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Genetic causal association between lipidomic profiles, inflammatory proteomics, and aortic stenosis: a Mendelian randomization investigation

Linwen Zhu[1†], Ni Li[1,2†], Huoshun Shi[1], Guofeng Shao[1*] and Lebo Sun[1*]

Abstract

Background Aortic stenosis (AS) is a prevalent and serious valvular heart disease with a complex etiology involving genetic predispositions, lipid dysregulation, and inflammation. The specific roles of lipid and protein biomarkers in AS development are not fully elucidated. This study aimed to elucidate the causal relationships between lipidome, inflammatory proteins, and AS using Mendelian randomization (MR), identifying potential therapeutic targets.

Methods Utilizing data from large-scale genome-wide association studies (GWAS) and genome-wide protein quantitative trait loci (pQTL) studies, we conducted MR analyses on 179 plasma lipidome and 91 inflammatory proteins to assess their causal associations with AS. Our approach included Inverse Variance Weighting (IVW), Wald ratio, and robust adjusted profile score (RAPS) analyses to refine these associations. MR-Egger regression was used to address directional horizontal pleiotropy.

Results Our MR analysis showed that genetically predicted 50 lipids were associated with AS, including 38 as risk factors [(9 Sterol ester, 18 Phosphatidylcholine, 4 Phosphatidylethanolamine, 1 Phosphatidylinositol and 6 Triacylglycerol)] and 12 as protective. Sterol ester (27:1/17:1) emerged as the most significant risk factor with an odds ratio (OR) of 3.11. Additionally, two inflammatory proteins, fibroblast growth factor 19 (FGF19) (OR = 0.830, $P = 0.015$), and interleukin 6 (IL-6) (OR = 0.729, $P = 1.79E-04$) were significantly associated with reduced AS risk. However, a two-step MR analysis showed no significant mediated correlations between these proteins and the lipid–AS pathway.

Conclusion This study reveals complex lipid and protein interactions in AS, identifying potential molecular targets for therapy. These results go beyond traditional lipid profiling and significantly advance our genetic and molecular understanding of AS, highlighting potential pathways for intervention and prevention.

Keywords Aortic stenosis, Lipidome, Inflammatory proteins, Mendelian randomization, Sterol ester, Fibroblast growth factor 19, Interleukin 6

[†]Linwen Zhu and Ni Li have equal contribution.

*Correspondence:
Guofeng Shao
sgf1958@sina.com
Lebo Sun
sunbentall@qq.com
Full list of author information is available at the end of the article

Introduction

Aortic stenosis (AS) is one of the most common and severe valvular heart diseases in developed countries with a prevalence of 1–3% in individuals over 70 years old, characterized by the narrowing of the aortic valve, significantly impacting global morbidity and mortality [1, 2]. The clinical significance of AS lies in its potential to cause serious symptoms and complications, including heart failure, stroke and even death [2]. Traditionally, the development of AS has been attributed to age-related degenerative processes, including calcification and fibrosis of the aortic valve. Emerging evidence suggests that the pathogenesis of AS is multifactorial, involving complex interactions between genetic factors, lipid infiltration, inflammation, and fibrocalcific pathways [3–5]. Lipid-lowering therapies, antihypertensive drugs, and anticalcification therapies are the main drug classes studied in AS [6]. Despite advancements in understanding its pathophysiology, the pathogenesis involving lipid metabolic pathways and inflammatory processes remains incompletely elucidated. Research has highlighted the potential roles of lipid dysregulation and inflammation in the progression of AS, suggesting a complex interplay between the two, which could be key in prognostic assessment and developing targeted therapeutic strategies [7–10]. Moreover, broader spectrum of AS-related lipidome identification contributes to personalized management of lipid-lowering therapy.

