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Mendelian randomization-based observational cohort study on drug targets

Impact of antihypertensive and lipid-lowering therapies on inflammatory cytokines

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Abstract

This study assesses the causal effects of antihypertensive and lipid-lowering drugs on inflammatory cytokines using a Mendelian randomization (MR) approach. We conducted a drug-targeted MR analysis using data from large-scale genome-wide association studies and eQTL datasets. SNPs near drug target genes served as instrumental variables to investigate the impact of antihypertensive (angiotensin-converting enzyme inhibitors [ACEIs], ARBs) and lipid-lowering drugs (HMGCR inhibitors, proprotein convertase subtilisin/Kexin type 9 [PCSK9] inhibitors, Niemann-Pick C1-like 1 inhibitors) on inflammatory cytokines. Sensitivity analyses, including leave-one-out and MR-Egger tests, were performed to confirm the robustness of the findings. ACEIs were associated with decreased levels of IL-1β, TNF-α, and CRP. ARBs did not show significant effects on inflammatory cytokines. HMGCR inhibitors significantly reduced MCP-1, MIP-1β, TNF-α, and IFN-γ, while PCSK9 inhibitors were linked to reductions in IL-1β and IL-6. Sensitivity analyses supported the reliability of these findings. The study demonstrated distinct anti-inflammatory effects of ACEIs, HMGCR inhibitors, and PCSK9 inhibitors. These findings support the potential use of these drugs to mitigate inflammation-related complications in patients with chronic conditions.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, CAD = coronary artery disease, CI = confidence interval, CRP = C-reactive protein, eQTL = expression Quantitative Trait Loci, GLGC = Global Lipids Genetic Consortium, GTEx = genotype-tissue expression, GWAS = genome-wide association studies, HMGCR = HMG-CoA reductase, ICBP = International Consortium for Blood Pressure, IFN-γ = interferon gamma, IL-1β = interleukin-1β, IL-6 = interleukin-6, IL-10 = interleukin-10, IL-17 = interleukin-17, IP10 = interferon gamma-induced protein 10 (CXCL10), IV = instrumental variable, IVW = inverse-variance weighting method, LDL-C = low-density lipoprotein cholesterol, MCP-1 = monocyte chemoattractant protein-1, MIP-1α/MIP-1β = macrophage inflammatory protein-1α/macrophage inflammatory protein-1β, MR = Mendelian randomization, MR-PRESSO = MR multi-effect residual and heterogeneity detection, NF-κB = nuclear factor Kappa-light-chain-enhancer of activated B cells, NPC1L1 = Niemann-Pick C1-like 1, PCSK9 = proprotein convertase subtilisin/Kexin type 9, RCT = randomized controlled trial, SBP = systolic blood pressure, SD = standard deviation, SNP = single nucleotide polymorphism, TNF-α = tumor necrosis factor-alpha, UKB = UK biobank, VEGF = vascular endothelial growth factor.

Keywords: antihypertensive drugs, coronary artery disease, genetic epidemiology, inflammatory cytokines, lipid-lowering therapies, Mendelian randomization

JX and ZX contributed equally to this work.

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1. Introduction

The inflammatory response is a critical immune defense mechanism by which the body responds to external damage. When tissues are injured by bacterial or viral infections, or physical and chemical stimuli, the body initiates an inflammatory response to repair the damage and maintain tissue function stability.[1] While a normal inflammatory response is beneficial in restoring tissue injury, excessive inflammation can lead to severe pathological conditions such as microcirculatory dysfunction, multiple organ failure, or even life-threatening "cytokine storms."[2,3] In patients with underlying comorbidities, excessive inflammatory responses not only accelerate disease progression but also cause extensive organ damage.[4] This phenomenon became particularly prominent during the COVID-19 pandemic, where the overactive immune response has been identified as a major cause of high mortality in elderly patients.[5]

Chronic conditions such as hypertension and dyslipidemia are closely associated with chronic inflammation, and patients with these conditions often exhibit more intense inflammatory responses when infected with COVID-19, leading to higher rates of complications and mortality.[6] Current research suggests that long-term use of antihypertensive and lipid-lowering drugs may influence inflammatory responses, though the precise mechanisms remain unclear. Furthermore, the regulatory effects of different drugs on inflammatory cytokines remain controversial.[7–9] For instance, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) exert different effects on inflammation, while lipid-lowering drugs, such as HMG-CoA reductase inhibitors (HMGCR inhibitors) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, also exhibit varying effects on inflammation.[10,11] Thus, selecting the appropriate antihypertensive and lipid-lowering drugs to control underlying diseases while simultaneously reducing inflammatory responses has become a critical issue in clinical practice.

Inflammatory cytokines play a pivotal role in the inflammatory response. Pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, activate immune cells and are involved in both local and systemic inflammation.[12] In contrast, anti-inflammatory cytokines, such as IL-10, help to balance the immune system by suppressing excessive pro-inflammatory reactions.[13] However, existing studies evaluating the relationship between drugs and inflammatory cytokines have produced inconsistent results. Some studies have found that ACEIs can suppress inflammation and reduce IL-6 levels, while ARBs have shown no significant effect.[10] Similarly, the effects of HMGCR inhibitors and PCSK9 inhibitors on reducing C-reactive protein (CRP) and other inflammatory markers are also inconsistent.[14–16] These studies, primarily based on observational data, are subject to confounding factors and reverse causality, limiting their ability to provide robust causal inferences.

Drug-targeted Mendelian randomization (MR) is an emerging research method that uses natural genetic variations to simulate randomized controlled trials, effectively avoiding confounding factors and reverse causality.[17] This allows for more accurate assessments of the causal effects of drugs on diseases or biomarkers.[18] Compared to traditional observational studies, MR provides stronger evidence for causal inference. In recent years, this method has been successfully applied to study causal relationships between various drugs and diseases, such as the potential effects of ACEIs on diabetes,[19] as well as drug repurposing studies targeting COVID-19-related proteins.[20]

This study employed the drug-targeted MR approach, utilizing large-scale genome-wide association studies (GWAS) and expression quantitative trait loci (eQTL) data to systematically assess the causal effects of antihypertensive and lipid-lowering drugs on key inflammatory cytokines. Our research not only confirms previous findings to a certain extent but also fills a gap in the existing literature regarding the regulation of inflammation by these drugs, offering new insights into personalized treatment strategies for patients with hypertension and dyslipidemia, with important clinical implications.

2. Methods

2.1. Data sources

2.1.1. Instrumental variable data sources. The instrumental variable (IV) data in this study were derived from multiple genome-wide association studies to analyze the causal relationship between antihypertensive and lipid-lowering drugs and inflammatory cytokines. In both exploratory and validation analyses, SNPs near drug target genes were selected and associated with systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C).

For the exploratory analysis, SBP data were derived from a GWAS meta-analysis involving 1028,980 individuals of European ancestry, with data contributed by the International Consortium for Blood Pressure, the UK Biobank (UKB), and the Million Veteran Program, excluding those currently on antihypertensive medications.[21] LDL-C data were sourced from the Global Lipids Genetic Consortium, consisting of 173,082 individuals, with those on lipid-lowering medications excluded[22] (Table 1).

For the validation analysis, SBP and LDL-C data were obtained from the UK Biobank, with sample sizes of 436,419 and 440,546 individuals, respectively.[23] All data were adjusted for gender, age, and body mass index.

Additionally, supplementary analyses used expression quantitative trait loci (eQTL) data from the Genotype-Tissue Expression (GTEx) project, which included 15,201 samples across 49 tissue types, to analyze tissue-specific gene expression levels of drug target genes.[24]

Table 1

Sources of exposure data.

Analysis type	Trait	Sample size	Ethnicity	Data source
Exploratory analysis	SBP	757,601	European	ICBP
	LDL-C	173,082	European	GLGC
Validation analysis	SBP	436,419	European	UKB
	LDL-C	440,546	European	UKB
Supplementary analysis	eQTL	31,684	European	GTEx

eQTL = Expression Quantitative Trait Loci, GLGC = Global Lipids Genetic Consortium, GTEx = genotype-tissue expression, ICBP = International Consortium for Blood Pressure, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, UKB = UK biobank.

Table 2

Sources of outcome data.

Subgroup	Inflammatory cytokines	Sample size
Pro-inflammatory cytokines	IL-1β, IL-6, TNF-α, IL-17	8293
Anti-inflammatory cytokines	IL-10	8293
Chemokines	MIP-1α, MIP-1β, IP10, MCP-1	8293
Acute phase protein	CRP	200,402
Interferons	IFN-γ	8293
Vascular endothelial growth factors	VEGF	8293

CRP = C-reactive protein, IFN-γ = interferon-gamma, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-1β = interleukin-1β, IL-6 = interleukin-6, IP10 = interferon gamma-induced protein 10 (CXCL10), MCP-1 = monocyte chemoattractant protein-1, MIP-1α = macrophage inflammatory protein-1α, MIP-1β = macrophage inflammatory protein-1β, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor.

2.1.2. Outcome variable data sources. The outcome data for inflammatory cytokines were obtained from previously published GWAS and related databases, including multiple pro-inflammatory and anti-inflammatory cytokines such as IL-1β, TNF-α, and CRP. These data were derived from GWAS projects and meta-analyses of aggregated data, all based on European ancestry populations, and were standardized to exclude confounding factors that might affect the results[25] (Table 2).

2.1.3. Positive control data sources. Previous studies have demonstrated the protective effects of antihypertensive and lipid-lowering drugs against coronary artery disease (CAD). Therefore, this study employed positive controls to assess the causal effects of these drugs on CAD through drug-targeted MR analyses. Data were obtained from the CARDIoGRAMplusC4D[26] GWAS, which included 88,192 cases and 162,544 controls, with participants predominantly of European ancestry. The average age of the case group was 61.5 years, while the control group had an average age of 55.8 years.

2.2. Study design

This study was conducted in accordance with international and national clinical guidelines, selecting 2 commonly used antihypertensive agents (ACEIs and angiotensin II receptor blockers [ARBs]) and 3 commonly used lipid-lowering agents (HMG-CoA reductase inhibitors, PCSK9 inhibitors, and Niemann-Pick C1-like 1 (NPC1L1) inhibitors; Table S1, Supplemental Digital Content, http://links.lww.com/MD/O473). To investigate the causal relationship between antihypertensive and lipid-lowering agents and inflammatory cytokines, stringent criteria were applied for the selection of IVs. This study was approved by the Ethics Committee of Shanghai Guanghua Hospital of Integrated Chinese and Western Medicine, and registered on ClinicalTrials.gov (NCT06622304).

