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Research article

Causal effects of inflammatory cytokines on cardiovascular diseases: Insights from genetic evidence

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ABSTRACT

Background: The causal relationship between inflammatory cytokines and cardiovascular diseases (CVDs) has not been fully elucidated. Exploring this relationship between circulating inflammatory cytokines and CVDs is crucial for early clinical diagnosis and effective treatment.
Methods and Results: This study investigated the causal relationships between 41 inflammatory cytokines and six CVDs: heart failure (HF), myocardial infarction (MI), unstable angina pectoris (UAP), stable angina pectoris (SAP), valvular heart disease (VHD), and aortic aneurysm (AA), using the Mendelian Randomization (MR) method. The primary analysis employed the inverse-variance weighted (IVW) method within MR. Heterogeneity and pleiotropy were assessed through MR-Egger regression and the Q statistic. Strong evidence supported the effect of macrophage inflammatory protein-1β (MIP-1β) on MI (OR = 1.062, $P < 0.001$, FDR <0.001). Suggestive evidence showed that the Beta nerve growth factor increased the risk of MI (OR = 1.145, $P = 0.025$), but the stem cell factor (SCF) demonstrated a potential protective effect against MI (OR = 0.910, $P = 0.04$). SCF and hepatocyte growth factor (HGF) exhibited potential protective effects against SAP. No inflammatory cytokine was associated with UAP. Monocyte chemotactic protein-1 was linked to an increased risk of VHD (OR = 1.056, $P = 0.049$). Higher levels of interleukin-13 (IL-13), interferon gamma-induced protein 10 (IP-10), and growth-regulated oncogene-alpha were associated with increased susceptibility to HF. Elevated basic fibroblast growth factor (bFGF) levels exhibited protective effects against AA (OR = 0.751, $P = 0.038$). Reverse MR analyses revealed that AA significantly decreased circulating TNF-related apoptosis-inducing ligand (TRAIL) levels (OR = 0.907, $P < 0.001$, FDR = 0.01). MI significantly increased circulating IL-12-p70 levels (OR = 1.146, $P < 0.001$, FDR = 0.014). Suggestive evidence indicated the Causal effects of six CVDs on 17 circulating inflammatory cytokines.
Conclusions: This study clarified the causal relationships between specific inflammatory cytokines and six CVDs, providing novel insights and evidence into the genetic involvement of inflammatory cytokines in CVDs. These inflammatory cytokines may be potential biomarkers for early disease diagnosis and treatment evaluation.

1. Introduction

Cardiovascular diseases (CVDs) encompass a spectrum of conditions affecting the heart or blood vessels, such as heart failure (HF),

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myocardial infarction (MI), and angina pectoris (AP). Globally, CVDs impose significant mortality and disability burdens, thereby constituting a formidable challenge to global health [1,2]. However, the pathogenesis of these diseases is intricate and multifactorial, impeding progress in their prevention and treatment strategies [3].

In recent years, numerous studies have elucidated the involvement of various inflammatory factors in both the onset and progression of cardiovascular diseases, underscoring their significant roles in disease pathogenesis [4,5]. Studies have found that Interleukin-1-beta (IL-1β), Tumor necrosis factor-alpha (TNF-α), and IL-8 can aggravate the progression of cardiovascular disease [6,7], while IL-10 and IL-9 demonstrate coronary protective effects [6]. Moreover, IL-22 has been shown to reduce cardiac rupture post-myocardial infarction and facilitate cardiac function recovery thereafter [8]. Despite these advancements, prior research predominantly focused on elucidating the mechanisms within cardiomyocytes and vascular tissue, neglecting the exploration of circulating inflammatory cytokines. Furthermore, existing research findings are primarily derived from observational studies and basic experiments, thus limiting our understanding of the causal relationship between inflammatory cytokines and cardiovascular diseases. To address this gap, we employed Mendelian randomization (MR) to investigate the relationship between circulating inflammatory cytokine and CVDs.

MR is a robust method employing genetic variants as instrumental variables (IVs) to estimate causal relationships between exposures and outcomes [9]. Grounded in Mendelian inheritance laws, MR capitalizes on the random distribution of genetic variation in a population, thereby mitigating confounding factors and reverse causation [10]. Consequently, MR is a valuable tool for analyzing causal relationships between various factors and diseases, including inter-disease relationships [10]. In this study, we selected forty-one circulating inflammatory cytokines as exposures and six CVDs, namely HF, MI, unstable angina pectoris (UAP), stable angina pectoris (SAP), valvular heart disease (VHD), and aortic aneurysm (AA), were chosen as outcomes. We aim to leverage bidirectional MR to elucidate the causal relationship between these circulating inflammatory cytokines and the risk of developing CVDs.

2. Materials and methods

2.1. Mendelian randomization assumptions

MR is founded on three key assumptions: 1) IVs exhibit a strong association with the exposure under investigation; 2) IVs are independent of potential confounding factors; and 3) IVs solely affect outcomes through their influence on the exposure being studied [10]. This study was conducted with the guideline of STROBE-MR [11]. The schematic representation of our study design is in Fig. 1.

2.2. Data sources

Genome-wide association study (GWAS) summary data for 41 circulating inflammatory cytokines were obtained from three separate Finnish cohorts: the Finnish Youth Cardiovascular Risk Study, FINRISK 1997, and FINRISK 2002, comprising a total cohort of 8293 Finnish participants [12]. These studies conducted adjustments for potential confounding variables, including age, gender, and body mass index (BMI), to address the association between genetic variants and inflammatory cytokines.

Summary data for HF [13], MI [14], UAP [15], SAP [15], VHD [15], and AA [15] were extracted from three large-scale GWAS meta-analyses, encompassing 47,309, 14,825, 9,481, 17,894, 25,070, and 20,857 participants of European ancestry, respectively. All