The advent of genomics research and the advancements in proteomics have ushered in a new era of cardiovascular research, enabling a deeper exploration of the genetic and molecular mechanisms underlying AS. Recent genome-wide association studies (GWAS) of AS have identified 6 new genomic regions associated with the disease, underscoring the roles of lipid metabolism, inflammation, cellular senescence, and obesity in the pathophysiology of AS [11]. Additionally, a phenome-wide association study indicated the importance of lipid abnormalities and inflammation in the etiology of AS, specifically, Mendelian randomization (MR) studies supported the potential causal relationships of specific lipid species and inflammatory proteins in AS, providing insights into its molecular etiology [12, 13]. These studies suggest that in addition to traditional risk factors, such as hypertension and hypercholesterolemia, specific components of the lipidome and proteome could significantly influence the risk and progression of AS. Furthermore, GWAS extending the plasma lipidome has fundamentally changed our understanding of the genetic variations behind lipid levels, aiding in the improvement of cardiovascular disease risk assessment [14]. Very large-scale genetic studies have been performed on standard lipids [15], and despite the much smaller sample size of the lipidome GWAS, they have identified novel lipid-associated genetic variants. Newly published GWAS on 179 lipid species and 91 inflammatory proteins promise to establish new perspectives on potential genetic targets associated with AS [14, 16].

This study builds upon these foundational insights, utilizing MR to investigate the causal relationships between a broad spectrum of lipids, inflammatory proteins, and AS. By integrating genomic data with lipidomic and proteomic analyses, we seek to elucidate the complex molecular landscape of AS, identifying potential biomarkers and therapeutic targets. Understanding these intricate relationships hopes to advance personalized medicine approaches for the prevention and treatment of AS, potentially transforming the prognosis for patients with this challenging condition.

Methods

Study program

Our research aimed to discern the heritable risk factors associated with AS by focusing on lipid profiles and inflammatory markers. Utilizing a two-sample MR approach, we evaluated the genetic predisposition to 179 distinct lipid groups and 91 inflammatory protein groups. This endeavor leveraged genetic instrumental variables (IVs) representing the heritability of these lipid and inflammatory markers, drawing from comprehensive GWAS of the respective traits. Moreover, we explored the intermediary role of inflammation in the lipid-induced AS risk pathway, applying a two-step MR to deduce potential mediating effects [17].

Access to the GWAS dataset

The genetic underpinnings of our analysis stem from a cutting-edge genetic cohort study on AS, incorporating a genome-wide meta-analysis spanning 11.6 million genetic variants across ten cohorts with 653,867 individuals of European descent, including 13,765 AS cases [12]. The complete GWAS summary is accessible via the Common Metabolic Diseases Knowledge Portal (CMDKP, https://cvd.hugeamp.org/dinspector.html?dataset=Chen2023_AorticStenosis_EU). Furthermore, lipidomic data were sourced from an exhaustive genome-wide investigation of 179 lipid species in a Finnish cohort [14], with findings and data available for download from the HGRI-EBI Catalog (https://www.ebi.ac.uk/gwas/publications/37907536) (accession numbers: GCST90277238-GCST90277416). Detailed information on each summary data is provided in Supplementary Table 1. Inflammatory protein data were derived from a genome-wide protein quantitative trait loci (pQTL) study, also cataloged in the HGRI-EBI, encompassing 14,824 European participants [16] (https://www.ebi.ac.uk/gwas/publicatio

ns/37563310) (accession numbers: GCST90274758 to GCST90274848). Detailed information on each GWAS is available in Supplementary Table 2. All datasets adhered to ethical guidelines established in their original studies, negating the need for additional ethical approval for this reanalysis.

Genetic proxies for causal analysis

The causality inference between lipid profiles, inflammatory proteins, and AS necessitated IVs as genetic proxies. Selection of gene IVs for each trait was based on the most significant genetic correlations ($P < 5 \times 10$^-8) identified in the GWAS datasets, adhering to stringent criteria for independence and minimal linkage disequilibrium ($r^2 < 0.001$ in a 10,000 kb window). In addition, SNPs were excluded if the value of the F-statistic was less than 10, indicating that the SNP had a weak instrumental likelihood. The assumptions of strong correlation and IV independence are essential requirements for MR analyses to be valid, and those phenotypes that do not satisfy these requirements for SNPs will be considered to have no usable genetic tools and will not be used in subsequent analyses [18]. Based on the hypothesis of MR's hypothesis of exclusion restriction, to ensure the validity of our MR analysis, we performed an extensive review of the literature and relevant genetic databases to compile a list of known risk factors for AS, such as hypertension, cholesterol levels, smoking status, diabetes, and other cardiovascular conditions. For each SNP identified as an IV, secondary GWAS analyses were conducted to determine associations with these potential confounders. SNPs showing significant associations ($P < 1 \times 10$^-5 and $r^2 > 0.8$) with any confounders were flagged, and those showing significant associations ($P < 1 \times 10$^-8) in the outcome GWAS were removed. This exclusion process ensured that the remaining SNPs were associated only with lipid and inflammatory protein levels and not with confounding factors that may influence AS risk.