Within the framework of drug-targeted MR, the inverse-variance weighting method (IVW) method was employed as the primary analytical approach. In addition, 5 other MR methods based on different model assumptions were used to estimate causal relationships between the drugs and inflammatory cytokines. Sensitivity analyses were performed using leave-one-out analyses, Cochran *Q* test, and MR-Egger intercept tests to assess the robustness of the results by identifying potential outliers and evaluating horizontal pleiotropy and heterogeneity. Furthermore, eQTL data were used to investigate the expression of drug target genes across various tissues to explore their influence on inflammatory cytokines (Fig. 1).

2.3. IV selection

In this study, we selected 2 classes of antihypertensive drugs (ACE inhibitors and ARBs) and 3 classes of lipid-lowering drugs (HMGCR inhibitors, PCSK9 inhibitors, and NPC1L1 inhibitors). Based on the target genes of these drugs and the nearby genetic variants, we identified IVs for MR analysis (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O473). All selected SNPs were located within or near the target genes, ensuring the strength and validity of the IVs.

2.3.1. Exploratory and validation analyses IV selection. The selection of IVs followed strict criteria:

a. Select SNPs located within or near the target gene (±300 kb).
b. Identify SNPs associated with SBP or LDL-C, with a selection threshold of $P < 1 \times 10^{-5}$.
c. From the initially selected SNPs, choose independent variants with a linkage disequilibrium coefficient (r^2) ≤ 0.1.
d. Calculate the *F*-statistic for each IV, and include SNPs with an *F* value >10 to avoid weak IV bias.
e. Conduct an MR Steiger directionality test to exclude SNPs with ambiguous causal direction.

2.3.2. Supplemental analysis IV selection. In the supplemental analysis, we utilized eQTL data from the GTEx V8 database to identify IVs representing gene expression of the drug targets in different tissues. Specific steps are as follows:

a. Select SNPs located within or near the drug target gene (±1 Mb).
b. Identify SNPs significantly associated with target gene expression in individual tissues, applying false discovery rate correction ($P < .05$).
c. From the selected SNPs, choose independent variants, ensuring a linkage disequilibrium coefficient (r^2) ≤ 0.1.
d. Calculate the *F*-statistic, selecting SNPs with an *F* value >10 to avoid weak IV bias, and confirm the causal direction using the MR Steiger test.

2.4. Causal analysis and statistical methods

This study employed integrative multi-omics data and IV analysis to evaluate the causal effects of antihypertensive and lipid-lowering drugs on inflammatory cytokines. IV data from various sources underwent quality control, including SNP selection to ensure consistency and reliability. The primary causal analysis method was the IVW approach, complemented by other MR methods such as MR-Egger and weighted median. Sensitivity analyses used the leave-one-out method, Cochran *Q* test, and MR-Egger intercept test to evaluate the robustness of the results. The leave-one-out analysis identified influential outliers, Cochran *Q* test assessed heterogeneity, and the MR-Egger intercept test evaluated potential pleiotropic bias.

Statistical analyses were performed using R software (version 4.0.3) with the packages "Mendelian Randomization," "TwoSampleMR," "MRPRESSO," and "MR.rap." The "mr leaveoneout" and "mr scatter plot" functions generated leave-one-out forest plots. Categorical outcomes were presented as odds ratios with 95% confidence intervals (CI), and continuous outcomes as effect sizes (β) with 95% CI. Statistical significance was set at $P < .05$.

3. Results

3.1. Causal analysis of antihypertensive drugs and inflammatory cytokines via drug-targeted MR

3.1.1. Selection of IVs for ACEIs and ARBs. IVs for ACEIs and ARBs were selected based on independent SNPs located near the corresponding drug target genes. The selection criteria included a significant association with SBP and passing the weak instrument test (*F*-statistic > 10). For ACEIs, 4 SNPs were identified as IVs, while for ARBs, 7 SNPs were selected. The *F*-statistics for the IVs were 41.12 for ACEIs and 23.29 for ARBs, indicating strong instrument strength. Positive control analysis showed that the association between antihypertensive drugs and CAD was consistent with previous research findings, further supporting the validity of the IVs. All IVs passed the validity checks, ensuring robustness and reliability of the results (Table S3, Supplemental Digital Content, http://links.lww.com/MD/O473).

3.1.2. Positive control analysis. In the positive control analysis, the IVs for both ACEIs and ARBs demonstrated a significant inverse relationship with the risk of CAD, suggesting that both drug classes may have protective effects in reducing CAD risk.

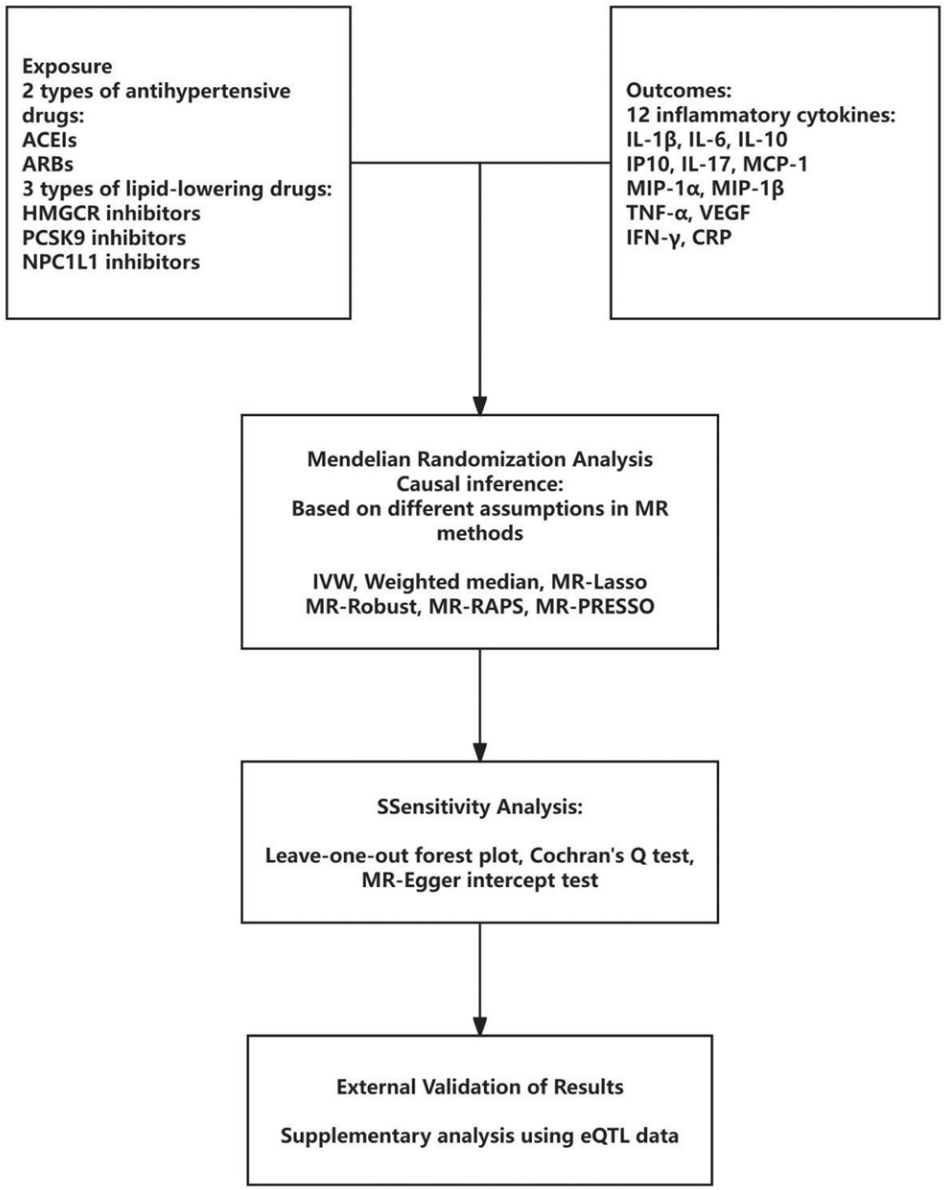

Figure 1. Study design flow chart.

The causal effect estimate for ACEIs was 0.961 ($P = .026$), and for ARBs, the estimate was 0.931 ($P = .002$), consistent with previous clinical research. These findings further validate the reliability of the IVs (Table S4, Supplemental Digital Content, http://links.lww.com/MD/O473).

3.1.3. Causal effect estimates of ACEIs on inflammatory cytokines. ACEIs were found to have significant causal relationships with 4 inflammatory cytokines (IL-1β, TNF-α, CRP, IL-10), while the associations with other cytokines (IL-6, IL-17, interferon gamma-induced protein 10 (CXCL10) [IP10], MCP-1, MIP-1α, MIP-1β, IFN-γ, VEGF) were not statistically significant. Specifically, the causal effect estimate of ACEIs on reducing IL-1β levels was −0.116 ($P = .013$), indicating that lowering SBP by 1 mm Hg is associated with a 0.116 SD decrease in IL-1β. Similarly, the causal estimate for TNF-α was −0.198 ($P = .00192$), showing that ACEIs significantly reduce TNF-α levels by 0.198 SD per 1 mm Hg reduction in SBP. The causal effect on CRP was −0.022 ($P = .038$), while the effect on IL-10 was positive but marginally significant at 0.086 ($P = .033$). However, ACEIs did not show a statistically significant association with other inflammatory cytokines ($P > .05$). The results from other MR methods, based on different model assumptions, were consistent in both direction and magnitude with the primary IVW results, further confirming the robustness and reliability of the findings (Table 3).

3.1.4. Causal effect estimation of ARBs on inflammatory cytokines. No statistically significant causal effect was found between ARBs and inflammatory cytokines (IL-1β, IL-6, IL-10, IP10, IL-17, MCP-1, MIP-1α, MIP-1β, TNF-α, VEGF, IFN-γ, CRP). Other MR methods based on different model assumptions produced consistent results with IVW in both direction and effect size, verifying the reliability and robustness of the findings (Table 4).

3.1.5. Sensitivity analysis. The study conducted sensitivity analyses for traits with statistically significant causal relationships using the leave-one-out method, confirming that no SNPs could alter the causal effect estimates and further demonstrating the robustness of the MR analysis results(Fig. 2A–D). Cochran

Table 3

Causal effect of antihypertensive drug ACEIs on inflammatory cytokines.

