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ORIGINAL RESEARCH

Circulating Inflammatory Factors and Bidirectional Mendelian Randomization Analysis in Patients with Kawasaki Disease

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Background: Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a systemic immune vasculitis with an unclear etiology. It is often complicated by coronary artery disease. This study uses bidirectional Mendelian randomization (MR) to investigate the interaction between KD and circulating inflammatory factors, providing insights into their causal relationships.

Methods: We conducted a two-way pooled MR analysis to examine the causal links between 41 circulating inflammatory regulators and the risk of KD. Genetic data related to inflammation were sourced from three genome-wide association studies (GWASs) involving CRP, PCT, and cytokines, while KD data were derived from other studies. Inverse-variance weighting (IVW) was the primary MR method, with sensitivity analyses performed using MR–Egger, weighted median, weighted mode, and MR–PRESSO to ensure robustness.

Results: Forward MR analyses showed no significant relationship between inflammatory factors and KD outcomes. In contrast, reverse MR, with KD as the exposure factor, revealed that interleukin-2 (IL-2) and interleukin-8 (IL-8) were significantly associated with KD (IL-2: OR=1.0085, P=0.037; IL-8: OR=1.0099, P=0.014). Borderline significant associations were observed for factors such as B_NGF, EOTAXIN, HGF, and IL_12_P70 in MR–Egger and weighted median analyses.

Conclusion: This bidirectional MR study highlights the role of circulating inflammatory modulators in KD risk, offering insights into KD pathogenesis and potential therapeutic targets.

Keywords: bidirectional Mendelian randomization, circulating inflammatory regulators, Mendelian randomization, Kawasaki disease, GWAS catalog

Introduction

Kawasaki disease (KD) is an acute nonspecific vasculitis that involves mainly small arteries, especially coronary arteries, in children. Although the exact cause of KD is unknown, it is widely believed to be related to a systemic immune response induced by infectious agents.[1] Typical clinical manifestations include persistent high fever, conjunctival hemorrhage in both eyes, chapped lips and mouth, redness and swelling of the hands and feet, rash, and, in severe cases, cardiovascular complications such as coronary aneurysms.[2]

Epidemiological studies show that KD primarily affects children under 5 years old, with a higher incidence in males. The incidence is notably higher in Northeast Asian countries, particularly Japan, compared to Western nations. In addition, KD exhibits a seasonal peak in the winter and spring months, and higher incidence rates are observed in populations with higher socioeconomic status, possibly linked to differences in vaccination rates and healthcare conditions. Although the incidence of KD is also increasing in developing countries, it remains the most common cause of acquired heart disease in children in developed countries.[3]

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Inflammatory factors play important roles in the pathogenesis of KD. Studies have shown that the levels of inflammatory markers such as CRP and interleukins are significantly elevated in patients with KD.[4] Most of the current studies on the causal relationship between inflammatory factors and the risk of developing KD are observational and susceptible to bias via confounding factors and reverse causation; therefore, there is a lack of clear mechanistic evidence revealing the exact role of inflammatory factors in the risk of developing KD.

In this study, the potential causal relationship between the levels of 41 circulating inflammatory factors and the risk of developing KD was explored for the first time via bidirectional Mendelian randomization (MR). Bidirectional MR can be used to overcome the limitations of observational studies and provide stronger causal inference by using genetic variants as instrumental variables.[5] The mechanism of inflammatory factors in the pathogenesis of KD was systematically analyzed by integrating data from genome-wide association studies (GWASs), with the aim of identifying new biomarkers and potential targets for early intervention and individualized treatment of KD.[6]

Materials and Methods

Research Program and Data Sources

The overview of the two-way MR analysis is shown in Figure 1. MR analysis depends on three main assumptions (1): the genetic variants selected as instrumental variables are strongly associated with exposure. (2): Genetic variation is independent of confounders. (3): Genetic variation affects outcomes only through exposure.[7] In the present work, we utilized summary level GWAS data of 41 known circulating inflammatory factors and KD. First, correlations between circulating inflammatory factors and KD were inferred by selecting genetic variants in circulating inflammatory factors. The correlations between the risk of developing KD and each circulating inflammatory factor were subsequently inferred by selecting genetic variants associated with KD.