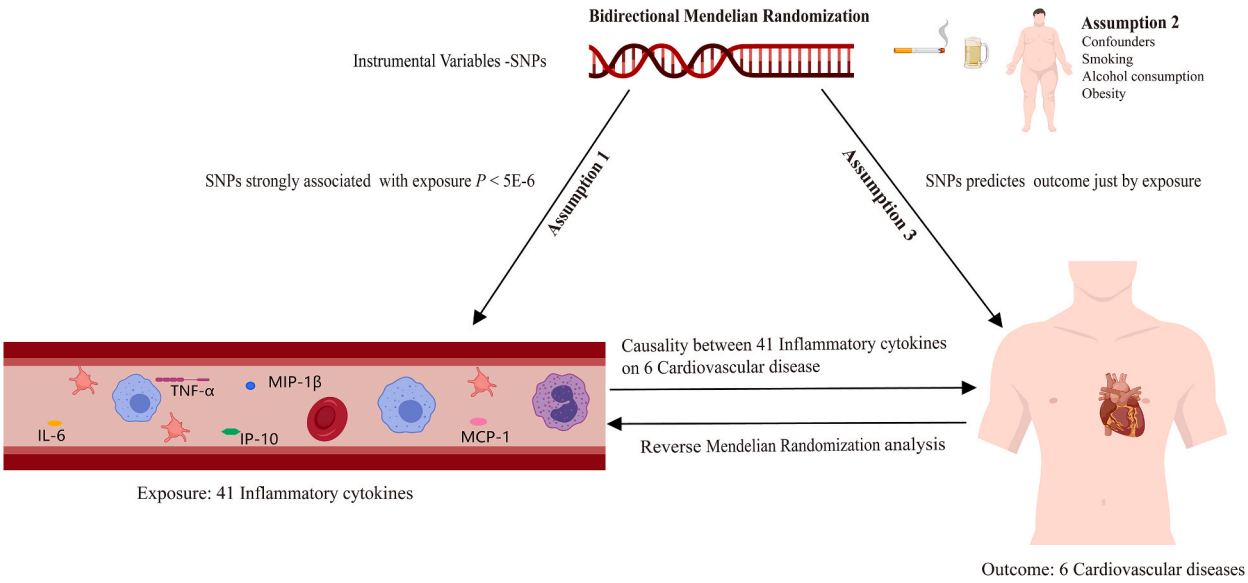

Fig. 1. The schematic representation of the study design. SNPs: Single nucleotide polymorphisms.

GWAS summary data used in this study are available online from the IEU Open GWAS database. The sources of these GWAS summary data are detailed in Supplementary Table 1.

2.3. Selection of instrumental variables

Single-nucleotide polymorphisms (SNPs) meeting a genome-wide significance threshold of $P < 5E\text{-}6$ [16,17] were selected as IVs to predict the circulating inflammatory cytokines. SNPs within a 5000 kb window were also selected using linkage disequilibrium (LD) threshold of $r^2 < 0.01$ to ensure unbiased estimates. In the reverse MR analysis, SNPs achieving a genome-wide significance level of $P < 5E\text{-}8$ ($P < 5E\text{-}6$ for AA and VHD) were used as IVs to predict CVDs outcomes, with SNPs selected within a 10,000 kb window and an LD threshold of $r^2 < 0.001$. Risk factors for CVD encompassed smoking, alcohol consumption, and obesity. To mitigate potential confounding effects, we utilized the PhenoScannerV2 (http://www.PhenoScanner.medschl.cam.ac.uk/) and LDlink website, excluding SNPs ($P < 1E\text{-}5$) directly linked to the aforementioned risk factors. SNPs significantly influencing the outcome ($P < 5E\text{-}8$) were likewise excluded. Furthermore, a harmonization process was conducted before the MR analysis to eliminate SNPs exhibiting a palindromic relationship between the exposure and outcome variables. To ensure the validity of IVs, the F-statistic was calculated to estimate their statistical strength and mitigate bias arising from weak instruments. The formula employed to compute the F-statistic was $F = (\beta_{exposure})\hat{}2/(SE_{exposure})\hat{}2$. SNPs with F-statistics below ten were eliminated. SNPs meeting rigorous selection criteria were utilized as IVs for the MR analysis.

2.4. Mendelian randomization analysis

The approach for calculating causal effects was inverse-variance weighted (IVW), augmented by weighted median (WM) and MR-Egger methods, and IVW was the primary approach. IVW utilizes meta-analysis to amalgamate the Wald ratios of causal effects for each instrumental variable (IV), offering the most precise estimates when all SNPs serve as valid IVs [18]. Conversely, the WM method computes the median of SNP-specific causal estimates weighted by their precision, furnishing a consistent estimate when at least 50 %