Expose	Denouement	MR method	β (95%CI)	*P*
ACEIs	IL-1β	IVW	−0.116 (−0.208, −0.025)	.013
		Weighted median	−0.132 (−0.241, −0.023)	.017
		MR-Lasso	−0.116 (−0.208, −0.025)	.013
		MR-Robust	−0.116 (−0.191, −0.042)	.002
		MR-RAPS	−0.118 (−0.217, −0.018)	.021
		MR-PRESSO	−0.116 (−0.183, −0.050)	.042
ACEIs	IL-6	IVW	0.007 (−0.070, 0.084)	.855
		Weighted median	0.003 (−0.085, 0.090)	.951
		MR-Lasso	0.007 (−0.070, 0.084)	.855
		MR-Robust	0.007 (−0.040, 0.054)	.778
		MR-RAPS	0.007 (−0.075, 0.089)	.864
		MR-PRESSO	0.007 (−0.024, 0.039)	.688
ACEIs	IL-10	IVW	0.086 (0.007, 0.165)	.003
		Weighted median	0.088 (−0.002, 0.179)	.056
		MR-Lasso	0.086 (0.007, 0.165)	.033
		MR-Robust	0.087 (0.003, 0.171)	.042
		MR-RAPS	0.086 (0.000, 0.172)	.049
		MR-PRESSO	0.086 (0.076, 0.096)	.001
ACEIs	IL-17	IVW	−0.051 (−0.130, 0.027)	.201
		Weighted median	−0.043 (−0.136, 0.050)	.364
		MR-Lasso	−0.051 (−0.130, 0.027)	.201
		MR-Robust	−0.051 (−0.108, 0.007)	.085
		MR-RAPS	−0.052 (−0.136, 0.032)	.333
		MR-PRESSO	−0.051 (−0.126, 0.023)	.267
ACEIs	IP10	IVW	−0.056 (−0.171, 0.059)	.344
		Weighted median	−0.083 (−0.214, 0.049)	.219
		MR-Lasso	−0.056 (−0.171, 0.059)	.344
		MR-Robust	−0.129 (−0.192, 0.067)	.322
		MR-RAPS	−0.056 (−0.171, 0.067)	.370
		MR-PRESSO	−0.056 (−0.136, 0.024)	.266
ACEIs	MIP-1α	IVW	−0.036 (−0.153, 0.081)	.548
		Weighted median	−0.037 (−0.168, 0.095)	.584
		MR-Lasso	−0.036 (−0.153, 0.081)	.548
		MR-Robust	−0.036 (−0.144, 0.072)	.511
		MR-RAPS	−0.036 (−0.161, 0.089)	.573
		MR-PRESSO	−0.036 (−0.076, 0.004)	.177
ACEIs	MIP-1β	IVW	−0.040 (−0.116, 0.037)	.310
		Weighted median	−0.020 (−0.106, 0.067)	.654
		MR-Lasso	−0.040 (−0.116, 0.037)	.310
		MR-Robust	−0.039 (−0.088, 0.010)	.115
		MR-RAPS	−0.040 (−0.121, 0.042)	.340
		MR-PRESSO	−0.040 (−0.075, −0.004)	.117
ACEIs	TNF-α	IVW	−0.188 (−0.307, −0.069)	1.92E−03
		Weighted median	−0.190 (−0.328, −0.052)	6.97E−03
		MR-Lasso	−0.188 (−0.307, −0.069)	1.92E−03
		MR-Robust	−0.193 (−0.540, 0.155)	2.77E−01
		MR-RAPS	−0.188 (−0.319, −0.058)	4.56E−03
		MR-PRESSO	−0.188 (−0.243, −0.133)	6.79E−03
ACEIs	VEGF	IVW	0.045 (−0.037, 0.128)	.282
		Weighted median	0.042 (−0.054, 0.138)	.389
		MR-Lasso	0.045 (−0.037, 0.128)	.282
		MR-Robust	0.039 (−0.200, 0.279)	.747
		MR-RAPS	0.046 (−0.042, 0.134)	.308
		MR-PRESSO	0.045 (−0.020, 0.110)	.267
ACEIs	IFN-γ	IVW	0.026 (−0.054, 0.105)	.525
		Weighted median	0.031 (−0.063, 0.124)	.517
		MR-Lasso	0.026 (−0.054, 0.105)	.525
		MR-Robust	0.026 (−0.024, 0.077)	.312
		MR-RAPS	0.026 (−0.058, 0.110)	.542
		MR-PRESSO	0.026 (−0.043, 0.094)	.515
ACEIs	CRP	IVW	−0.022 (−0.042, −0.001)	.038
		Weighted median	−0.021 (−0.044, 0.001)	.067
		MR-Lasso	−0.022 (−0.042, −0.001)	.038
		MR-Robust	−0.022 (−0.035, −0.009)	.001
		MR-RAPS	−0.022 (−0.044, 0.000)	.052

ACEIs = angiotensin-converting enzyme inhibitors, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-1P = interleukin-1p, IL-6 = interleukin-6, IP10 = interferon gamma-induced protein 10 (CXCL10), IVW = inverse-variance weighting method, MR-Robust = MR-IVW method based on robust regression, MR-RAPS = Contour score method for MR Robust adjustment, MR-Lasso = MR method based on Lasso algorithm, MR-PRESSO = MR multi-effect residual and heterogeneity detection, WME = weighted median method.

Table 4

Causal effect of antihypertensive drug ARBs on inflammatory cytokines.

Expose	Denouement	MR method	β (95%CI)	*P*
ARBs	IL-1β	IVW	0.040 (−0.076, 0.156)	.501
		Weighted median	0.048 (−0.098, 0.195)	.518
		MR-Lasso	0.040 (−0.076, 0.156)	.501
		MR-Robust	0.044 (−0.066, 0.153)	.435
		MR-RAPS	0.041 (−0.086, 0.168)	.526
		MR-PRESSO	0.040 (−0.059, 0.139)	.473
ARBs	IL-6	IVW	−0.006 (−0.104, 0.092)	.901
		Weighted median	0.007 (−0.120, 0.134)	.913
		MR-Lasso	−0.006 (−0.104, 0.092)	.901
		MR-Robust	−0.003 (−0.096, 0.090)	.951
		MR-RAPS	−0.012 (−0.129, 0.105)	.841
		MR-PRESSO	−0.006 (−0.101, 0.089)	.904
ARBs	IL-10	IVW	−0.031 (−0.144, 0.082)	.590
		Weighted median	−0.056 (−0.184, 0.071)	.389
		MR-Lasso	−0.031 (−0.144, 0.082)	.590
		MR-Robust	−0.033 (−0.135, 0.069)	.523
		MR-RAPS	0.048 (−0.238, 0.143)	.625
		MR-PRESSO	−0.031 (−0.144, 0.082)	.619
ARBs	IL-17	IVW	−0.076 (−0.177, 0.025)	.139
		Weighted median	−0.092 (−0.217, 0.034)	.152
		MR-Lasso	−0.076 (−0.177, 0.025)	.139
		MR-Robust	−0.075 (−0.171, 0.020)	.123
		MR-RAPS	−0.078 (−0.189, 0.032)	.165
		MR-PRESSO	−0.076 (−0.169, 0.016)	.182
ARBs	IP10	IVW	0.026 (−0.125, 0.177)	.736
		Weighted median	0.095 (−0.091, 0.280)	.317
		MR-Lasso	0.026 (−0.125, 0.177)	.736
		MR-Robust	0.034 (−0.120, 0.189)	.663
		MR-RAPS	0.036 (−0.121, 0.193)	.653
		MR-PRESSO	0.026 (−0.125, 0.177)	.753
ARBs	MCP-1	IVW	0.010 (−0.087, 0.108)	.833
		Weighted median	0.014 (−0.101, 0.128)	.818
		MR-Lasso	0.010 (−0.087, 0.108)	.833
		MR-Robust	0.010 (−0.056, 0.077)	.757
		MR-RAPS	0.011 (−0.097, 0.118)	.848
		MR-PRESSO	0.010 (−0.010, 0.031)	.381
ARBs	MIP-1α	IVW	0.029 (−0.119, 0.177)	.701
		Weighted median	0.078 (−0.109, 0.264)	.415
		MR-Lasso	0.029 (−0.119, 0.177)	.701
		MR-Robust	0.033 (−0.169, 0.236)	.746
		MR-RAPS	0.030 (−0.132, 0.191)	.718
		MR-PRESSO	0.029 (−0.089, 0.147)	.653
ARBs	MIP-1β	IVW	0.051 (−0.056, 0.157)	.350
		Weighted median	−0.005 (−0.138, 0.129)	.947
		MR-Lasso	0.051 (−0.056, 0.157)	.350
		MR-Robust	0.050 (−0.030, 0.130)	.221
		MR-RAPS	0.052 (−0.064, 0.168)	.382
		MR-PRESSO	0.051 (−0.037, 0.138)	.341
ARBs	TNF-α	IVW	0.001 (−0.148, 0.151)	.984
		Weighted median	−0.017 (−0.211, 0.177)	.863
		MR-Lasso	0.001 (−0.148, 0.151)	.984
		MR-Robust	−0.005 (−0.204, 0.194)	.960
		MR-RAPS	0.002 (−0.160, 0.163)	.985
		MR-PRESSO	0.001 (−0.132, 0.135)	.984
ARBs	VEGF	IVW	−0.049 (−0.176, 0.079)	.455
		Weighted median	−0.068 (−0.205, 0.069)	.332
		MR-Lasso	−0.049 (−0.176, 0.079)	.455
		MR-Robust	−0.049 (−0.173, 0.075)	.436
		MR-RAPS	−0.064 (−0.198, 0.070)	.349
		MR-PRESSO	−0.049 (−0.176, 0.079)	.496
ARBs	IFN-γ	IVW	−0.007 (−0.138, 0.124)	.913
		Weighted median	0.024 (−0.115, 0.163)	.732
		MR-Lasso	−0.007 (−0.138, 0.124)	.913
		MR-Robust	−0.004 (−0.132, 0.124)	.950
		MR-RAPS	−0.072 (−0.281, 0.136)	.497
		MR-PRESSO	−0.007 (−0.138, 0.124)	.918
ARBs	CRP	IVW	−0.023 (−0.049, 0.003)	.080
		Weighted median	−0.027 (−0.057, 0.003)	.082
		MR-Lasso	−0.023 (−0.049, 0.003)	.080
		MR-Robust	−0.024 (−0.049, 0.002)	.066
		MR-RAPS	−0.024 (−0.051, 0.002)	.068
		MR-PRESSO	−0.023 (−0.049, 0.003)	.178

ARBs = Angiotensin II receptor blockers, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-6 = interleukin-6, IL-I = interleukin-1, IP10 = interferon gamma-induced protein 10 (CXCL10), IVW = inverse-variance weighting method, MR-Robust = MR-IVW method based on robust regression, MR-Lasso = MR method based on lasso algorithm, MR-PRESSO = MR multi-effect residual and heterogeneity detection, MR-RAPS = Contour score method of Robust adjustment, WME = weighted median method.

Q statistic showed a *P*-value >.05, indicating no significant heterogeneity among the IVs. Similarly, the MR-Egger intercept had a *P*-value above .05, suggesting that horizontal pleiotropy did not introduce bias into the results (Table 5).