Statistical analysis

Causal effects of the lipidome, inflammatory proteome, and AS

Upon the selection of IVs for each category within the lipid and inflammatory proteomes, our investigation proceeded to evaluate their potential causal relationships with AS using the TwoSampleMR package (version 0.5.8) in R (version 4.3.1). This analysis utilized distinct methodologies based on the number and nature of the available IVs per trait. For analyses involving multiple IVs per trait, we applied the Inverse Variance Weighting (IVW) method. This approach assumes the validity of all selected IVs and posits that there are no interactive effects between them, making it particularly suited for complex IVs scenarios. Conversely, in cases where only a single IV was available for a given trait, we utilized the Wald ratio method, offering a direct estimation of causality for singular exposures [19]. Additionally, to enhance the reliability of our findings and mitigate the incidence of false positives (Type I errors), we incorporated the MR-robust adjusted profile score (MR-RAPS) method through mr.raps package (version 0.4.1) [20]. This technique adjusts profile scores to achieve a consistent and asymptotically normal estimation, thereby refining the precision of our MR analyses. Given the exploratory nature of this work, we set a significance threshold of $P < 0.05$, opting not to adjust for multiple comparisons via Bonferroni correction [21]. This strategy aimed to maximize the identification of potential targets associated with AS. In instances where more than three IVs were analyzed for a single trait, we employed MR-Egger regression to assess whether the identified SNPs exhibited pleiotropic effects that could confound the relationship between the primary exposures (lipids and proteins) and AS [22]. MR-RAPS accounts for potential pleiotropy and provides robust causal estimates. An intercept P value exceeding 0.05 indicated a lack of significant pleiotropic effects, further validating our causal inferences.

Investigating the intermediary role of inflammatory proteins

Given that lipid abnormalities can stimulate the immune-inflammatory response of the body affecting inflammatory protein levels, this segment of our study focused on exploring the potential pathway through which lipids may modulate the risk of AS via their influence on inflammatory proteins. We employed a two-step MR approach to quantify the indirect effects of lipids on AS risk via inflammatory proteins. The purpose of this mediation analysis was to determine whether and to what extent inflammatory proteins serve as a conduit through which lipids can influence the risk of developing AS. Initially, our analysis identified the direct causal relationship between lipid profiles and AS. This relationship was quantified as the overall effect size (β_total). Next, we identified inflammatory proteins that were demonstrably linked to AS through causal associations. The effect size of these proteins on AS was denoted as β_1, which was calculated contingent upon statistical significance. Building on these foundations, we explored the relationship between AS-pertinent lipids and the identified inflammatory proteins. This relationship was marked as β_2. This process allowed us to propose a speculative indirect pathway where lipids could potentially alter the risk of AS through shifts in the levels of specific inflammatory proteins. The direct mediated effect was calculated using the formula $\beta' = \beta\_total - \beta\_1 * \beta\_2$. Figure 1 outlines the key steps of our mediation analysis, from identifying