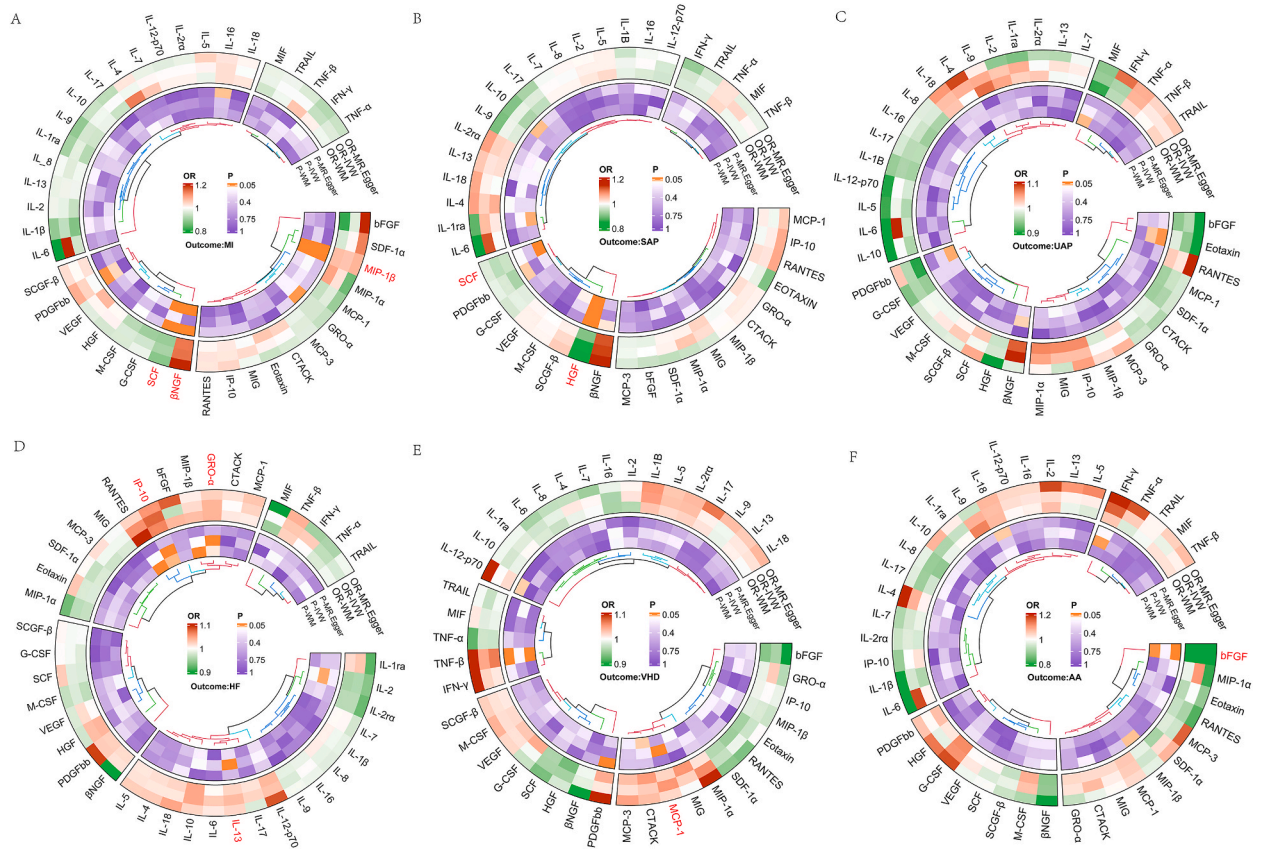

Fig. 2. Visualization of causal estimates of inflammatory cytokines on CVDs. (A) The MR results of MI; (B) The MR results of SAP; (C) The MR results of UAP; (D) The MR results of HF; (E) The MR results of VHD; (F) The MR results of AA. MI: myocardial infarction; AA: aortic aneurysm; HF: heart failure. SAP: stable angina pectoris; VHD: valvular heart disease. UAP: unstable angina pectoris. When $P < 0.05$ in IVW analysis, inflammatory cytokines are marked red.

of the IVs are valid. Similarly, the MR-Egger method yields a consistent estimate even if invalid IVs existed. Emphasizing the necessity of maintaining a consistent direction of effect in MR analysis is crucial. The results were presented as odds ratios (OR). The Benjamini and Hochberg method was employed to correct P-values for multiple testing. A false discovery rate (FDR) less than 0.05 indicates strong evidence of association, while P-values less than 0.05 that did not survive the FDR correction were considered suggestive associations.

2.5. Sensitivity analysis

Horizontal pleiotropy was assessed using the MR-Egger intercept, with significance at $P < 0.05$ [18]. Cochran's Q test and the MR-PRESSO method were used to assess heterogeneity and identify outlier SNPs. Leave-one-out analysis was used to evaluate the robustness of the results and the influence of individual SNPs. All analyses in this study were conducted using the two-sample MR package (version 0.5.6) and the MR-PRESSO package (version 1.0) in R (version 4.2.3).

3. Results

3.1. Selection of instrumental variables

From 3 to 44 SNPs were selected as instrumental variables (IVs) for various inflammatory cytokines.

Details of these SNPs are provided in Supplementary Tables 2–7. Each SNP had an F-statistic greater than 10, indicating no weak IVs (Supplementary Tables 2–7). In the MR analysis of CVDs on circulating inflammatory cytokines, 7 to 43 SNPs were chosen as IVs for different CVDs (Supplementary Tables 8–13). These SNPs also had an F-statistic greater than 10, indicating the absence of weak IVs (Supplementary Tables 8–13).

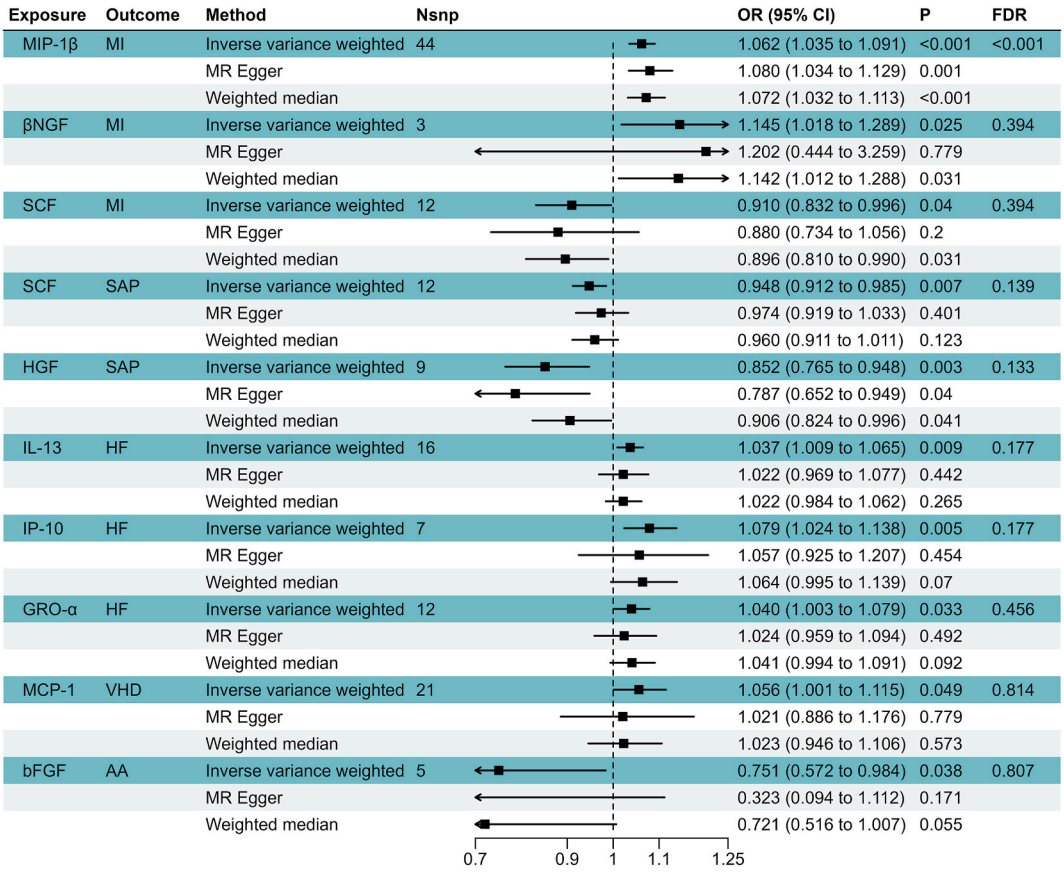

Fig. 3. Causal estimation of the relationship between inflammatory cytokines and CVDs with positive IVW results. MI: myocardial infarction; HF: heart failure. SAP: stable angina pectoris; AA: Aortic aneurysm; VHD: valvular heart disease; OR: odds ratio; CI: confidence interval; FDR: false discovery rate.

3.2. Causal relationship of inflammatory cytokine on cardiovascular diseases

Fig. 2 presents the results of the MR analysis for each inflammatory cytokine and their associations with MI (Fig. 2A), SAP (Fig. 2B), UAP (Fig. 2C), HF (Fig. 2D), VHD (Fig. 2E), and AA (Fig. 2F). Fig. 3 shows explicitly the associations of 10 inflammatory cytokines with CVDs. The MR analysis of 41 circulating inflammatory markers provided strong evidence for the effects of Macrophage inflammatory protein-1β (MIP-1β) on MI.