3.1.6. Validation analysis. To ensure the robustness of the results, SBP data from the UK Biobank database were utilized for IV validation of antihypertensive drugs. Three SNPs were selected as valid IVs for ACEIs, with each SNP having an *F*-statistic exceeding 10 and an overall *F*-statistic of 26.09, indicating no evidence of weak instrument bias (Table S5, Supplemental Digital Content, http://links.lww.com/MD/O473).

In this section, MR analysis was performed to assess the causal effects of ACEIs on inflammatory cytokines, including IL-1β, IL-10, TNF-α, and CRP. The results demonstrated significant causal associations between ACEIs and reductions in IL-1β, TNF-α, and CRP levels, with causal estimates of −0.194 (*P* = .002) for IL-1β, −3.037 (*P* = .000189) for TNF-α, and −0.918 (*P* = .003) for CRP. The consistency in both direction and effect size across multiple MR methods, including IVW, MR-Egger, and weighted median, reinforced the reliability of these findings. However, no statistically significant causal effect was observed for ACEIs on IL-10, with an estimate of 0.485 (*P* = .371), and no significant causal relationships were identified for other inflammatory cytokines (Table S6, Supplemental Digital Content, http://links.lww.com/MD/O473).

3.1.7. Supplementary analysis. To further investigate the potential influence of drug target gene expression on inflammatory cytokines, eQTL data from the GTEx V8 database were employed. This analysis evaluated the relationship between the expression levels of target genes for ACEIs and ARBs in various tissues and their impact on inflammatory cytokines. The findings revealed that reduced expression of the ACE gene in adipose tissue and liver was significantly associated with lower levels of IL-1β and CRP, with consistent effects observed across multiple tissues (Table S7, Supplemental Digital Content, http://links.lww.com/MD/O473).

Additionally, the supplementary analysis indicated that the expression of the ARBs target gene AGTR1 in vascular smooth muscle tissue was positively associated with several pro-inflammatory cytokines, suggesting a potential tissue-specific regulatory role of ARBs in inflammation. These results, derived from eQTL data, provide further insights into the mechanisms by which drug target gene expression in different tissues influences inflammatory cytokine levels, offering valuable direction for future research.

3.2. Causal analysis of lipid-lowering drugs and inflammatory cytokines via drug-targeted MR

3.2.1. IVs for lipid-lowering drugs. Following strict IV selection criteria, independent SNPs associated with LDL-C located within or near the drug target genes were selected as IVs for HMGCR inhibitors, NPC1L1 inhibitors, and PCSK9 inhibitors. A total of 11 SNPs were selected as IVs for HMGCR inhibitors, 3 SNPs for NPC1L1 inhibitors, and 19 SNPs for PCSK9 inhibitors. The *F*-statistics for each IV were all >10, with an overall *F*-statistic of 144.68 for HMGCR inhibitors, 58.33 for NPC1L1 inhibitors, and 193.60 for PCSK9 inhibitors, indicating no evidence of weak instrument bias (Table S8, Supplemental Digital Content, http://links.lww.com/MD/O473).

3.2.2. Positive control analysis. Through MR analysis, it was found that HMGCR inhibitors, NPC1L1 inhibitors, and PCSK9 inhibitors were all significantly negatively associated with CAD. The causal effect estimate for HMGCR inhibitors on CAD was 0.854 (*P* = .033), indicating a relationship between HMGCR inhibitors and a lower risk of CAD. NPC1L1 inhibitors had a causal effect estimate of 0.460 (*P* = 3.19E−08), which also showed an association with lower CAD risk. PCSK9 inhibitors had a causal effect estimate of 0.694 (*P* = 1.16E−15), similarly showing a significant association with a lower risk of CAD. The results are broadly consistent with the direction and magnitude of effects seen in clinical trials, further validating the effectiveness of these IVs (Table S9, Supplemental Digital Content, http://links.lww.com/MD/O473).

3.2.3. Causal effects of HMGCR inhibitors on inflammatory cytokines. HMGCR inhibitors showed significant causal relationships with IP10, MCP-1, MIP-1β, TNF-α, and IFN-γ. Based on IVW results, for every 1 SD reduction in LDL-C levels, HMGCR inhibitors were associated with an increase in IP10 levels by 0.335 SD (*P* = .041), a decrease in MCP-1 levels by 0.298 SD (*P* = 6.26E−03), an increase in MIP-1β levels by 0.302 SD (*P* = .032), a decrease in TNF-α levels by 0.563 SD (*P* = 8.35E−04), and a decrease in IFN-γ levels by 0.234 SD (*P* = .039). No significant causal relationships were found for other cytokines. Results from different models were consistent, confirming the robustness of the findings (Table 6).

3.2.4. Causal effect estimation of NPC1L1 inhibitors on inflammatory cytokines. The NPC1L1 inhibitors showed no statistically significant causal effects on inflammatory cytokines (IL-1β, IL-6, IL-10, IP10, IL-17, MCP-1, MIP-1α, MIP-1β, TNF-α, VEGF, IFN-γ, CRP; Table 7). Various other MR methods based on different model assumptions yielded causal estimates consistent in direction and magnitude with the IVW method, further confirming the robustness and reliability of the results.

3.2.5. Causal estimates of PCSK9 inhibitors on inflammatory cytokines. A statistically significant causal relationship was identified between PCSK9 inhibitors and the inflammatory cytokines IL-1β and IL-6. IVW analysis revealed that PCSK9 inhibitors were associated with a reduction in IL-1β levels (estimate: −0.255, *P* = .017) and IL-6 levels (estimate: −0.271, *P* = .003). These results were consistent across other MR methods, reinforcing the robustness and reliability of the findings (Table 8).

3.2.6. Sensitivity analysis. For causal relationships with statistical significance, sensitivity analysis was conducted using the leave-one-out method. The results showed no SNPs that significantly altered the causal effect estimates (Fig. 3A–G), further confirming the robustness of the MR findings. The *P*-values for Cochran *Q* statistic were all >0.05, indicating no significant heterogeneity among the included IVs. Similarly, the *P*-values for the MR-Egger intercept were >.05, suggesting that horizontal pleiotropy did not bias the causal estimates (Table 9).

3.2.7. Validation analysis. To ensure robustness of the findings, LDL-C data from the UK Biobank was utilized for IV validation of lipid-lowering agents. A total of 46 IVs were identified for HMGCR inhibitors and 46 for PCSK9 inhibitors, with *F*-statistics for each variable exceeding 10. The overall *F*-statistics for HMGCR inhibitors and PCSK9 inhibitors were 112.82 and 132.21, respectively, indicating no evidence of weak instrument bias (Table S10, Supplemental Digital Content, http://links.lww.com/MD/O473).

In exploratory analyses, the causal associations between HMGCR inhibitors and inflammatory cytokines MCP-1, MIP-1β, TNF-α, and IFN-γ remained statistically significant. Specifically, the causal effect estimates were −0.382 for MCP-1 (*P* = .00234), −0.302 for MIP-1β (*P* = .017), −0.666 for TNF-α (*P* = 6.13E−05), and −0.351 for IFN-γ (*P* = .00448). However, in validation analyses, the association between HMGCR inhibitors and IP10 was no longer significant (*P* = .181; Table S11, Supplemental Digital Content, http://links.lww.com/MD/O473).

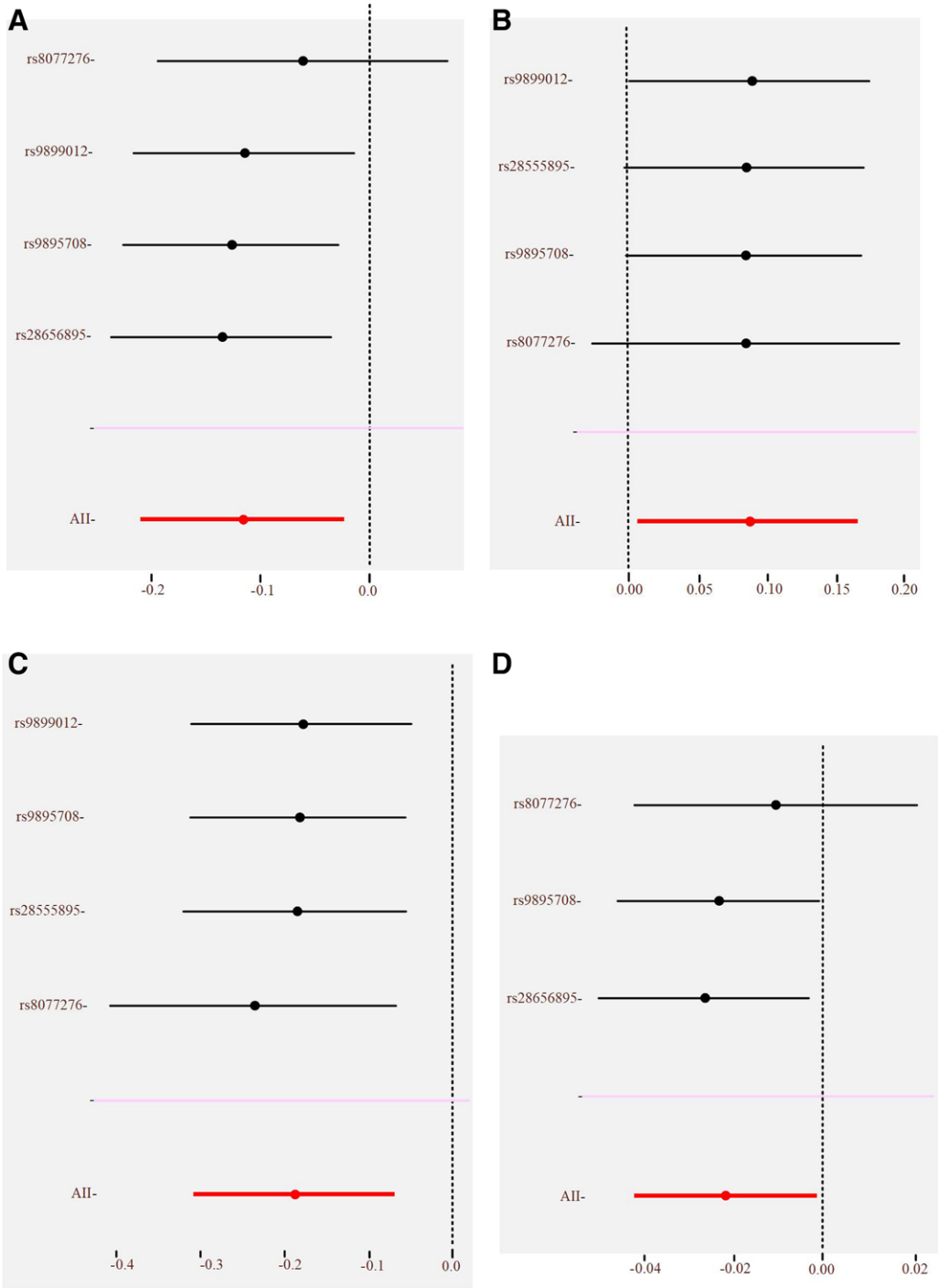

Figure 2. Leave-one-out forest plot for the causal effect of ACEIs on CRP. (A) Leave-one-out analysis of ACEIs on IL-1β; (B) Leave-one-out analysis of ACEIs on IL-10; (C) Leave-one-out analysis of ACEIs on TNF-α; (D) Leave-one-out analysis of ACEIs on CR. Note: The leave-one-out analysis was conducted for the ACEIs to assess their causal effect on various inflammatory cytokines. The forest plots show the impact of removing each SNP from the analysis and its influence on the causal effect estimates. Each point represents the causal effect when excluding a specific SNP, while the red dot represents the combined estimate for all SNPs included. The x-axis indicates the effect size, with a 95% confidence interval, for each cytokine: IL-1β, IL-10, TNF-α, and CRP. ACEIs = angiotensin-converting enzyme inhibitors, CRP = C-reactive protein, SNP = single nucleotide polymorphism.