Genetic Instrumental Variables of Circulating Inflammatory Factors

Genetic predictors of 41 circulating inflammatory regulators were derived from the most comprehensive cytokine-related GWAS meta-analyses of three independent cohorts, including 8293 Finnish participants from the Finnish Youth Cardiovascular Risk Study (YFS) and the "FINRISK" studies (FINRISK1997 and FINRISK2002) in Finnish participants (see Table 1).[8] A two-step inverse transformation was performed to normalize the distributions of these 41 modifiers. Another genetic model was adjusted for age, sex, body mass index (BMI) and the first ten genetic principal components to assess univariate associations between the concentrations of the 41 modifiers and 10.7 million genetic polymorphisms.

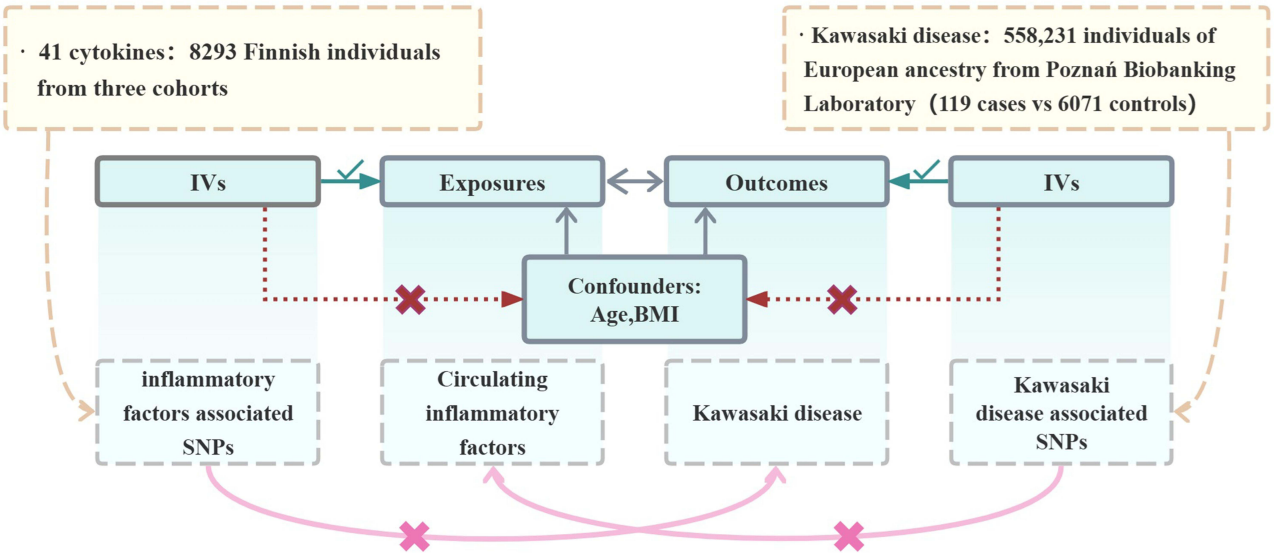

Figure 1 Hypothesis and study design of bidirectional MR for the association of circulating inflammatory cytokines with Kawasaki disease. BMI, body mass index; Genetic tool variables: SNPs, single nucleotide polymorphisms.

Table 1 Detailed Summary of Data Included in This Study

Variables	Population	No. of Case	No. of Controls	Sample size	No. of SNPs	Source	Year of Release
KD[9]	European	119	6071	6190	164395	IPCZD	2021
Circulating inflammatory factors[8]	European	NA	NA	8393	10.7 million	YES/FINRISK	2020

Abbreviations: KD, Kawasaki disease; NA, not available; No. SNPs, number of single-nucleotide polymorphisms.

Genetic Instrumental Variables in KD

Blood samples from patients with KD were collected, separated and stored at the Department of Paediatrics, Nutrition and Metabolic Diseases of the Children's Memorial Health Institute in Warsaw between 2016 and 2020. Controls were based on donors registered at the Poznań Biobanking Laboratory (POPULOUS collection). In total, 119 patients of European origin and 6071 control participants of European origin were included (see Table 1).[9] DNA samples were genotyped for a total of 558,231 single-nucleotide polymorphisms (SNPs) via 24×1 Infinium HTS Human Core Exome microarrays following the protocol provided by the manufacturer. PLINK 1.9 was used to identify and validate genetic risk factors for KD.