According to the IVW method, higher MIP-1β levels (OR = 1.062, 95 % Confidence Interval (CI) = 1.035–1.091, $P < 0.001$, FDR <0.001) were linked to an increased risk of MI. The WM and MR Egger methods showed similar effect size and direction trends. The Scatter plot and leave-one-out analysis plot illustrate these results, presented in Fig. 4A and B.

There was suggestive evidence supporting the association of nine inflammatory markers with different CVDs. Specifically, β nerve growth factor (βNGF) (OR = 1.145, 95 % CI = 1.018–1.289, $P = 0.025$, FDR = 0.394) was associated with a potentially increased risk of MI, while stem cell factor (SCF) (OR = 0.910, 95 % CI = 0.832–0.996, $P = 0.04$, FDR = 0.394) showed a potential protective effect against MI. SCF (OR = 0.948, 95 % CI = 0.912–0.985, $P = 0.007$, FDR = 0.139) and hepatocyte growth factor (HGF) (OR = 0.852, 95 % CI = 0.765–0.948, $P = 0.003$, FDR = 0.133) had potential protective effects against SAP, with other MR methods showing consistent results with the IVW method. Notably, no inflammatory cytokines were found to be associated with UAP. Monocyte chemotactic protein-1 (MCP-1) (OR = 1.056, 95 % CI = 1.001–1.115, $P = 0.049$, FDR = 0.814) had the potential to increase the risk of VHD, with other MR methods showing consistent findings with the IVW method.

With the IVW Method, higher levels of interleukin-13 (IL-13) (OR = 1.037, 95 % CI = 1.009–1.065, $P = 0.009$, FDR = 0.177), Interferon gamma-induced protein 10 (IP-10) (OR = 1.079, 95 % CI = 1.024–1.138, $P = 0.005$, FDR = 0.177), and Growth-regulated oncogene-alpha (GRO-α) (OR = 1.040, 95 % CI = 1.003–1.079, $P = 0.033$, FDR = 0.456) exhibited a potential correlation with increased susceptibility to HF. The MR analysis revealed that elevated levels of basic fibroblast growth factor (bFGF) (OR = 0.751, 95 % CI = 0.572–0.984, $P = 0.038$, FDR = 0.807) potentially had protective effects against AA using the IVW approach. Scatter plots and leave-one-out analysis plots illustrating these results are presented in Supplementary Figs. 1–2.

3.3. Causal relationship of cardiovascular diseases on the circulating levels of inflammatory cytokine

Fig. 5 presents the results of the reverse MR analysis for the associations of AA (Fig. 5A), MI (Fig. 5B), HF (Fig. 5C), VHD (Fig. 5D), SAP (Fig. 5E), and UAP (Fig. 5F) with 41 inflammatory cytokines. Strong or potential evidence supports associations between six CVDs and 17 circulating inflammatory cytokines (Figs. 5–6). There is strong evidence that AA significantly decreases circulating levels of TNF-related apoptosis-inducing ligand (TRAIL) (OR = 0.907, 95 % CI = 0.861–0.956, $P < 0.001$, FDR = 0.01). Circulating levels of interleukin-12 p70 (IL-12-p70) (OR = 1.146, 95 % CI = 1.064–1.235, $P < 0.001$, FDR = 0.014) are significantly increased in individuals who have suffered a MI. Scatter plots (Fig. 7A and B) and leave-one-out analysis plots (Fig. 7C and D) illustrating these results are presented in Fig. 7.

There is suggestive evidence that circulating levels of MCP-1 (OR = 0.946, 95 % CI = 0.898–0.996, $P = 0.036$, FDR = 0.610) and Eotaxin (OR = 0.948, 95 % CI = 0.900–0.999, $P = 0.045$, FDR = 0.610) may be reduced in patients with AA. Additionally, MI has the

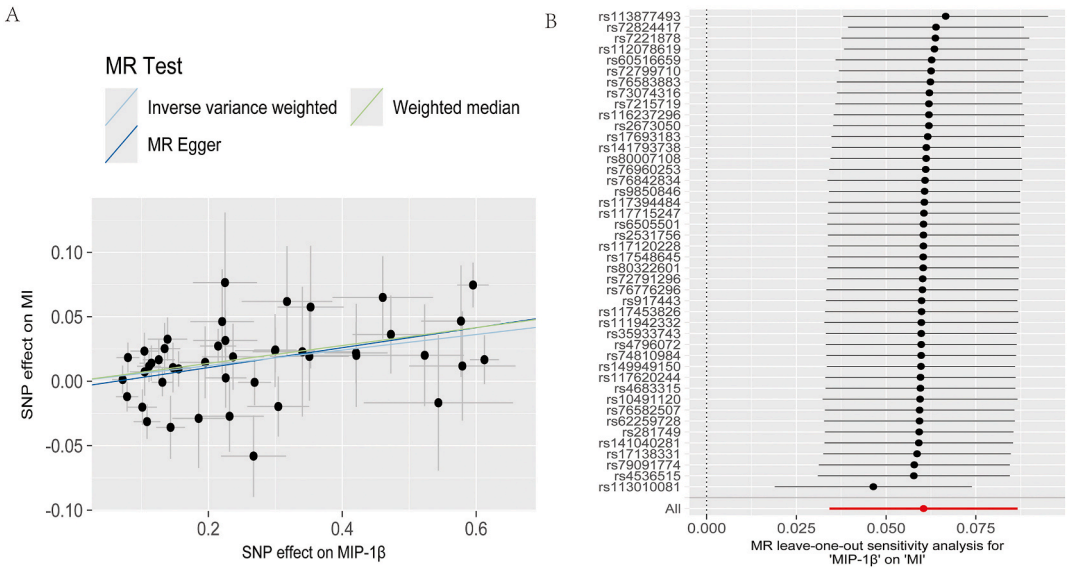

Fig. 4. Scatterplot and Leave-one-out plots of causal estimates of MIP-1β on MI. (A) Causal estimates for MIP-1β on MI. (B) Sensitivity analysis of the association of MIP-1β and risk of MI by sequentially removing each single-nucleotide polymorphism (SNP) from the analysis. MI: myocardial infarction.