The causal relationships between PCSK9 inhibitors and the inflammatory cytokines IL-1β and IL-6 were also statistically significant. In exploratory analyses, the causal effect estimate of PCSK9 inhibitors on IL-1β was −0.303 (P = .004), and on IL-6 was −0.231 (P = .008). Other MR methods confirmed the reliability and consistency of the results (Table S12, Supplemental Digital Content, http://links.lww.com/MD/O473).

3.2.8. Supplemental analysis. The IVs for HMGCR and PCSK9 inhibitors were selected from GTEx V8 data. A total of 12 SNPs were selected for HMGCR inhibitors and 30 SNPs for PCSK9 inhibitors, with F-statistics all >10, indicating no bias in the IVs. Reduced HMGCR gene expression was significantly associated with reductions in MIP-1β, TNF-α, and IFN-γ, with effect estimates of −0.127 (P = .011), −0.190 (P = .014), and −0.190 (P = .014), respectively (Table S13, Supplemental Digital

Table 5

Heterogeneity and gene pleiotropy of antihypertensive drugs.

		MR-Egger		Heterogeneity test		
Expose	**Denouement**	**Intercepts (95%CI)**	***P***	***Q***	**df**	***P***
ARBs	IFN-γ	0.136 (−0.138, 0.410)	.330	2.255	4	.689
	CRP	0.000 (−0.070, 0.071)	.994	1.049	2	.592
	IL-1β	−0.064 (−0.309, 0.180)	.606	2.894	4	.576
	IL-6	0.101 (−0.105, 0.307)	.338	3.736	4	.443
	IL-10	0.076 (−0.188, 0.340)	.574	4.971	4	.290
	IL-17	0.066 (−0.147, 0.279)	.544	3.361	4	.499
	IP10	−0.267 (−0.573, 0.038)	.086	4.323	4	.364
	MCP-1	0.036 (−0.169, 0.242)	.728	0.183	4	.996
	MIP-1α	0.089 (−0.222, 0.399)	.575	2.519	4	.641
	MIP-1β	0.070 (−0.175, 0.316)	.574	2.056	3	.561
	IL-1β	−0.064 (−0.309, 0.180)	.606	2.894	4	.576
	TNF-α	0.077 (−0.233, 0.387)	.627	3.192	4	.526
	VEGF	0.213 (−0.009, 0.436)	.061	5.813	4	.214
ACEIs	IFN-γ	0.099 (−0.201, 0.399)	.519	6.664	4	.155
	CRP	−0.021 (−0.171, 0.128)	.780	3.487	3	.322
	IL-1β	−0.041 (−0.383, 0.301)	.814	3.627	4	.459
	IL-6	0.062 (−0.203, 0.328)	.645	0.535	4	.970
	IL-10	−0.168 (−0.441, 0.105)	.227	2.179	4	.703
	IL-17	−0.159 (−0.431, 0.114)	.254	2.052	4	.726
	IP10	−0.088 (−0.481, 0.305)	.660	1.248	4	.870
	MCP-1	−0.123 (−0.387, 0.141)	.361	2.992	4	.559
	MIP-1α	−0.263 (−0.664, 0.138)	.199	2.116	4	.714
	MIP-1β	0.049 (−0.215, 0.313)	.714	1.015	4	.908
	TNF-α	−0.029 (−0.434, 0.376)	.890	0.766	4	.943
	VEGF	−0.198 (−0.482, 0.087)	.173	2.620	4	.623

ARBs = angiotensin II receptor blockers, CRP = C-reactive protein, IFN-γ = interferon-gamma, IL-1 = interleukin-1, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-6 = interleukin-6, IP10 = interferon gamma-induced protein 10 (CXCL10), MCP-1 = monocyte chemoattractant protein-I, MIP-1α = macrophage inflammatory protein-1α, MIP-1β = macrophage inflammatory protein-1β, TNF = tumor necrosis factor.

Content, http://links.lww.com/MD/O473). Reduced PCSK9 gene expression was significantly associated with reduced IL-1β levels, with an effect estimate of −0.174 (P = .026; Table S14, Supplemental Digital Content, http://links.lww.com/MD/O473).

4. Discussion

The inflammatory response is a crucial mechanism in the body's immune defense. When tissues are damaged by bacterial or viral infections, or physical or chemical stimuli, the body initiates an inflammatory response to repair the damage and protect itself. Thus, inflammation serves as a defense mechanism against external stimuli. A normal inflammatory response aids in tissue repair and reflects the proper function of the immune system, which is beneficial to human health. However, when the immune system is excessively activated, it leads to the release of large amounts of inflammatory cytokines, which, in severe cases, can progress to multiple organ dysfunction syndrome. For elderly individuals with underlying chronic diseases, excessive inflammation is particularly dangerous and is often the main cause of worsening conditions and even death.

Hypertension and dyslipidemia, both common chronic conditions in the elderly, are closely associated with chronic inflammation. Additionally, the use of antihypertensive and lipid-lowering drugs may influence the inflammatory response. Therefore, for patients with hypertension and dyslipidemia, the rational selection of these medications not only helps manage the underlying disease but also effectively mitigates the inflammatory response, preventing and controlling excessive inflammation. Targeting key cytokines involved in the inflammatory process and reducing or inhibiting their overexpression can help prevent multi-organ damage caused by inflammation. Hence, evaluating the relationship between commonly used antihypertensive and lipid-lowering drugs and inflammatory cytokines is of great importance for high-risk individuals with chronic diseases.

This study utilized large-scale multi-omics association data and applied the drug-targeted MR method to systematically explore the causal relationship between antihypertensive and lipid-lowering drugs and key inflammatory cytokines. The results showed that ACE inhibitors (ACEIs) were causally linked to reduced levels of IL-1β, TNF-α, and CRP, with ACE gene expression levels in multiple tissues also showing a causal link to reduced TNF-α and CRP levels. Additionally, HMGCR inhibitors were causally associated with lower levels of MCP-1, MIP-1β, TNF-α, and IFN-γ, while decreased HMGCR gene expression in skeletal muscle was also linked to reductions in MIP-1β, TNF-α, and IFN-γ levels. PCSK9 inhibitors were causally linked to lower levels of IL-1β and IL-6, with decreased PCSK9 gene expression in whole blood being associated with reduced IL-1β levels. The consistency of results across different MR models in terms of direction and effect size supports the robustness of the findings. Tests for heterogeneity and pleiotropy indicated no significant heterogeneity or horizontal pleiotropy in the IVs.

Although existing preclinical and clinical studies have suggested associations between antihypertensive and lipid-lowering drugs and inflammatory cytokines, this study further clarifies the causal relationships between ACEIs, HMGCR inhibitors, and PCSK9 inhibitors and multiple inflammatory cytokines through MR analysis. These findings not only confirm the anti-inflammatory effects of these drugs but also provide scientific evidence for their rational selection, offering new avenues for future drug development and repurposing.

4.1. Causal relationship between antihypertensive drugs and inflammatory cytokines

The results of this study suggest that ACEIs may exert protective effects on the inflammatory response by reducing the levels of pro-inflammatory cytokines such as IL-1β, TNF-α, and CRP. Furthermore, the reduction in ACE gene expression

Table 6

Estimation of causal effects of lipid-lowering HMGCR inhibitors on inflammatory cytokines.