Selection of Genetic Instrumental Variables

To comply with MR design rules (Figure 1), all GWAS SNPs were independent and had strong ($R2 < 0.001$) genome-wide significance ($P < 5\times10\text{-}8$). As only a small number of circulating inflammatory factors with ≥3 unique SNPs reached significance, a broader threshold of 1×10-5 was used to collect SNPs for circulating inflammatory factors, whereas a larger threshold of 0.001 was used for KD. Additionally, the study assessed whether there was an association with confounding factors (BMI). Obesity may lead to systemic chronic low-grade inflammation; therefore, BMI was used as a confounder.[10] To reduce the bias, we excluded SNP related to the age-related survival rate of recruitment.[11] Ultimately, this study used the F value statistic to determine the strength of each SNP. The F value statistic is a function of the magnitude and precision of the genetic effect of the trait: $F=R2(N-2)/(1-R2)$, where R2 represents the proportion of variance in the trait that is explained by the SNP, with a larger R^2 indicating greater explanatory power for the instrumental variable. N represents the sample size of the GWAS for the SNP associated with the trait. The formula $R2= 2\times EAF\times(1-EAF)\times b2$ was used to determine the value of R2, where EAF denotes the effect allele frequency (EAF) of the SNP and indicates the determined effect of the SNP on the trait. Generally, F values greater than 10 indicate that the instrumental variable is strongly valid.[12]

Two-Way MR Analysis

In this study, a bidirectional MR approach was used to analyze the directionality of the correlation between KD and circulating inflammatory factors via pooled data. The analysis required detailed information on SNPs, effect sizes, alleles, se, EAFs, and P values.[13] Strict data harmonization was performed to ensure that SNP effects on outcome and exposure corresponded to the same alleles. For SNPs with different effect alleles induced by different strands, strand correction was performed to ensure identical effect alleles. In addition, palindromic sequences (which are more difficult to reconcile because the allele is the same on both strands) were excluded to avoid ambiguity on the basis of whether the exposure and outcome GWASs reported the same effect allele. Estimates from significance analyses were summarized via inverse-variance weighting (IVW) with multiple random effects, which provides fast estimates and accounts for potential heterogeneity between Wald ratios calculated from SNPs.[14]

Sensitivity Analysis

The set of sensitivity analyses consisted of MR–Egger, weighted median, weighted mode, and MR pleiotropy residual sum and outlier (MR–PRESSO). MR–Egger analyses provide a nonzero-intercept estimate of instrumental variable multivalence, indicating bias in IVW assessment.[15] The weighted median method is used to select the median MR result that is considered the causal estimate, accounting for multiple invalid genetic variants or the presence of pleiotropy.[16]

MR–PRESSO is used to assess horizontal pleiotropy via a global test and can be used to correct for potential pleiotropic outliers.[17] The heterogeneity of the IVW estimates was determined via Q tests and I2 indices.

$P < 0.05$ was considered to indicate a significant association. Two-way analyses were conducted via the MRPRESSO (version 1.0) and TwoSampleMR (version 0.5.6) packages in R software (version 4.4.0). This report was written in accordance with the STROBE-MR statement guidelines.

Results

Influence of Circulating Inflammatory Factors on the Risk of Developing KD

The ORs for most of the exposure factors (eg, eotaxin, GROa, MCP_1_MCAF, MIG, and MIP_1b) were close to 1, with P values >0.05, suggesting that there was no significant correlation between these circulating inflammatory factors as exposure factors and the risk of developing KD as an outcome variable. The confidence intervals were generally wide, indicating that the estimates were only subject to high uncertainty. This may be due to small sample sizes or weak SNP effects (see Figure 2).

Effect of KD Status on the Circulating Levels of Inflammatory Factors

One hundred and fifty-five SNPs that were strongly and independently associated with KD ($P < 0.001$) were selected to assess reverse causality. Among the experimental results obtained via the IVW method, interleukin-2 (IL-2) and interleukin-8 (IL-8) were significantly associated with the risk of developing KD: IL-2 [OR=1.0085, 95% CI: 1.0005–1.0165; P=0.037] and IL-8 [OR=1.0099, 95% CI: 1.0020–1.0179; P=0.014] (see Figure 3). IL-2 and IL-8 may be predictive factors for the development of KD, but no significant effect was found when MR–Egger, weighted median, weighted mode, or simple mode were used (see Figure 4A-D and Figure 5A-D). Among these 41 circulating inflammatory factors, MR–Egger analysis revealed four inflammatory factors with borderline significance: B_NGF [OR=1.0242, 95% CI: 0.9960–1.0532; P=0.0951]; EOTAXIN [OR=1.0191, 95% CI: 1.0001–1.0385; P= 0.0511] (with significant horizontal pleiotropy, pval=0.0433); HGF [OR=1.0165, 95% CI: 0.9972–1.0361; P=0.0965]; and IL_12_P70 [OR=1.0160, 95% CI: 0.9978–1.0346; P=0.0880]. Weighted median analysis revealed one inflammatory factor with borderline significance: IL_2 [OR=1.0107, 95% CI: 0.9992–1.0223; P=0.0675]; IVW analysis revealed one inflammatory factor with borderline significance: B_NGF [OR= 1.0068, 95% CI: 0.9989–1.0147; P=0.0945]; and simple mode analysis