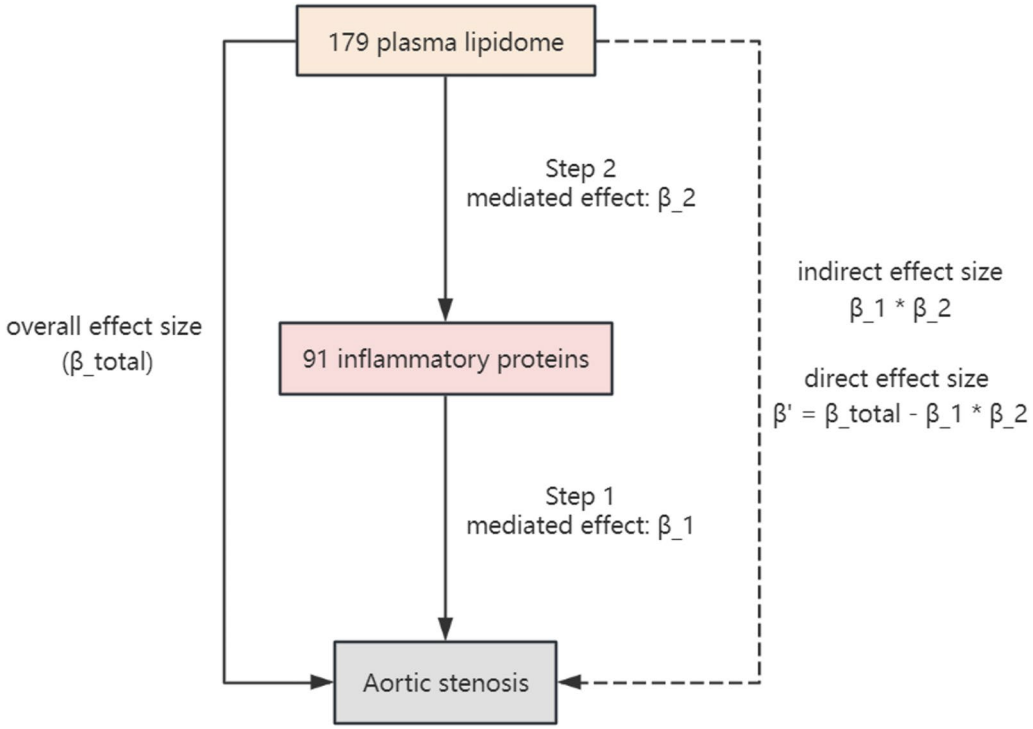

Fig. 1 Two-step Mendelian randomization design for investigating the mediating role of inflammatory proteins in the relationship between lipids and aortic stenosis. The direct causal relationship between the 179 plasma lipidome and AS is quantified as the overall effect size (β_total). Step 1 assessed the causal relationship between inflammatory proteins and AS, and Step 2 assessed the causal relationship between lipid profiles significantly associated with AS and 91 inflammatory proteins. The indirect pathway was calculated using the product of β_1 and β_2, indicating how lipids affect AS through changes in inflammatory protein levels. The overall direct effect was calculated as $\beta' = \beta\_total — \beta\_1 * \beta\_2$, which helps to discern the indirect effect of lipids on AS risk mediated through inflammatory proteins

direct causal relationships to exploring indirect pathways and calculating mediated effects. Given the complex and varied nature of lipid and inflammatory protein phenotypes, we maintained a discovery-oriented approach. The threshold for significance in our IVW or Wald ratio tests, along with robust analytical methods, was consistently set at $P < 0.05$. This threshold facilitated the exploration of genetic correlations, aiming to unearth potential mechanistic links between lipid levels, inflammatory response, and the emergence of AS.

Results

Lipids genetically associated with AS

Our comprehensive analysis begins with identifying [23] genetic IVs for a broad spectrum of 179 lipids to investigate their potential causal relationships [23]with AS through MR. Adhering to the MR hypothesis criteria, we successfully pinpoint IVs for 162 lipid species, with F-statistic values indicating strong instrumental validity, ranging between 29.79 and 1946.15, thereby mitigating concerns over potential weak instrument bias (Supplementary Table 3). Subsequent application of the IVW/Wald ratio methods, post harmonization with AS GWAS data, reveals that 54 lipid species exhibit significant causal associations with AS. This initial finding underscores a substantial subset of the lipidome's potential influence on AS risk (Fig. 2A, Supplementary Table 4). Further scrutiny through robust RAPS analysis leads to the exclusion of four lipids due to statistical insignificance, narrowing down the list to 50 lipid species with demonstrable causal relationships with AS. Among these, 38 lipids (9 Sterol ester, 18 Phosphatidylcholine, 4 Phosphatidylethanolamine, 1 Phosphatidylinositol, and 6 Triacylglycerol) are identified as risk factors associated with an increased likelihood of AS (Odds Ratio, $OR > 1$), while 12 exhibit protective characteristics ($OR < 1$). Notably, Sterol ester (27:1/17:1) emerges as the lipid with the highest OR of 3.11, indicating a robust association with elevated AS risk (Fig. 2B, Table 1). To address potential concerns regarding the multiplicity of levels, the Egger intercept test is applied for phenotypes with more than three IVs, consistently showing P values greater than 0.05. This result suggests an absence of directional pleiotropy, thus reinforcing the validity of our causal inferences (Table 2).