Expose	Denouement	MR method	β (95%CI)	*P*
HMGCR inhibitors	IL-1β	IVW	−0.121 (−0.380, 0.139)	.362
		Weighted median	−0.208 (−0.528, 0.112)	.202
		MR-Lasso	−0.121 (−0.380, 0.139)	.362
		MR-Robust	−0.144 (−0.352, 0.065)	.177
		MR-RAPS	−0.142 (−0.411, 0.126)	.299
		MR-PRESSO	−0.121 (−0.362, 0.121)	.360
HMGCR inhibitors	IL-6	IVW	0.034 (−0.180, 0.249)	.754
		Weighted median	0.118 (−0.144, 0.380)	.376
		MR-Lasso	0.034 (−0.180, 0.249)	.754
		MR-Robust	0.036 (−0.121, 0.194)	.651
		MR-RAPS	0.034 (−0.188, 0.257)	.762
		MR-PRESSO	0.034 (−0.074, 0.143)	.551
HMGCR inhibitors	IL-10	IVW	−0.081 (−0.301, 0.140)	.474
		Weighted median	−0.089 (−0.357, 0.179)	.515
		MR-Lasso	−0.081 (−0.301, 0.140)	.474
		MR-Robust	−0.080 (−0.205, 0.045)	.208
		MR-RAPS	−0.081 (−0.309, 0.148)	.489
		MR-PRESSO	−0.081 (−0.215, 0.054)	.274
HMGCR inhibitors	IL-17	IVW	−0.193 (−0.413, 0.027)	.085
		Weighted median	−0.213 (−0.480, 0.055)	.119
		MR-Lasso	−0.193 (−0.413, 0.027)	.085
		MR-Robust	−0.194 (−0.336, −0.052)	.007
		MR-RAPS	−0.194 (−0.422, 0.035)	.097
		MR-PRESSO	−0.193 (−0.327, −0.060)	.022
HMGCR inhibitors	IP10	IVW	0.335 (0.014, 0.656)	.041
		Weighted median	0.262 (−0.142, 0.665)	.204
		MR-Lasso	0.335 (0.014, 0.656)	.041
		MR-Robust	0.336 (0.114, 0.557)	.003
		MR-RAPS	0.350 (0.019, 0.681)	.038
		MR-PRESSO	0.335 (0.014, 0.656)	.075
HMGCR inhibitors	MCP-1	IVW	−0.298 (−0.512, −0.084)	6.26E−03
		Weighted median	−0.247 (−0.510, 0.016)	.066
		MR-Lasso	−0.298 (−0.512, −0.084)	6.26E−03
		MR-Robust	−0.302 (−0.419, −0.184)	4.85E−07
		MR-RAPS	−0.304 (−0.526, −0.082)	7.27E−03
		MR-PRESSO	−0.298 (−0.475, −0.121)	.011
HMGCR inhibitors	MIP-1α	IVW	0.309 (−0.097, 0.715)	.136
		Weighted median	0.267 (−0.158, 0.691)	.218
		MR-Lasso	0.309 (−0.097, 0.715)	.136
		MR-Robust	0.291 (−0.043, 0.625)	.087
		MR-RAPS	0.281 (−0.133, 0.695)	.183
		MR-PRESSO	0.309 (−0.097, 0.715)	.174
HMGCR inhibitors	MIP-1β	IVW	−0.302 (−0.577, −0.026)	.032
		Weighted median	−0.226 (−0.494, 0.043)	.100
		MR-Lasso	−0.302 (−0.577, −0.026)	.032
		MR-Robust	−0.281 (−0.443, −0.119)	.001
		MR-RAPS	−0.295 (−0.573, −0.017)	.037
		MR-PRESSO	−0.302 (−0.577, −0.026)	.064
HMGCR inhibitors	TNF-α	IVW	−0.563 (−0.893, −0.233)	8.35E−04
		Weighted median	−0.570 (−0.979, −0.162)	6.24E−03
		MR-Lasso	−0.563 (−0.893, −0.233)	8.35E−04
		MR-Robust	−0.568 (−0.786, −0.351)	2.89E−07
		MR-RAPS	−0.565 (−0.908, −0.221)	1.28E−03
		MR-PRESSO	−0.563 (−0.791, −0.334)	1.21E−03
HMGCR inhibitors	VEGF	IVW	0.070 (−0.232, 0.371)	.649
		Weighted median	0.048 (−0.243, 0.340)	.745
		MR-Lasso	0.061 (−0.191, 0.313)	.633
		MR-Robust	0.071 (−0.108, 0.250)	.436
		MR-RAPS	0.064 (−0.248, 0.375)	.689
		MR-PRESSO	0.070 (−0.232, 0.371)	.662
HMGCR inhibitors	IFN-γ	IVW	−0.234 (−0.455, −0.012)	.039
		Weighted median	−0.212 (−0.478, 0.054)	.118
		MR-Lasso	−0.234 (−0.455, −0.012)	.039
		MR-Robust	−0.233 (−0.361, −0.104)	3.83E−04
		MR-RAPS	−0.234 (−0.464, −0.003)	.047
		MR-PRESSO	−0.234 (−0.328, −0.139)	1.28E−03
HMGCR inhibitors	CRP	IVW	−0.003 (−0.053, 0.048)	.913
		Weighted median	−0.012 (−0.077, 0.054)	.724
		MR-Lasso	−0.003 (−0.053, 0.048)	.913
		MR-Robust	−0.003 (−0.044, 0.037)	.875
		MR-RAPS	−0.003 (−0.055, 0.049)	.916
		MR-PRESSO	−0.003 (−0.053, 0.048)	.913

HMGCR inhibitor = 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-1P = interleukin-1p, IL-6 = interleukin-6, IP10 = interferon gamma-induced protein 10 (CXCL10), IVW = inverse-variance weighting method, MR-Robust = MR-IVW method based on robust regression, MR-RAPS = Contour score method for MR Robust adjustment, MR-Lasso = MR method based on Lasso algorithm, MR-PRESSO = MR-multi-effect residual and heterogeneity detection, WME = weighted median method.

Table 7

Estimation of causal effects of lipid-lowering NPC1L1 inhibitors on inflammatory cytokines.

Expose	Denouement	MR method	β (95%CI)	*P*
NPCIL1 inhibitors	IL-1β	IVW	0.435 (−0.383, 1.253)	.297
		Weighted median	0.552 (−0.334, 1.438)	.222
		MR-Lasso	0.435 (−0.383, 1.253)	.297
		MR-Robust	0.443 (−0.121, 1.008)	.123
		MR-RAPS	0.436 (−0.424, 1.296)	.320
NPCIL1 inhibitors	IL-6	IVW	0.129 (−0.417, 0.674)	.644
		Weighted median	0.156 (−0.439, 0.752)	.607
		MR-Lasso	0.129 (−0.417, 0.674)	.644
		MR-Robust	0.129 (−0.103, 0.361)	.276
		MR-RAPS	0.129 (−0.443, 0.702)	.658
NPCIL1 inhibitors	IL-10	IVW	−0.233 (−0.780, 0.313)	.402
		Weighted median	−0.238 (−0.823, 0.346)	.424
		MR-Lasso	−0.233 (−0.780, 0.313)	.402
		MR-Robust	−0.233 (−0.551, 0.084)	.150
		MR-RAPS	−0.234 (−0.809, 0.342)	.426
NPCIL1 inhibitors	IL-17	IVW	0.026 (−0.537, 0.589)	.927
		Weighted median	0.038 (−0.566, 0.641)	.902
		MR-Lasso	0.026 (−0.537, 0.589)	.927
		MR-Robust	0.026 (−0.321, 0.378)	.875
		MR-RAPS	0.026 (−0.564, 0.617)	.930
NPCIL1 inhibitors	IP10	IVW	−0.170 (−0.823, 0.483)	.611
		Weighted median	−0.205 (−0.930, 0.519)	.578
		MR-Lasso	−0.170 (−0.881, 0.542)	.641
		MR-Robust	−0.174 (−0.808, 0.460)	.591
		MR-RAPS	−0.171 (−0.854, 0.511)	.622
NPCIL1 inhibitors	MCP-1	IVW	−0.138 (−1.623, 1.347)	.856
		Weighted median	−0.150 (−1.739, 1.439)	.853
		MR-Lasso	−0.138 (−1.623, 1.347)	.856
		MR-Robust	−0.138 (−0.971, 0.694)	.745
		MR-RAPS	−0.138 (−1.699, 1.423)	.862
NPCIL1 inhibitors	MIP-1α	IVW	0.142 (−0.693, 0.977)	.739
		Weighted median	−0.068 (−0.976, 0.841)	.884
		MR-Lasso	0.142 (−0.791, 1.076)	.765
		MR-Robust	0.121 (−0.540, 0.782)	.720
		MR-RAPS	0.124 (−0.749, 0.996)	.781
NPCIL1 inhibitors	MIP-1β	IVW	−0.233 (−0.776, 0.310)	.400
		Weighted median	−0.227 (−0.812, 0.359)	.447
		MR-Lasso	−0.233 (−0.776, 0.310)	.400
		MR-Robust	−0.233 (−0.549, 0.082)	.147
		MR-RAPS	−0.234 (−0.805, 0.338)	.423
NPCIL1 inhibitors	TNF-α	IVW	−0.454 (−1.298, 0.390)	.292
		Weighted median	−0.428 (−1.341, 0.485)	.358
		MR-Lasso	−0.454 (−1.298, 0.390)	.292
		MR-Robust	−0.455 (−1.926, 1.015)	.544
		MR-RAPS	−0.455 (−1.344, 0.434)	.316
NPCIL1 inhibitors	VEGF	IVW	−0.257 (−0.845, 0.332)	.393
		Weighted median	−0.302 (−0.933, 0.328)	.348
		MR-Lasso	−0.257 (−0.845, 0.332)	.393
		MR-Robust	−0.256 (−0.684, 0.172)	.241
		MR-RAPS	−0.258 (−0.877, 0.361)	.414
NPCIL1 inhibitors	IFN-γ	IVW	−0.072 (−0.633, 0.490)	.803
		Weighted median	−0.233 (−0.845, 0.398)	.481
		MR-Lasso	−0.072 (−0.633, 0.490)	.803
		MR-Robust	−0.083 (−0.569, 0.403)	.738
		MR-RAPS	−0.072 (−0.661, 0.516)	.810
NPCIL1 inhibitors	CRP	IVW	−0.032 (−0.188, 0.123)	.682
		Weighted median	−0.034 (−0.207, 0.138)	.695
		MR-Lasso	−0.032 (−0.188, 0.123)	.682
		MR-Robust	−0.032 (−0.114, 0.051)	.449
		MR-RAPS	−0.033 (−0.196, 0.131)	.697

IVW = inverse-variance weighting method, MR-Lasso = MR method based on Lasso algorithm, MR-PRESSO = MR multi-effect residual and heterogeneity detection, MR-RAPS = Contour score method of MR Robust adjustment, MR-Robust = MR-IVW method based on robust regression, NPC1L1 inhibitor = Niemann-Pick C1-like 1 inhibitor, IL-6 = interleukin-6, IL-17 = interleukin-17, IL-10 = interleukin-10, IL-1β = interleukin-1β, IP10 = interferon gamma-induced protein 10 (CXCL10), WME = weighted median method.

levels across multiple tissues was also causally linked to decreased TNF-α and CRP levels, indicating that ACEIs may modulate the inflammatory response not only by lowering pro-inflammatory cytokines but also by regulating gene expression in various tissues.

IL-1β is a pro-inflammatory cytokine secreted by adipocytes, macrophages, and endothelial cells, playing a critical role in the pathogenesis of several diseases. It is involved in initiating the inflammatory response and is crucial in the development of conditions such as gout, diabetes, and heart failure. Reducing IL-1β

Table 8

Causal estimates of PCSK9 inhibitors on inflammatory cytokines.