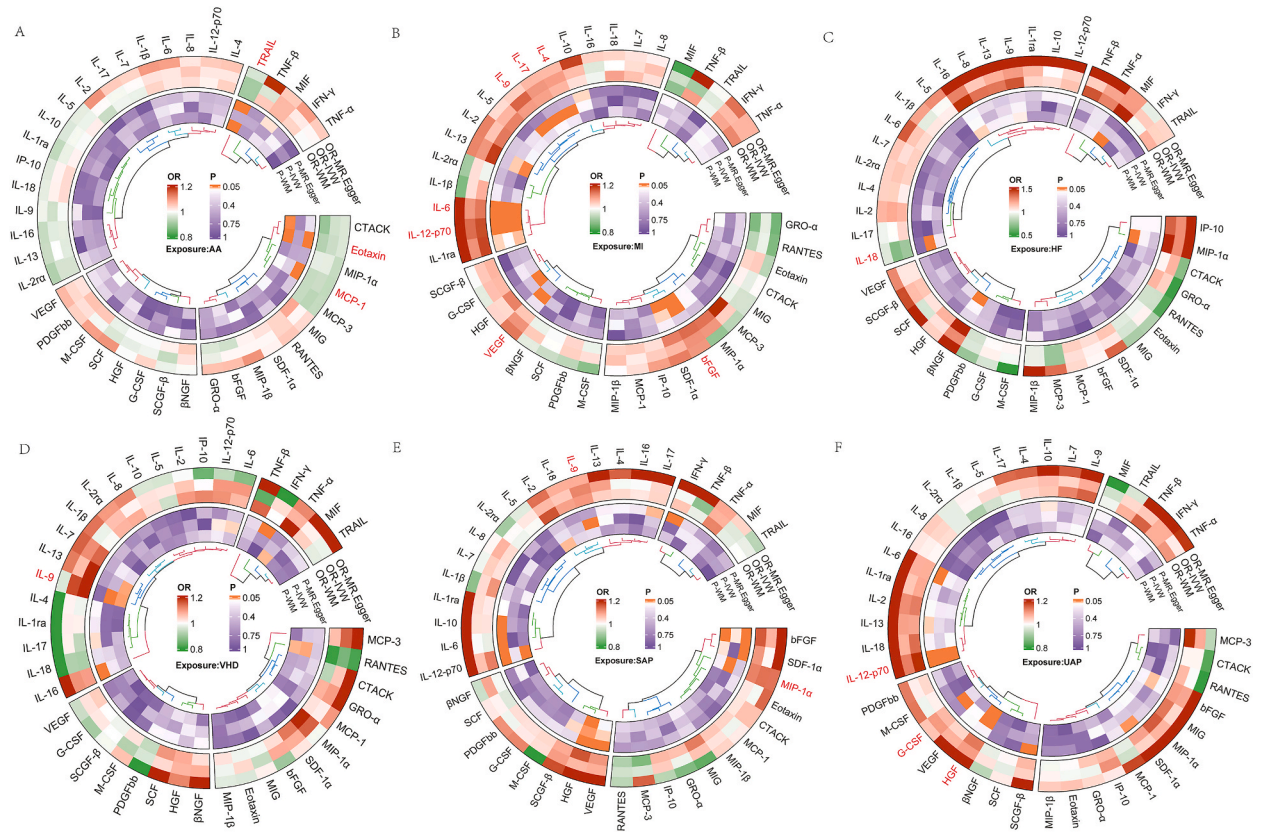

Fig. 5. Visualization of causal estimates between CVDs on inflammatory cytokines. (A) The MR results of AA; (B) The MR results of MI; (C) The MR results of HF; (D) The MR results of VHD; (E) The MR results of SAP; (F) The MR results of UAP. MI: myocardial infarction; AA: aortic aneurysm; HF: heart failure. SAP: stable angina pectoris; VHD: valvular heart disease. UAP: unstable angina pectoris. When $P < 0.05$ in IVW analysis, inflammatory cytokines are marked red.

potential to increase circulating levels of IL-4 (OR = 1.098, 95 % CI = 1.011–1.192, $P = 0.026$, FDR = 0.175), IL-6 (OR = 1.107, 95 % CI = 1.025–1.195, $P = 0.009$, FDR = 0.162), IL-9 (OR = 1.151, 95 % CI = 1.029–1.289, $P = 0.014$, FDR = 0.162), IL-17 (OR = 1.105, 95 % CI = 1.007–1.213, $P = 0.036$, FDR = 0.208), bFGF (OR = 1.111, 95 % CI = 1.020–1.210, $P = 0.016$, FDR = 0.162) and vascular endothelial growth factor (VEGF) (OR = 1.108, 95 % CI = 1.013–1.213, $P = 0.025$, FDR = 0.175). There is also suggestive evidence that HF increases circulating levels of circulating IL-18 (OR = 0.681, 95 % CI = 0.491–0.945, $P = 0.022$, FDR = 0.854) levels, whereas VHD (OR = 1.172, 95 % CI = 1.004–1.369, $P = 0.045$, FDR = 0.808) and SAP (OR = 1.122, 95 % CI = 1.006–1.253, $P = 0.039$, FDR = 0.632) may increase circulating IL-9 levels. SAP may also affect the levels of circulating macrophage inflammatory protein-1α (MIP-1α) (OR = 1.141, 95 % CI = 1.021–1.275, $P = 0.020$, FDR = 0.632). There is suggestive evidence that UAP may affect the levels of certain circulating inflammatory cytokine, including IL-12-p70(OR = 1.129, 95 % CI = 1.034–1.233, $P = 0.007$, FDR = 0.29), hepatocyte growth factor (HGF) (OR = 1.099, 95 % CI = 1.010–1.195, $P = 0.028$, FDR = 0.501), and granulocyte colony-stimulating factor (G-CSF) (OR = 1.102, 95 % CI = 1.006–1.208, $P = 0.037$, FDR = 0.501). Scatter plots and leave-one-out analysis plots illustrating these results are presented in Supplementary Figs. 3–6.

3.4. Sensitivity analysis

Heterogeneity was observed in the relationship between SCF and MI (Q = 19.014, $P_{\text{MR-Egger}} = 0.040$), with no outlier SNP identified by MR-PRESSO ($P = 0.0796$). However, pleiotropy was insignificant (intercept = 0.005; $P = 0.685$), as shown in Table 1. Heterogeneity and pleiotropy were negligible for the other above MR results (Tables 1–2), suggesting they did not reach statistical significance in the current data. The Leave-one-out analysis indicated that excluding any SNP did not significantly alter the causal relationship between inflammatory cytokines and CVDs. The heterogeneity assessments, and pleiotropy analyses for all inflammatory cytokines related to CVDs are provided in Supplementary Tables 14–17.