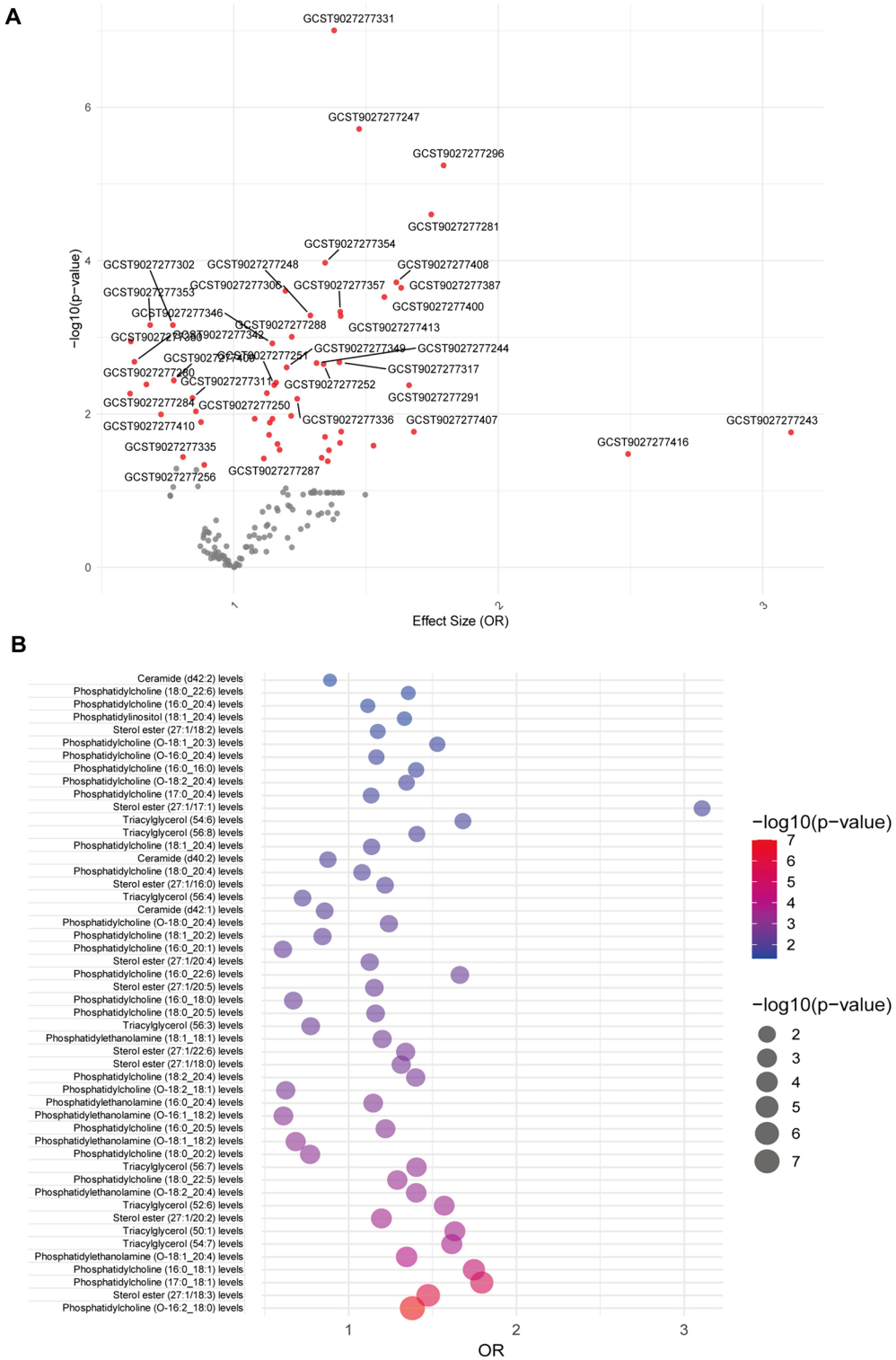

Fig. 2 Mendelian randomization results for lipidome and aortic stenosis. **A** Volcano plot reveals that 54 lipid species exhibited significant causal associations with AS (red dots). **B** Bubble plot shows that significant causal associations of 50 lipid species with AS were assessed by robust MR, of which 38 were risk factors and 12 were protective factors. OR, odds ratio

Table 1 Robust adjusted profile score (RAPS) assessment of lipids and inflammatory proteins with significant causal association to aortic stenosis (AS)