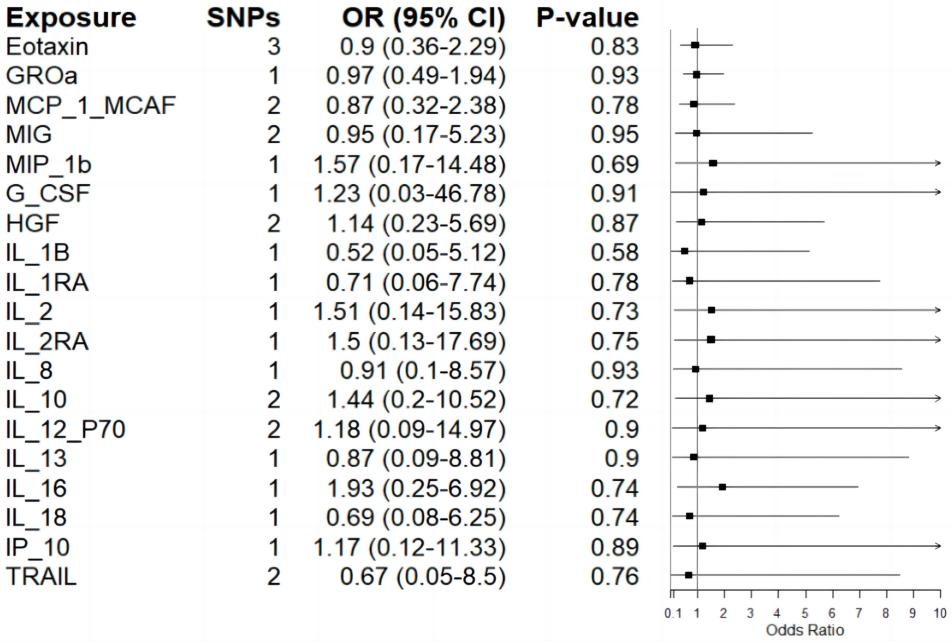

Figure 2 Effect of circulating inflammatory factors on the risk of Kawasaki disease.

Exposure	SNPs	OR (95% CI)	P-value
B_NGF	151	1.007 (0.999-1.015)	0.0945
CTACK	152	0.994 (0.987-1.002)	0.1503
EOTAXIN	155	1 (0.995-1.005)	0.9626
FGF_BASIC	155	1.001 (0.996-1.006)	0.7308
G_CSF	155	1 (0.995-1.005)	0.9938
GROA	152	1.005 (0.997-1.013)	0.2038
HGF	153	1.002 (0.997-1.007)	0.4497
IFN_G	155	1.004 (0.999-1.009)	0.1385
IL_1B	152	1.006 (0.998-1.014)	0.1715
IL_1RA	152	1.004 (0.996-1.012)	0.348
IL_2	152	1.008 (1-1.016)	0.0372
IL_2RA	152	1 (0.992-1.008)	0.9794
IL_4	155	1 (0.995-1.005)	0.9538
IL_5	152	1 (0.992-1.008)	0.9268
IL_6	155	1.001 (0.996-1.006)	0.6349
IL-7	152	1.005 (0.997-1.013)	0.2594
IL_8	152	1.01 (1.002-1.018)	0.0139
IL_9	152	1.002 (0.995-1.01)	0.5604
IL_10	155	1.001 (0.996-1.006)	0.6742
IL_12_P70	155	1 (0.995-1.005)	0.92
IL_13	152	1 (0.993-1.008)	0.898
IL_16	152	1.004 (0.996-1.012)	0.3559
IL_17	155	1.001 (0.996-1.006)	0.6635
IL_18	152	0.995 (0.988-1.003)	0.2366
IP_10	152	1.006 (0.998-1.014)	0.1502
M_CSF	150	1.004 (0.994-1.013)	0.4274
MCP_1_MCAF	155	1.004 (0.999-1.009)	0.1666
MCP_3	145	1.004 (0.99-1.018)	0.5729
MIF	151	1.003 (0.995-1.011)	0.4847
MIG	152	1.005 (0.997-1.013)	0.223
MIP_1A	152	1.004 (0.995-1.012)	0.4417
MIP_1B	155	1.001 (0.996-1.006)	0.7327
PDGF_BB	155	1.001 (0.996-1.006)	0.7733
RANTES	152	1.002 (0.995-1.01)	0.5455
SCF	155	1.002 (0.997-1.007)	0.5078
SCGF_B	152	1.007 (0.999-1.014)	0.0951
SDF_1A	155	1.002 (0.997-1.008)	0.4312
TNF_A	152	1.007 (0.999-1.015)	0.0953
TNF_B	137	0.998 (0.986-1.01)	0.7623
TRAIL	155	1.005 (1-1.01)	0.0798
VEGF	155	1.001 (0.995-1.006)	0.7486