4. Discussion

In this study, we conducted a two-sample MR analysis involving 41 inflammatory cytokines and CVDs. Strong evidence supported

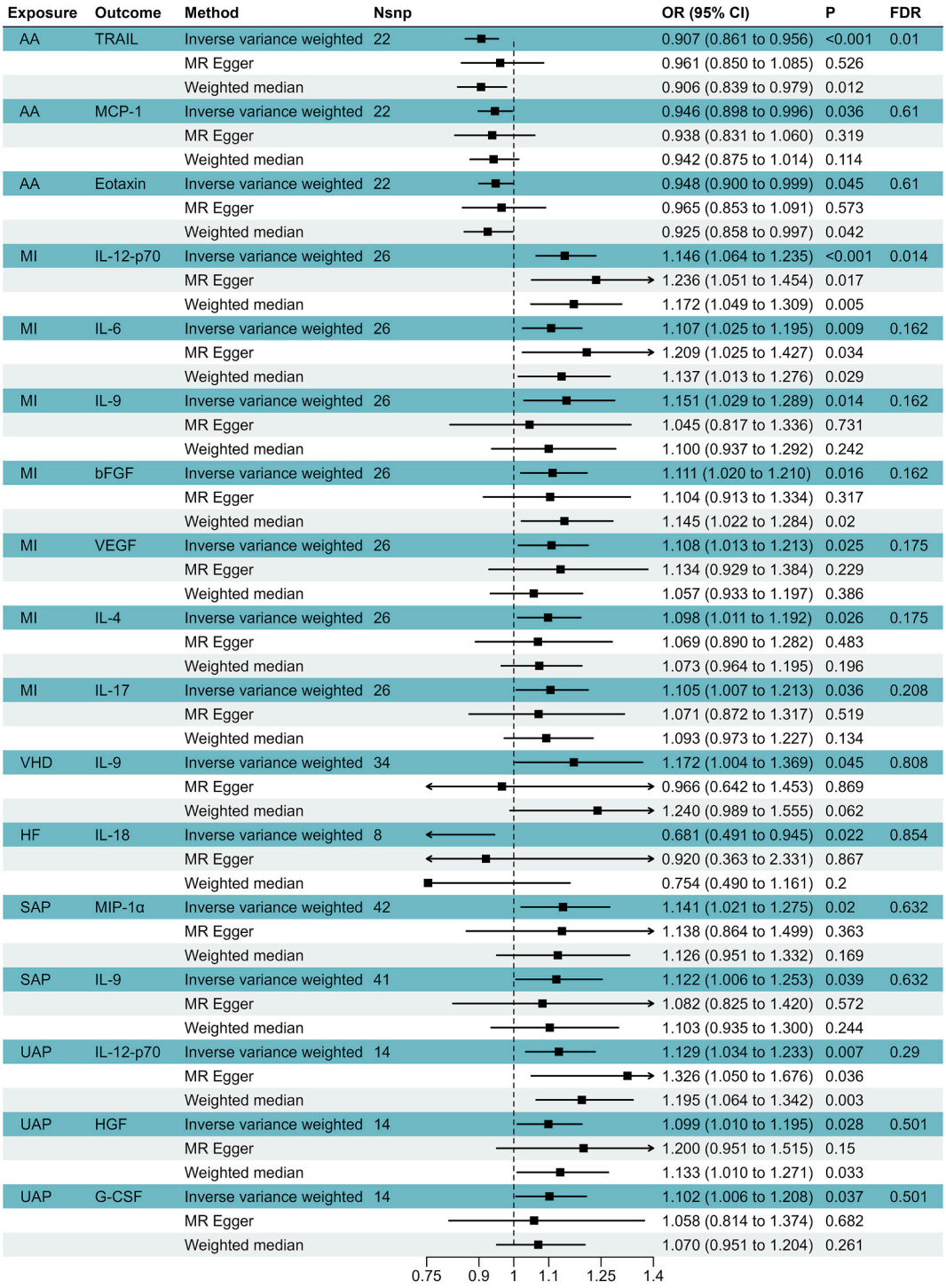

Fig. 6. Causal estimation of the relationship between CVDs on inflammatory cytokines with positive IVW results. MI: myocardial infarction; HF: heart failure; SAP: stable angina pectoris; AA: aortic aneurysm; VHD: valvular heart disease. UAP: unstable angina pectoris.

the association between circulating MIP-1β and an increased risk of MI. Additionally, there was suggestive evidence for the association of nine other inflammatory markers with different CVDs. Reverse MR analysis results indicated strong or potential evidence for associations between six CVDs and 17 circulating inflammatory cytokines. These findings elucidate the causal relationship between inflammatory cytokine and diseases from a genetic perspective.

Previous studies have found that circulating inflammatory cytokine and inflammatory cells are involved in the occurrence and

