D) MR funnel plot for the impact of IgD-CD38br lymphocyte on MI. IgD = immunoglobulin D, MI = myocardial infarction, MR = Mendelian randomization.

exposure	outcome	nsnp	method	pval	OR(95% CI)
IgD− CD38br _lymphocyte	Glycerol to palmitoylcarnitine (C16) ratio	31	MR Egger	0.367	0.987 (0.960 to 1.015)
		31	Weighted median	0.443	0.988 (0.958 to 1.019)
		31	Inverse variance weighted	**0.040**	0.977 (0.955 to 0.999)
		31	Simple mode	0.274	0.974 (0.929 to 1.021)
		31	Weighted mode	0.311	0.986 (0.960 to 1.013)
Glycerol to palmitoylcarnitine (C16) ratio	Myocardial infarction	21	MR Egger	0.870	0.999 (0.991 to 1.008)
		21	Weighted median	0.105	0.997 (0.994 to 1.001)
		21	Inverse variance weighted	**0.005**	0.996 (0.994 to 0.999)
		21	Simple mode	0.705	0.999 (0.993 to 1.005)
		21	Weighted mode	0.700	0.999 (0.993 to 1.005)
IgD− CD38br _lymphocyte	Myocardial infarction	29	MR Egger	**0.049**	1.001 (1.000 to 1.001)
		29	Weighted median	**0.006**	1.001 (1.000 to 1.002)
		29	Inverse variance weighted	**<0.001**	1.001 (1.000 to 1.001)
		29	Simple mode	**0.034**	1.001 (1.000 to 1.003)
		29	Weighted mode	**0.016**	1.001 (1.000 to 1.002)

Figure 5. Forest plot that illustrated the causal relationships among IgD-CD38br lymphocyte, the glycerol to palmitoylcarnitine (C16) ratio, and myocardial infarction. IgD = immunoglobulin D.

Additionally, this study has its limitations. Although MR analysis was utilized to address confounding factors caused by pleiotropy, the inherent limitations of MR studies mean that some biases may persist. Additionally, the reliability of the IVs is heavily influenced by the sample size of the genetic association studies. The sample used in this study predominantly consisted of individuals of European descent, which restricts the generalizability of our findings to other populations. Therefore, future research involving more diverse and extensive populations is crucial for validating the causal relationships identified in our study.

5. Conclusion

In conclusion, this study provided new insights into the associations among plasma metabolites, immune characteristics, and MI. It was found that IgD-CD38br lymphocytes could negatively regulate the glycerol to palmitoylcarnitine (C16) ratio, thereby exerting a deleterious effect on MI. These findings paved the way for developing early diagnostic tools and targeted therapies for MI.

Author contributions

Conceptualization: Jing Wang, Ying Wang, Zhengyan Wang, Jingyuan Li, Yuyan Jia.
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Investigation: Ying Wang, Yuyan Jia.
Methodology: Ying Wang, Yuyan Jia.
Project administration: Yuyan Jia.
Resources: Shuang Ding.
Software: Shuang Ding.
Supervision: Shuang Ding.
Visualization: Jing Wang.
Writing – original draft: Jing Wang, Ying Wang, Shuang Ding, Jingyuan Li, Yuyan Jia.
Writing – review & editing: Jing Wang, Yuyan Jia.

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