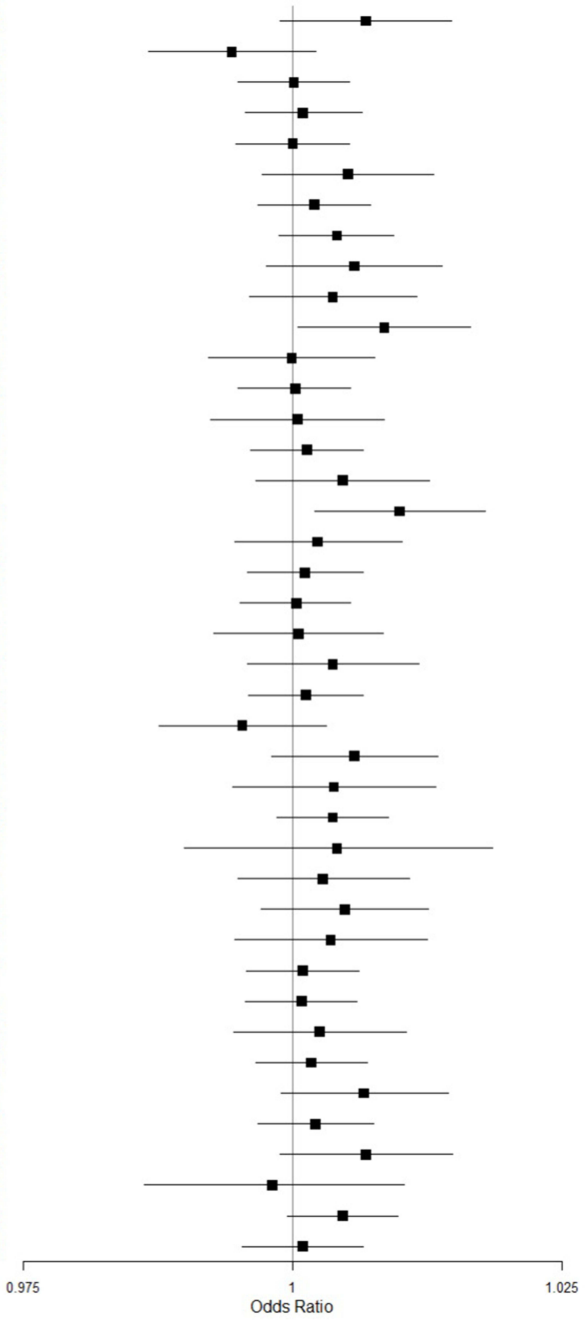

Figure 3 Effect of Kawasaki disease on circulating inflammatory factor levels.

revealed one inflammatory factor with borderline significance: MCP_1_MCAF [OR=1.0192, 95% CI: 0.9978–1.0412; P=0.0945]. The remaining MR–PRESSO methods did not reveal any outliers.

Discussion

In this study, we assessed the potential causal relationship between circulating inflammatory factors and the risk of developing KD through pooled GWAS data via bidirectional MR analysis. Bidirectional MR can be used to effectively distinguish between upstream and downstream factors in the disease process and reduce the interference of reverse causality. To ensure the robustness of the findings, various methods, such as MR–PRESSO, the weighted median method,