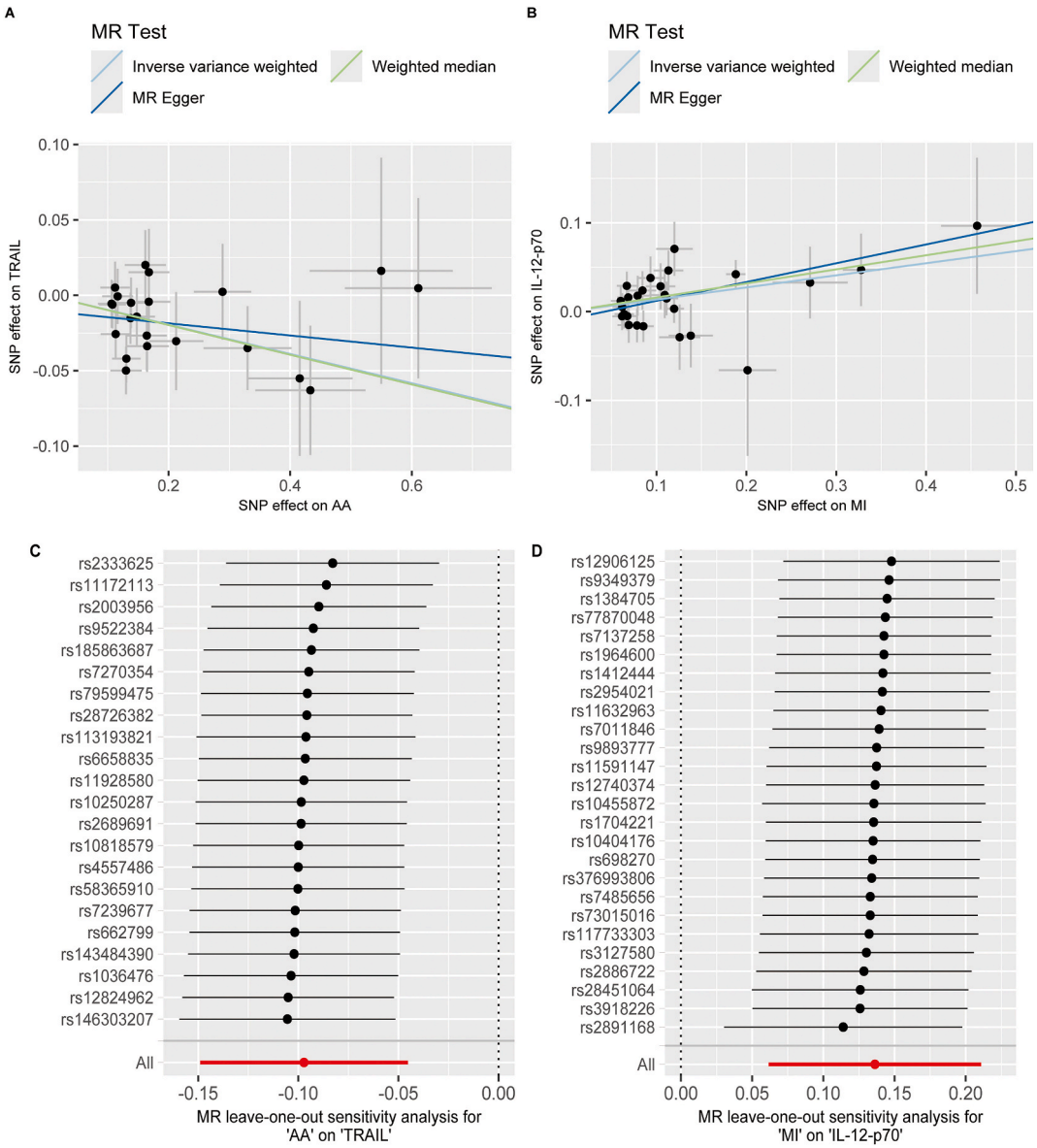

Fig. 7. Scatterplot and Leave-one-out plots for causal estimation of CVDs on two inflammatory cytokines. (A) Causal estimates for AA on TRAIL. (B) Causal estimates for MI on IL-12-p70. The slope of each line corresponds to the causal estimates for each method. Individual SNP effect on the outcome (point and vertical line) against its effect on the exposure (point and horizontal line) is delineated in the background. (C–D) Sensitivity analysis of the association of CVDs and risk of inflammatory cytokines by sequentially removing each single-nucleotide polymorphism (SNP) from the analysis. MI: myocardial infarction; AA: aortic aneurysm.

development of MI, and anti-inflammation may be an ideal strategy for treating ventricular remodeling after MI [19,20]. For example, plasma TNF-α levels 48 h after symptom onset and C-reactive protein (CRP) levels on admission are independent risk factors for ST-segment elevation myocardial infarction (STEMI) [21]. Notably, TNF-α, IL-1β, and IL-6 exacerbate myocardial damage following MI [22], whereas IL-10 and VEGF exhibit protective effects against MI. Furthermore, a recent study demonstrated the therapeutic potential of a novel anti-inflammatory hydrogel, SN50/IL-10/NapFFY, in mitigating the inflammatory milieu and enhancing cardiac function in MI rat models [19]. IL-1α deficiency attenuates systemic inflammation and ventricular remodeling post-MI in mice, characterized by decreased myocardial expression of hypertrophy and profibrotic genes, alongside reduced inflammatory monocyte infiltration [23]. Prior investigations have linked GRO-α (also referred to as CXCL1) to the occurrence and progression of MI [24]. Compared to the sham operation group, elevated levels of IL-4, IL-6, IL-13, IL-27, MIP-1β, MCP-3, and GRO-α were observed in injured heart tissue and serum [25]. Interestingly, A MR analysis found that GRO-α was causally linked to a decreased incidence of MI [26]. However, this finding was not supported by our study nor the study by Ruan et al. [27]. Concurrently, we observed an association between MIP-1β and a heightened risk of MI. Kalinskaya et al. discovered elevated levels of MIP-1β in non-STEMI patients [28].

Table 1
Tests for heterogeneity and pleiotropy in forward Mendelian randomization analysis.

Exposures	Outcomes	Heterogeneity test (MR-Egger)		Pleiotropy test (MR-Egger)	
		Q	*p*-value	intercept	*p*-value
MIP-1β	MI	50.103	0.183	−0.005	0.357
βNGF	MI	2.734	0.098	−0.007	0.938
SCF	MI	19.014	0.040	0.005	0.685
SCF	SAP	8.235	0.606	−0.007	0.261
HGF	SAP	8.953	0.256	0.019	0.140
MCP-1	VHD	21.384	0.316	0.005	0.614
GRO-α	HF	2.350	0.993	0.004	0.588
IL-13	HF	7.443	0.916	0.003	0.544
IP-10	HF	1.504	0.913	0.004	0.750
bFGF	AA	0.457	0.928	0.088	0.264

Abbreviations: MI: myocardial infarction; HF: heart failure. SAP: stable angina pectoris; VHD: valvular heart disease. AA: aortic aneurysm.

Table 2
Tests for heterogeneity and pleiotropy in reverse Mendelian randomization analysis.

Exposures	Outcomes	Heterogeneity test (MR-Egger)		Pleiotropy test (MR-Egger)	
		Q	*p*-value	intercept	*p*-value
AA	TRAIL	18.905	0.528	−0.011	0.325
AA	MCP-1	18.161	0.577	0.001	0.888
AA	Eotaxin	19.698	0.477	−0.003	0.759
MI	IL-12-p70	21.861	0.588	−0.009	0.315
MI	IL-6	24.539	0.431	−0.011	0.250
MI	IL-9	24.539	0.431	0.012	0.392
MI	bFGF	29.916	0.188	0.001	0.941
MI	VEGF	30.905	0.157	−0.003	0.805
MI	IL-4	29.443	0.204	0.003	0.744
MI	IL-17	36.155	0.053	0.004	0.745
VHD	IL-9	23.760	0.853	0.015	0.322
HF	IL-18	3.493	0.745	−0.021	0.523
SAP	MIP-1α	32.482	0.795	0.000	0.983
SAP	IL-9	35.398	0.635	0.003	0.775

Abbreviations: MI: myocardial infarction; HF: heart failure. SAP: stable angina pectoris; VHD: valvular heart disease. AA: aortic aneurysm. UAP: unstable angina pectoris.

Tocilizumab induces a substantial selective elevation in IP-10 and MIP-1β during the acute phase of non-STEMI [29]. Additionally, MIP-1β mirrors the inflammatory response in MI patients with cardiogenic shock [30].