Expose	Denouement	MR method	β (95%CI)	*P*
PCSK9 inhibitors	IL-1β	IVW	−0.225 (−0.465, −0.045)	.017
		Weighted median	−0.314 (−0.589, −0.039)	.025
		MR-Lasso	−0.225 (−0.465, −0.045)	.017
		MR-Robust	−0.263 (−0.438, −0.088)	.003
		MR-RAPS	−0.256 (−0.475, −0.038)	.022
		MR-PRESSO	−0.225 (−0.405, −0.105)	.004
PCSK9 inhibitors	IL-6	IVW	−0.271 (−0.447, −0.094)	.003
		Weighted median	−0.220 (−0.464, 0.023)	.076
		MR-Lasso	−0.271 (−0.447, −0.094)	.003
		MR-Robust	−0.264 (−0.438, −0.090)	.003
		MR-RAPS	−0.271 (−0.456, −0.086)	.004
		MR-PRESSO	−0.271 (−0.429, −0.113)	.004
PCSK9 inhibitors	IL-10	IVW	−0.089 (−0.246, 0.068)	.269
		Weighted median	−0.008 (−0.163, 0.148)	.923
		MR-Lasso	−0.089 (−0.246, 0.068)	.269
		MR-Robust	−0.037 (−0.179, 0.105)	.612
		MR-RAPS	−0.051 (−0.180, 0.077)	.423
		MR-PRESSO	−0.089 (−0.246, 0.068)	.284
PCSK9 inhibitors	IL-17	IVW	−0.114 (−0.241, 0.013)	.079
		Weighted median	−0.027 (−0.184, 0.130)	.738
		MR-Lasso	−0.114 (−0.241, 0.013)	.079
		MR-Robust	−0.118 (−0.340, 0.105)	.299
		MR-RAPS	−0.114 (−0.244, 0.017)	.087
		MR-PRESSO	−0.114 (−0.241, 0.013)	.097
PCSK9 inhibitors	IP10	IVW	0.028 (−0.151, 0.207)	.759
		Weighted median	0.032 (−0.197, 0.260)	.786
		MR-Lasso	0.028 (−0.151, 0.207)	.759
		MR-Robust	0.028 (−0.074, 0.130)	.594
		MR-RAPS	0.029 (−0.156, 0.213)	.762
		MR-PRESSO	0.028 (−0.130, 0.187)	.733
PCSK9 inhibitors	MCP-1	IVW	−0.052 (−0.171, 0.066)	.386
		Weighted median	−0.029 (−0.179, 0.120)	.700
		MR-Lasso	−0.052 (−0.171, 0.066)	.386
		MR-Robust	−0.052 (−0.133, 0.028)	.204
		MR-RAPS	−0.053 (−0.176, 0.069)	.392
		MR-PRESSO	−0.052 (−0.161, 0.056)	.358
PCSK9 inhibitors	MIP-1α	IVW	0.205 (−0.064, 0.475)	.135
		Weighted median	0.156 (−0.195, 0.506)	.385
		MR-Lasso	0.205 (−0.064, 0.475)	.135
		MR-Robust	0.189 (−0.042, 0.419)	.108
		MR-RAPS	0.201 (−0.080, 0.481)	.160
		MR-PRESSO	0.205 (−0.007, 0.404)	.060
PCSK9 inhibitors	MIP-1β	IVW	0.072 (−0.079, 0.223)	.349
		Weighted median	0.072 (−0.076, 0.220)	.340
		MR-Lasso	0.072 (−0.079, 0.223)	.349
		MR-Robust	0.075 (−0.024, 0.174)	.136
		MR-RAPS	0.057 (−0.092, 0.205)	.456
		MR-PRESSO	0.072 (−0.079, 0.223)	.363
PCSK9 inhibitors	TNF-α	IVW	0.002 (−0.184, 0.187)	.987
		Weighted median	0.074 (−0.160, 0.308)	.536
		MR-Lasso	0.002 (−0.184, 0.187)	.987
		MR-Robust	0.000 (−0.151, 0.152)	.996
		MR-RAPS	0.002 (−0.190, 0.193)	.987
		MR-PRESSO	0.002 (−0.127, 0.130)	.981
PCSK9 inhibitors	VEGF	IVW	−0.111 (−0.245, 0.023)	.104
		Weighted median	−0.027 (−0.190, 0.136)	.747
		MR-Lasso	−0.111 (−0.245, 0.023)	.104
		MR-Robust	−0.102 (−0.277, 0.072)	.252
		MR-RAPS	−0.095 (−0.233, 0.043)	.177
		MR-PRESSO	−0.111 (−0.245, 0.023)	.122
PCSK9 inhibitors	IFN-γ	IVW	−0.114 (−0.237, 0.008)	.068
		Weighted median	−0009 (−0.170, 0.152)	.912
		MR-Lasso	−0.114 (−0.237, 0.008)	.068
		MR-Robust	−0.308 (−0.478, −0.137)	.000
		MR-RAPS	−0.155 (−0.283, −0.026)	.018
		MR-PRESSO	−0.114 (−0.232, 0.003)	.074
PCSK9 inhibitors	CRP	IVW	0.004 (−0.043, 0.051)	.867
		Weighted median	0.001 (−0.063, 0.064)	.985
		MR-Lasso	0.004 (−0.043, 0.051)	.867
		MR-Robust	0.002 (−0.054, 0.059)	.937
		MR-RAPS	0.005 (−0.044, 0.055)	.833
		MR-PRESSO	0.004 (−0.034, 0.043)	.840

IL-10 = interleukin-10, IL-17 = interleukin-17, IL-1β = interleukin-1β, IL-6 = interleukin-6, IVW = inverse-variance weighting method, MR-Robust = MR-IVW method based on robust regression, MR-Lasso = MR method based on Lasso algorithm, MR-PRESSO = MR multi-effect residual and heterogeneity detection, MR-RAPS = Contour score method of MR Robust adjustment, PCSK9 inhibitor = proprotein convertase subtilisin/Kexin type 9 inhibitor, IP10 = interferon gamma-induced protein 10 (CXCL10), WME = weighted median method.

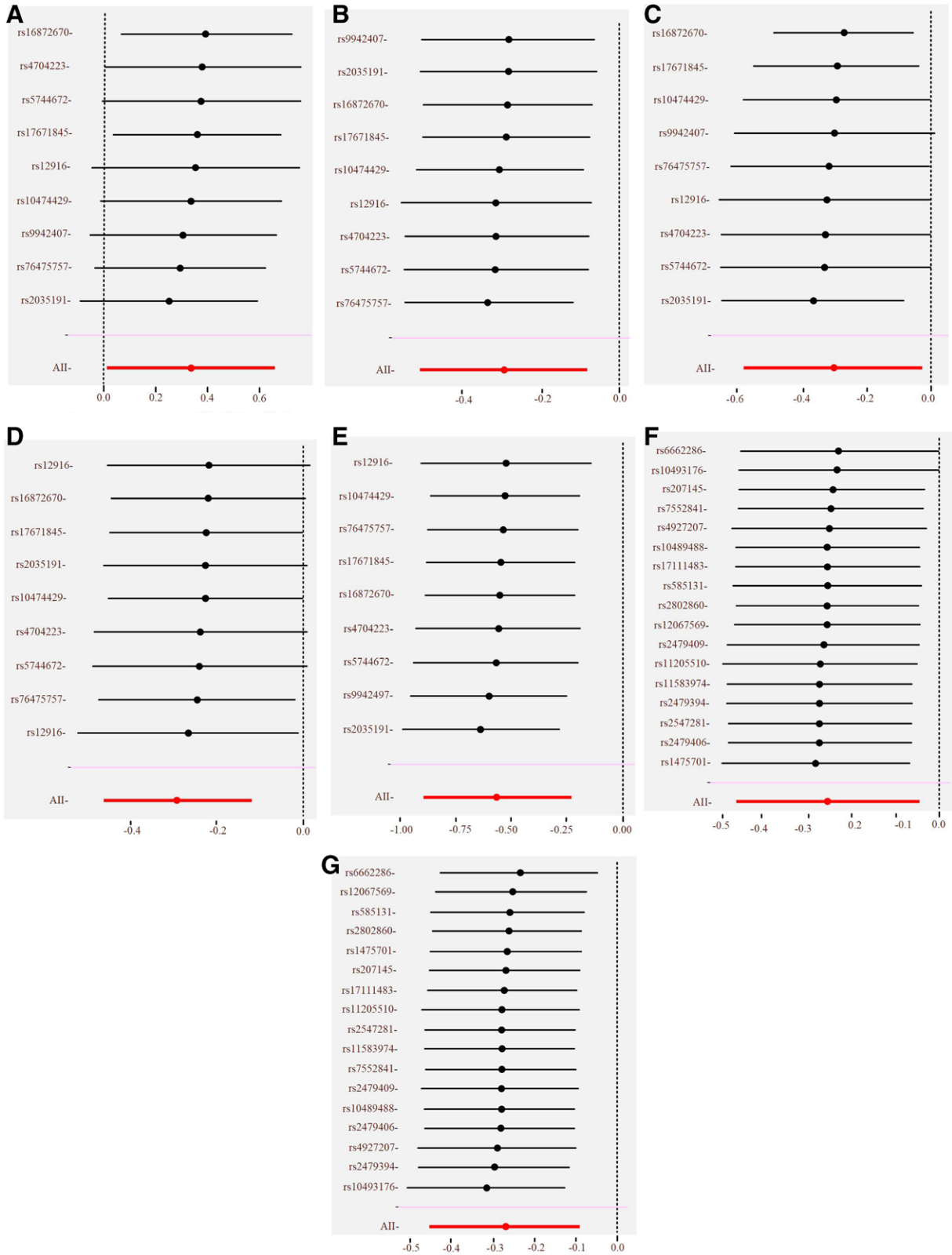

Figure 3. Leave-one-out analyses of the causal effects of HMGCR and PCSK9 on inflammatory cytokines (A) leave-one-out analysis of HMGCR on IP-10; (B) leave-one-out analysis of HMGCR on MCP-1; (C) leave-one-out analysis of HMGCR on MIP-1β; (D) leave-one-out analysis of HMGCR on IFN-γ; (E) leave-one-out analysis of HMGCR on TNF-α; (F) leave-one-out analysis of PCSK9 on IL-1β; (G) leave-one-out analysis of PCSK9 on IL-6. Note: Forest plots from leave-one-out analysis illustrating the causal effects of HMGCR and PCSK9 on various inflammatory cytokines. Each panel shows the results for individual SNPs, and the overall estimate (in red) is derived from an inverse-variance weighting method (IVW) method. The analysis demonstrates the robustness of the Mendelian randomization results by ensuring no single SNP is driving the observed causal effect. All represents the aggregate result for the included SNPs. HMGCR = HMG-CoA reductase, IFN-γ = interferon gamma, IL-1β = interleukin-1β, IL-6 = interleukin-6, MCP-1 = monocyte chemoattractant protein-1, MIP-1α/MIP-1β = macrophage inflammatory protein-1α/macrophage inflammatory protein-1β, PCSK9 = proprotein convertase subtilisin/Kexin type 9, TNF-α = tumor necrosis factor-alpha.

Table 9

Heterogeneity and gene pleiotropy of lipid-lowering drugs.