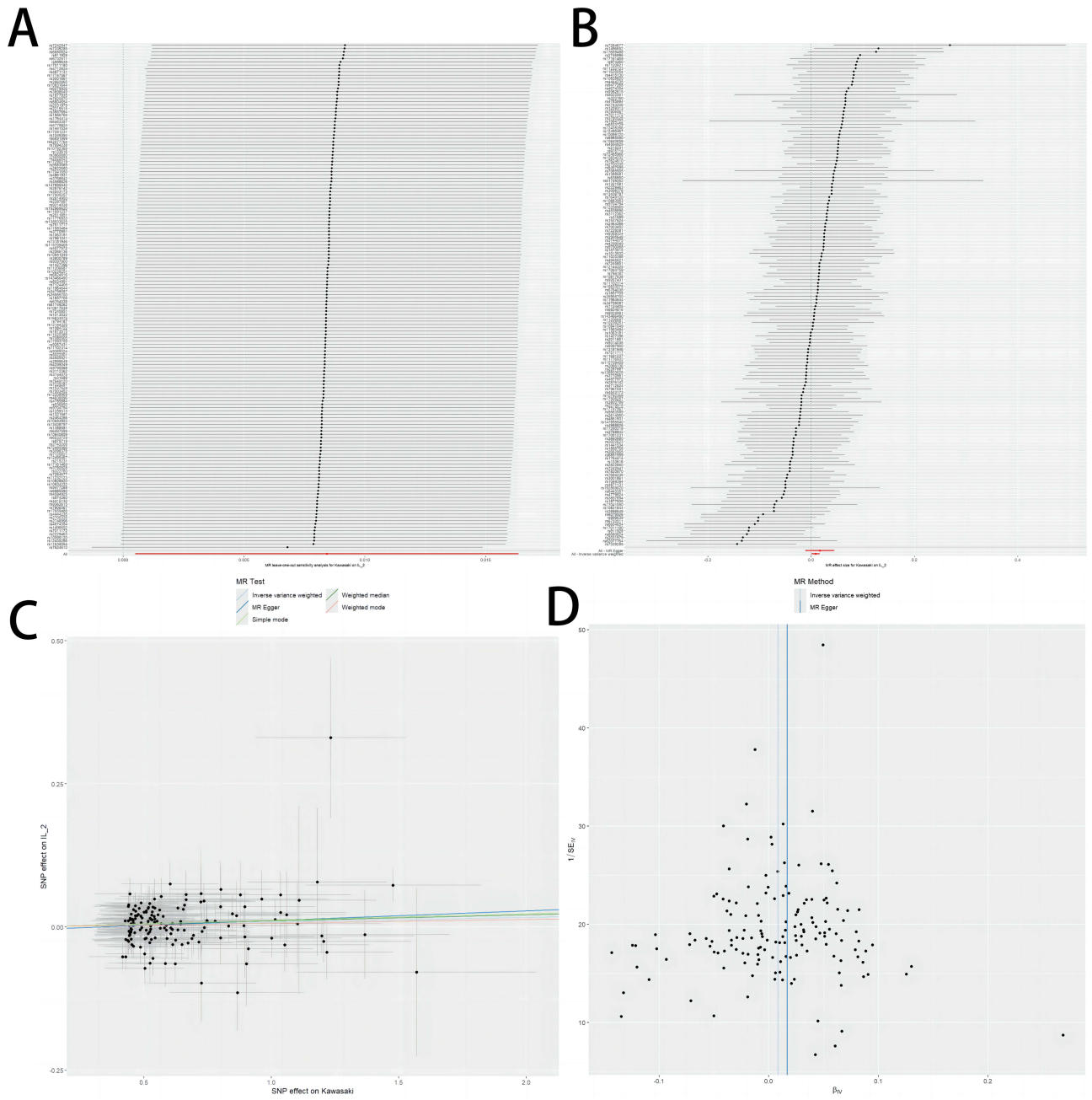

Figure 4 Sensitivity analysis of the bidirectional causal associations between KD and IL_2. (**A**) MR leave-one out sensitivity analysis for KD on IL_2. (**B**) MR effect size for KD on IL_2. (**C**) Causal estimate for different MR tests. (**D**) Funnel plot from single SNP analyses.

the weighted mode method, and the MR–Egger test, were used to minimize bias due to pleiotropy. The results revealed that elevated IL-2 and IL-8 levels were significantly associated with the development of KD, suggesting that they are not only potential predictors of KD but also potential targets for future therapy. IL-2, a key factor regulating T-cell proliferation, may play a central role in the dysregulation of the immune response in KD; IL-8, a chemokine, attracts neutrophils to the site of inflammation, which may exacerbate the vascular inflammatory response in patients.[18,19]