Prior research suggests the SCF in angiogenesis and tissue repair [31]. Post-myocardial infarction, SCF levels escalate, and individuals with elevated baseline SCF levels exhibit a decreased risk of MI [32]. Our study further confirms that SCF has a potential protective effect against MI. This study suggests elevated levels of βNGF may increase the risk of MI. NGF amplifies inflammation by triggering a cascade of mediator release from eosinophils and basophils [33]. NGF has been implicated in various inflammatory conditions, including asthma [34], allergic rhinitis [35], and allergic contact eczema [36]. Moreover, studies have revealed a significant increase in βNGF expression in a canine model of atrial fibrillation [37]. βNGF levels correlate with fatigue severity [38] and serve as a prognostic predictor of pulmonary hypertension [39]. Consequently, we speculate that βNGF may heighten MI risk by promoting myocardial cell inflammation. Further research is warranted to investigate the direct association between βNGF and MI pathogenesis.

In the reverse MR analysis, we observed that MI is associated with elevated levels of circulating IL-12-p70, consistent with prior research indicating increased expression of IL-12 family members in various coronary atherosclerotic heart diseases [40]. Furthermore, this study provides suggestive evidence that MI induces a broad increase in inflammatory cytokines such as IL-4, IL-6, IL-9, and IL-17. Our findings contribute to distinguishing inflammatory cytokine influencing MI in two dimensions: influencing disease onset and predicting disease prognosis, thereby offering significant clinical insights.

Recent studies have indicated that various inflammatory cytokines contribute to the formation and progression of AA through diverse pathways [41–43]. bFGF is an important mitogenic factor and an inducing factor for morphogenesis and differentiation. Prior research demonstrated that stents coated with bFGF and PLGA microspheres containing argatroban could mitigate the risk of severe bleeding in animal models of intracranial aneurysms [44]. However, a separate Mendelian randomization study did not establish a causal link between bFGF and intracranial aneurysms [45].

Interestingly, this study found that bFGF may have a potential protective effect on AA, warranting further investigation in more extensive studies. Reverse Mendelian analysis revealed that AA is associated with decreased circulating TRAIL levels, aligning with previous studies suggesting a beneficial role for TRAIL in cardiovascular diseases [46,47], thereby offering insights for evaluating AA prognosis.

Previous research indicates a correlation between inflammation and the progression of AP. Patients with UAP exhibit lower serum levels of insulin-like growth factor 1 (IGF-1), IGF binding protein 4 (IGFBP-4), and stanniocalcin 2 (STC2), alongside elevated levels of serum inflammatory cytokines (hs-CRP, TNF-α, and IL-6) compared to healthy controls [48]. Following stent implantation for recurrent angina in elderly individuals, there is a notable increase in levels of malondialdehyde (MDA), acrolein (ACR), TNF-α, and toll-like receptor 4 (TLR4) ($P < 0.001$). Oxidative stress and pro-inflammatory mediators play crucial roles in recurrent angina in elderly patients post-coronary stent implantation [49]. Our findings suggest that SCF and HGF may mitigate the occurrence of SAP. However, no inflammatory cytokine associated with the risk of UAP was identified. Therefore, the specific impact of these factors on the incidence of SAP remains uncertain, necessitating further investigation. Notably, suggestive evidence from the study indicates that compared to SAP, UAP appears more likely to elevate circulating levels of circulating cell growth factor (such as HGF) and stimulatory factor (such as G-CSF), potentially implicating these factors in the pathological mechanism of UAP.

MCP-1, a member of the CC chemokine family, also known as chemokine (CC-motif) ligand 2 (CCL2), facilitates the migration and infiltration of monocytes/macrophages and other cytokines at inflammatory sites and plays a crucial role in the inflammatory process and is involved in the progression of various diseases, such as cancer, neuroinflammatory diseases, and CVD [50–54]. Enhanced MCP-1 expression is observed in the aortic valve of aging-accelerated mice P1 [55], and elevated mRNA expression levels of MCP-1 are detected in rheumatic VHD [56]. This study revealed the potential association between elevated circulating MCP-1 levels and increased VHD risk. This finding could aid in identifying individuals at heightened risk of VHD early. Additionally, suggestive evidence indicated elevated IL-9 levels in patients with VHD, suggesting IL-9 as a potential prognostic indicator for VHD.

Chronic inflammation is recognized as a significant contributor to the onset and progression of HF [60]. Patients with congestive heart failure exhibit significantly elevated levels of three CXC chemokines, with IL-8 and GRO-α demonstrating a gradual increase with worsening New York Heart Association (NYHA) classification [61]. Our MR study corroborated previous findings, indicating an association between GRO-α and heightened HF risk. Although we believe GRO-α can increase the risk of HF and may be an adjunctive tool for stratifying HF, no studies currently clarify its specific mechanism of involvement, and further exploration and validation through large-scale clinical trials are warranted.

Our study identified IL-13 as a potential risk factor for HF. IL-13, a pro-inflammatory cytokine, demonstrates increased levels in chronic heart failure, positively correlating with plasma brain natriuretic peptide and CRP levels while negatively correlating with left ventricular ejection fraction [57]. Furthermore, elevated levels of IP-10 were associated with increased HF risk, with mRNA expression of IP-10 correlating with the extent of myocardial inflammation [58]. Our study, along with a previous Mendelian analysis [59], concluded that IL-18 is not associated with the risk of HF. However, our findings indicate that the occurrence of HF may lead to increased circulating IL-18 levels, suggesting that IL-18 could serve as a potential biomarker for evaluating HF outcomes.

Nonetheless, our study has several limitations. Firstly, we selected IVs with a significance threshold of 5E-6 due to the limited availability of SNPs meeting the more stringent threshold of 5E-8. While this could introduce bias, the strong F statistic suggests minimal impact on our results. Secondly, the lack of detailed demographic data such as age and gender from GWAS summary data hindered further population stratification. Lastly, our study only analyzed data from individuals of European ancestry, limiting the generalizability of our findings to other ethnic groups.

5. Conclusion

This study provides evidence of an association between multiple inflammatory cytokines and CVDs. Strong evidence supports that high levels of MIP-1β increase the risk of MI. MI notably elevates circulating IL-12-p70 levels. Conversely, AA significantly decreases circulating TRAIL levels. These findings underscore the potential contributions of inflammatory cytokines to the onset and progression of CVD, enhancing our understanding of their pathophysiological roles. Future research could further investigate these factors across diverse populations and explore their potential applications in CVDs prevention and treatment.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Not applicable.

Availability of data and materials

All GWAS summary data used in this study are available online from the IEU Open GWAS database. The sources of these GWAS summary data are detailed in Supplementary Table 1.

CRediT authorship contribution statement

Yuxiu Chen: Writing – original draft, Formal analysis, Methodology, Visualization. **Aifang Zhong:** Writing – review & editing, Conceptualization, Supervision, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35447.

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