		MR-Egger		Heterogeneity test		
Expose	**Denouement**	**Intercepts (95%CI)**	***P***	***Q***	***df***	***P***
HMGCR inhibitors	IL-1β	−0.016 (−0.094, 0.062)	.679	0.067	7	.532
	IL-6	−0.038 (−0.104, 0.027)	.252	2.030	8	.980
	IL-10	−0.016 (−0.083, 0.051)	.640	2.980	8	.936
	IL-17	−0.024 (−0.092, 0.043)	.481	2.946	8	.938
	IP10	0.017 (−0.087, 0.120)	.750	8.062	8	.427
	MCP-1	−0.008 (−0.073, 0.057)	.805	5.496	8	.703
	MIP-1α	−0.013 (−0.145, 0.118)	.841	12.354	8	.136
	MIP-1β	−0.047 (−0.130, 0.035)	.262	13.283	8	.102
	TNF-α	−0.029 (−0.130, 0.071)	.570	3.828	8	.872
	VEGF	−0.017 (−0.115, 0.081)	.741	13.739	8	.089
	IFN-γ	−0.021 (−0.088, 0.047)	.549	1.455	8	.993
	CRP	0.000 (−0.014, 0.014)	.996	6.576	10	.765
NPC1L1 inhibitors	IL-1β	0.070 (−0.019, 0.160)	.123	2.378	2	.305
	IL-6	−0.017 (−0.092, 0.058)	.658	0.233	2	.890
	IL-10	−0.009 (−0.087, 0.068)	.814	0.142	2	.931
	IL-17	0.048 (−0.029, 0.125)	.224	1.653	2	.438
	IP10	−0.051 (−0.163, 0.061)	.369	0.843	2	.656
	MCP-1	0.015 (−0.060, 0.090)	.696	1.101	2	.577
	MIP-1α	0.037 (−0.129, 0.203)	.660	2.499	2	.287
	MIP-1β	0.023 (−0.052, 0.098)	.551	0.425	2	.809
	TNF-α	0.038 (−0.078, 0.154)	.517	0.461	2	.794
	VEGF	−0.037 (−0.118, 0.044)	.365	0.876	2	.645
	IFN-γ	−0.032 (−0.110, 0.045)	.417	0.660	2	.719
	CRP	−0.005 (−0.024, 0.015)	.640	0.603	2	.740
PCSK9 inhibitors	IL-1β	−0.006 (−0.025, 0.013)	.542	0.542	17	.946
	IL-6	−0.011 (−0.027, 0.005)	.177	15.913	17	.530
	IL-10	−0.014 (−0.035, 0.006)	.169	28.152	17	.043
	IL-17	−0.020 (−0.037, −0.004)	.215	18.235	17	.374
	IP10	−0.002 (−0.026, 0.022)	.894	13.355	17	.712
	MCP-1	−0.006 (−0.022, 0.010)	.436	14.314	17	.645
	MIP-1α	−0.005 (−0.030, 0.019)	.668	8.771	17	.947
	MIP-1β	0.000 (−0.022, 0.022)	.985	26.222	16	.051
	TNF-α	−0.007 (−0.032, 0.018)	.584	8.139	17	.963
	VEGF	−0.02 (−0.037, −0.002)	.325	18.555	17	.355
	IFN-γ	−0.018 (−0.034, −0.002)	.332	15.578	17	.554
	CRP	−0.002 (−0.011, 0.006)	.553	10.552	16	.836

CRP = C-reactive protein, HMGCR inhibitors = 3-hydroxy-3-methylglutaryl CoA reductase inhibitors, IFN-γ = interferon-gamma, IL-1 = interleukin-1, IL-10 = interleukin-10, IL-17 = interleukin-17, IL-6 = interleukin-6, IP10 = interferon gamma-induced protein 10 (CXCL10), MCP-1 = monocyte chemoattractant protein-1, MIP-1α = macrophage inflammatory protein-1α, MIP-1β = macrophage inflammatory protein-1β, NPC1L1 inhibitors = Niemann-Pick C1-like 1 inhibitors, PCSK9 = proprotein convertase subtilisin/Kexin type 9, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor.

levels can help alleviate the adverse effects of these diseases. Our study demonstrated that ACEIs significantly reduce IL-1β levels, consistent with previous research findings.[27] However, in a randomized, double-blind, placebo-controlled trial, ramipril was found to increase IL-1β levels over a short period, possibly due to a small sample size and a short observation period.[28]

TNF-α, mainly produced by macrophages, is a key pro-inflammatory cytokine involved in immune responses, inflammation, and tissue damage repair. Elevated local TNF-α levels can lead to symptoms such as fever, swelling, pain, and loss of function, while excessive systemic TNF-α may result in septic shock.[29] Our study found that ACEIs significantly reduced TNF-α levels, which is consistent with findings from several RCTs.[10] However, some smaller RCTs did not observe significant changes in TNF-α levels, potentially due to shorter follow-up periods.[30]

CRP is an acute-phase marker of inflammation. Previous studies have shown that CRP can exacerbate inflammatory responses by inhibiting endothelial nitric oxide synthase.[31] Our study supports the notion that ACEIs can reduce CRP levels, aligning with the findings of several RCT meta-analyses.[10] However, some RCTs found that ACEIs did not significantly reduce CRP levels in healthy volunteers, possibly due to population-specific factors.[32]

In summary, ACEIs may play a crucial role in the long-term regulation of the inflammatory response by lowering pro-inflammatory cytokines such as IL-1β, TNF-α, and CRP. Although some smaller RCTs have shown inconsistent results, our large-scale MR analysis provides stronger evidence of the long-term anti-inflammatory effects of ACEIs.

4.2. Causal relationship between lipid-lowering drugs and inflammatory cytokines

The results of this study support that HMGCR inhibitors may exert significant anti-inflammatory effects by reducing pro-inflammatory cytokines such as MCP-1, MIP-1β, TNF-α, and IFN-γ. Similarly, PCSK9 inhibitors were shown to reduce IL-1β and IL-6 levels, thereby exerting protective effects against inflammation. Additionally, the reduction in HMGCR gene expression in skeletal muscle was causally linked to lower levels of MIP-1β, TNF-α, and IFN-γ, further validating the anti-inflammatory effects of HMGCR inhibitors across different tissues.

MCP-1 and MIP-1β are key chemokines that recruit monocytes and macrophages to inflammation sites, playing a vital role in various pathological conditions. Previous studies have shown that HMGCR inhibitors can significantly reduce MCP-1

levels, a result widely validated in patients with cardiovascular diseases, diabetes, and nonalcoholic fatty liver disease. For example, an RCT involving patients with type 2 diabetes found that HMGCR inhibitors significantly reduced MCP-1 levels.[33] Another study demonstrated that HMGCR inhibitors suppress MCP-1 and MIP-1β secretion by regulating the downstream pathways of HMG-CoA reductase.[34]

Regarding TNF-α regulation, our study found that HMGCR inhibitors are closely associated with reduced TNF-α levels, consistent with several previous RCTs. For instance, in a 12-month RCT follow-up study of patients with impaired cardiac function, TNF-α levels were significantly reduced after treatment with HMGCR inhibitors.[35] Additionally, the reduction in TNF-α levels was more pronounced in diabetic hypertensive patients compared to those without diabetes,[36] further supporting the anti-inflammatory effects of HMGCR inhibitors in various pathological conditions.

IFN-γ is a crucial immune modulator that can activate the immune system and potentially contribute to the development of autoimmune diseases. Our study demonstrated that HMGCR inhibitors significantly reduced IFN-γ levels, consistent with findings from previous in vivo and in vitro studies.[37] Moreover, a study involving patients with metabolic syndrome showed that HMGCR inhibitors significantly reduced MIP-1B levels, further supporting our findings.[38]

PCSK9 inhibitors also exhibited significant regulatory effects on pro-inflammatory cytokines IL-1β and IL-6 in this study. Previous research has shown that PCSK9 modulates IL-1β secretion via the NF-κB signaling pathway.[39] Additionally, an RCT found that PCSK9 inhibitors not only reduced lipid levels but also significantly decreased IL-1β levels in patients with type 2 diabetes.[40] In a multi-center, double-blind, placebo-controlled trial, PCSK9 inhibitors were also shown to reduce IL-6 levels in healthy volunteers.[41] Animal studies further confirmed the anti-inflammatory effects of PCSK9 inhibitors, which downregulate both PCSK9 and IL-6 expression, thereby reducing the secretion of inflammatory cytokines.[42]

Notably, a multi-center, placebo-controlled RCT on the treatment of acute respiratory distress syndrome with simvastatin found that patients with high inflammation receiving simvastatin had a significantly lower 28-day mortality rate (32% vs 45%, $P = .008$), further demonstrating the potential protective effects of HMGCR inhibitors in patients with high levels of inflammation.[43] This finding highlights the significant anti-inflammatory effects of simvastatin and provides valuable clinical evidence for future research.

In conclusion, MCP-1, MIP-1β, TNF-α, and IFN-γ play critical roles in the inflammatory processes of various diseases. Our study indicates that HMGCR and PCSK9 inhibitors modulate these key cytokines through multiple pathways, exhibiting significant anti-inflammatory effects. The consistency of our findings with existing RCTs and MR analyses supports the potential protective role of these drugs in a range of inflammatory responses. However, further large-scale, multi-center, long-term RCTs are needed to validate the mechanisms by which HMGCR and PCSK9 inhibitors regulate inflammatory cytokines.

4.3. The application of drug-targeted MR

Drug-targeted MR is an innovative approach that leverages genetic variations to simulate the long-term effects of drug interventions, providing a robust tool for elucidating causal relationships between pharmacological agents and diseases. In this study, we rigorously adhered to the established protocols of drug-targeted MR analysis, utilizing large-scale genome-wide association studies and expression quantitative trait loci (eQTL) data to systematically evaluate the causal effects of antihypertensive and lipid-lowering drugs on inflammatory cytokines. This method not only offers significant insights for the development of novel therapeutics but also opens new avenues for the repurposing of existing drugs. Nevertheless, the drug-targeted MR approach is not without limitations. First, the effect sizes of genetic variants are often modest, and their cumulative long-term effects may not fully mirror the short-term impact of pharmacological interventions.[44] Second, most genetic data are derived from European populations, which may limit the generalizability of the findings to other ethnic groups.[45] Despite these challenges, drug-targeted MR remains a valuable tool in drug discovery and therapeutic research, with its potential expected to grow as genetic data resources expand and methodological advancements continue to be made.

5. Conclusion

This study utilized the drug-targeted MR method to elucidate the causal relationships between antihypertensive and lipid-lowering drugs and inflammatory cytokines. The results demonstrated a causal association between ACE inhibitors (ACEIs) and reductions in IL-1β, TNF-α, and CRP levels. HMGCR inhibitors were causally associated with decreases in inflammatory cytokines MCP-1, MIP-1β, TNF-α, and IFN-γ levels. Additionally, PCSK9 inhibitors were found to have a causal relationship with reduced levels of IL-1β and IL-6. Exploratory and validation analyses yielded consistent results, underscoring the robustness of the findings. These results suggest that different antihypertensive and lipid-lowering drugs exert distinct effects on inflammatory cytokines, potentially providing effective interventions to mitigate adverse inflammatory responses.

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