In addition to IL-2 and IL-8, studies have identified the potential relevance of inflammatory factors such as B_NGF, EOTAXIN, HGF, IL_12_P70, and MCP_1_MCAF in KD. B_NGF (brain-derived neurotrophic factor), which plays an important role in neurodevelopment, may be involved in the chronic progression of KD through the regulation of neuroimmune interactions, especially in the repair process after vascular injury.[20] EOTAXIN (eosinophil chemotactic

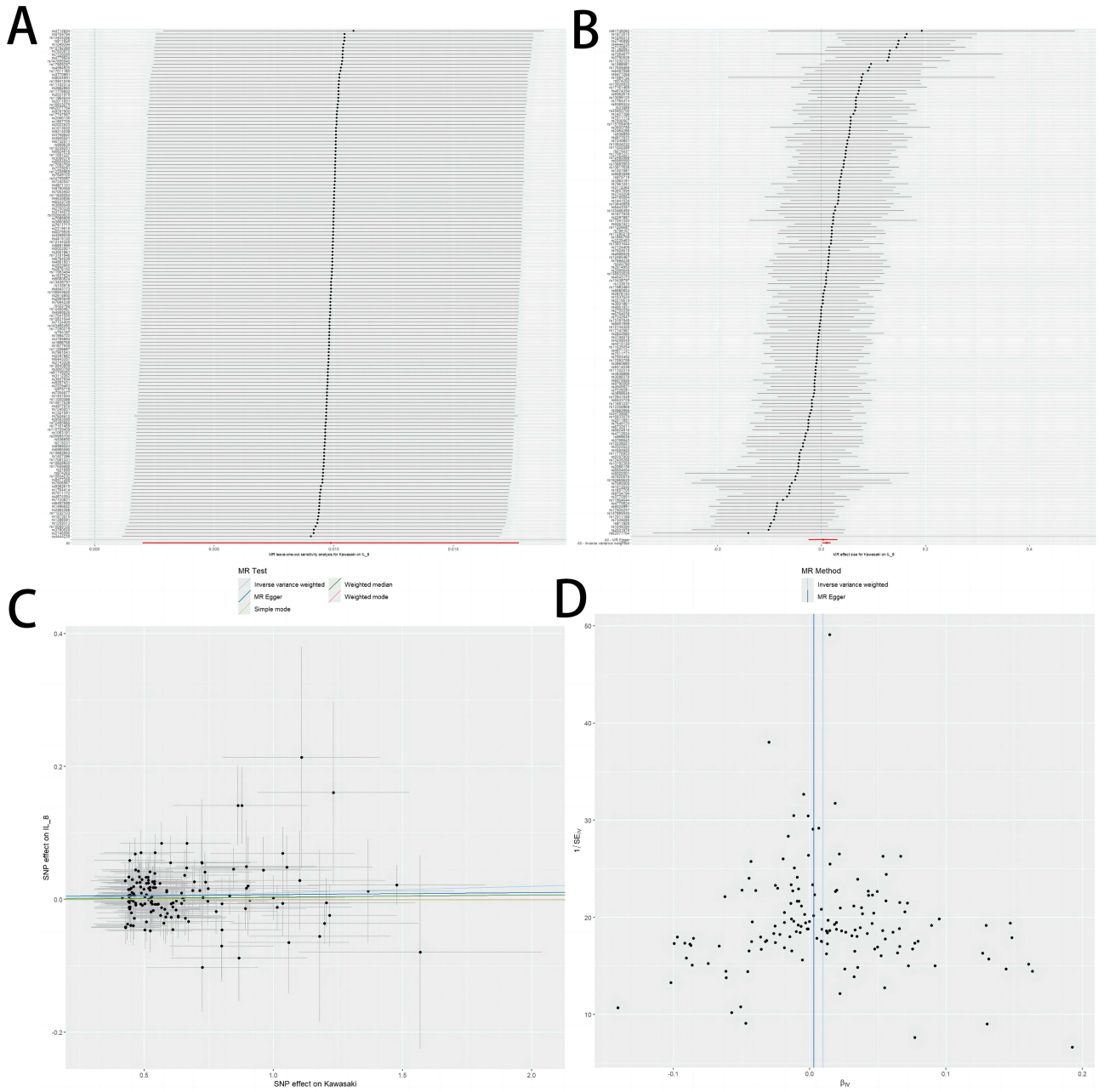

Figure 5 Sensitivity analysis of the bidirectional causal associations between KD and IL_8. (**A**) MR leave-one out sensitivity analysis for KD on IL_8. (**B**) MR effect size for KD on IL_8. (**C**) Causal estimate for different MR tests. (**D**) Funnel plot from single SNP analyses.

factor) is a key factor that attracts eosinophils, which may play an important role in the immune response to KD and enhance the inflammatory response by synergizing with IL-2 and IL-8.[21] Hepatocyte growth factor (HGF), a known tissue-repairing factor, may be important in the recovery from KD by promoting vascular regeneration,[22] whereas IL_12_P70, a key factor regulating natural and adaptive immune responses, may modulate the aberrant immune response in KD by activating T cells and natural killer cells.[23] MCP_1_MCAF (monocyte chemotactic protein-1/monocyte chemotactic activating factor) may play an important role in vascular inflammation in KD by recruiting monocytes to the site of inflammation.[24]

There may be complex interactions between IL-2 and IL-8 and other marginally significant factors. IL-2, by enhancing the immune response of T cells, may indirectly promote IL-8 expression, creating a positive feedback loop that further exacerbates the inflammatory response.[25] EOTAXIN may exacerbate immune dysregulation by attracting

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eosinophils and synergizing with the inflammatory effects of IL-2 and IL-8.[26] In addition, B_NGF and HGF may play important roles in vascular repair in the later stages of KD, whereas MCP_1_MCAF further exacerbates the local immune response by attracting immune cells to sites of inflammation.[27–29]

Although this study provided strong evidence for causal inference through the MR approach, we relied on existing genetic data for the MR analyses, which could not comprehensively account for the effects of non-genetic factors, such as lifestyle and environmental influences. Future studies should include the measurement of additional biomarkers, such as cerebrospinal fluid, to validate these findings. Moreover, the sample size of KD patients in this study was relatively small (119 cases), which may limit the accuracy and generalizability of the results. To enhance the reliability of the conclusions, future studies should aim to increase the sample size, particularly from diverse regions and ethnic groups. The current GWAS datasets primarily include individuals of European descent, which may impact the applicability of the findings across different populations. Therefore, future studies should incorporate data from multiple ethnic groups to extend the generalizability of the results. Finally, while this study employed multiple robustness checks, the lack of external validation using independent datasets may limit the generalizability and credibility of the results. Future research should utilize different external datasets for validation to further confirm the causal conclusions of this study.

In light of recent studies, such as Pan Y, Jiao F. Exploring Causal Correlations Between Inflammatory Cytokines and Kawasaki Disease (2024), which also utilized Mendelian randomization to investigate the role of inflammatory cytokines in KD, our research further extends this body of work. In their study, Pan et al identified significant associations between the levels of macrophage colony-stimulating factor (M-CSF), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) with the risk of KD.[30] While their study provided valuable insights into these cytokines' potential role in KD, our research adds further clarity by exploring a broader range of inflammatory factors, including IL-2 and IL-8, that may play a crucial role in the pathogenesis of KD. Notably, our study focuses on the potential of IL-2 and IL-8 as therapeutic targets, which have not been extensively addressed in the existing literature. Our findings also contribute to the understanding of how these cytokines interact with other factors like EOTAXIN, B_NGF, and HGF, offering new avenues for targeted interventions.

By combining genetic data from a diverse set of inflammatory factors and providing a more comprehensive analysis of the immune response in KD, our study enhances the overall understanding of KD's inflammatory mechanisms and lays a stronger foundation for future therapeutic research.

Conclusion

In this study, the causal associations between circulating inflammatory factors and the risk of developing KD were systematically assessed via two-way MR analysis. In the forward MR analysis, no significant causal associations were found between circulating inflammatory factors and the risk of developing KD, suggesting that these inflammatory factors may not be direct triggers of KD. However, the reverse MR results revealed that IL-2 and IL-8 levels were significantly correlated with the risk of developing KD, suggesting that KD may affect the levels of these inflammatory factors through feedback mechanisms. Other inflammatory factors, such as B_NGF, EOTAXIN, HGF, IL_12_P70 and MCP_1_MCAF, although their roles are not yet fully defined, may also be targets for future research and clinical intervention. More in-depth studies could further reveal the specific roles of these inflammatory factors in patients with various stages of KD.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Statement

After reviewing the guidelines and requirements, we confirm that this study was exempt from Institutional Review Board (IRB) approval in accordance with Article 32 of the *Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects* (China, February 18, 2023).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors state that the study was conducted without any involvement in commercial or financial interests that could be perceived as potential conflicts of interest.

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