Exposure	ID.exposure	Trait	nsnp	Beta	Stand error	*P* value	OR
Lipidome	GCST90277240	Sterol ester (27:1/16:0) levels	8	0.174	0.079	0.027	1.190
	GCST90277243	Sterol ester (27:1/17:1) levels	1	1.134	0.532	0.033	3.107
	GCST90277244	Sterol ester (27:1/18:0) levels	7	0.278	0.078	3.65E-04	1.321
	GCST90277246	Sterol ester (27:1/18:2) levels	7	0.145	0.057	0.011	1.156
	GCST90277247	Sterol ester (27:1/18:3) levels	5	0.389	0.089	1.14E-05	1.476
	GCST90277248	Sterol ester (27:1/20:2) levels	3	0.179	0.052	0.001	1.196
	GCST90277250	Sterol ester (27:1/20:4) levels	10	0.110	0.031	4.58E-04	1.116
	GCST90277251	Sterol ester (27:1/20:5) levels	3	0.143	0.051	0.005	1.153
	GCST90277252	Sterol ester (27:1/22:6) levels	2	0.297	0.088	0.001	1.346
	GCST90277254	Ceramide (d40:2) levels	2	− 0.133	0.054	0.014	0.875
	GCST90277255	Ceramide (d42:1) levels	2	− 0.155	0.062	0.013	0.857
	GCST90277256	Ceramide (d42:2) levels	8	− 0.116	0.046	0.011	0.891
	GCST90277277	Phosphatidylcholine (16:0_16:0) levels	5	0.455	0.126	3.15E-04	1.577
	GCST90277280	Phosphatidylcholine (16:0_18:0) levels	1	− 0.401	0.151	0.008	0.670
	GCST90277281	Phosphatidylcholine (16:0_18:1) levels	2	0.553	0.149	2.15E-04	1.738
	GCST90277284	Phosphatidylcholine (16:0_20:1) levels	1	− 0.498	0.199	0.012	0.608
	GCST90277287	Phosphatidylcholine (16:0_20:4) levels	4	0.106	0.038	0.005	1.111
	GCST90277288	Phosphatidylcholine (16:0_20:5) levels	1	0.198	0.062	0.001	1.219
	GCST90277291	Phosphatidylcholine (16:0_22:6) levels	1	0.508	0.196	0.009	1.663
	GCST90277296	Phosphatidylcholine (17:0_18:1) levels	1	0.584	0.160	2.69E-04	1.793
	GCST90277298	Phosphatidylcholine (17:0_20:4) levels	4	0.123	0.041	0.003	1.131
	GCST90277302	Phosphatidylcholine (18:0_20:2) levels	1	− 0.262	0.081	0.001	0.770
	GCST90277304	Phosphatidylcholine (18:0_20:4) levels	7	0.077	0.031	0.014	1.080
	GCST90277305	Phosphatidylcholine (18:0_20:5) levels	2	0.149	0.052	0.004	1.161
	GCST90277306	Phosphatidylcholine (18:0_22:5) levels	2	0.255	0.077	0.001	1.290
	GCST90277307	Phosphatidylcholine (18:0_22:6) levels	2	0.326	0.122	0.008	1.385
	GCST90277311	Phosphatidylcholine (18:1_20:2) levels	3	− 0.164	0.061	0.007	0.848
	GCST90277313	Phosphatidylcholine (18:1_20:4) levels	6	0.125	0.043	0.004	1.133
	GCST90277317	Phosphatidylcholine (18:2_20:4) levels	3	0.349	0.100	0.001	1.418
	GCST90277323	Phosphatidylcholine (O-16:0_20:4) levels	3	0.163	0.063	0.009	1.177
	GCST90277331	Phosphatidylcholine (O-16:2_18:0) levels	2	0.322	0.067	1.33E-06	1.380
	GCST90277336	Phosphatidylcholine (O-18:0_20:4) levels	2	0.215	0.073	0.003	1.240
	GCST90277339	Phosphatidylcholine (O-18:1_20:3) levels	1	0.424	0.208	0.042	1.528
	GCST90277342	Phosphatidylcholine (O-18:2_18:1) levels	1	− 0.471	0.167	0.005	0.624
	GCST90277344	Phosphatidylcholine (O-18:2_20:4) levels	2	0.311	0.106	0.003	1.365
	GCST90277346	Phosphatidylethanolamine (16:0_20:4) levels	5	0.134	0.043	0.002	1.143
	GCST90277349	Phosphatidylethanolamine (18:1_18:1) levels	6	0.167	0.064	0.010	1.181
	GCST90277350	Phosphatidylethanolamine (O-16:1_18:2) levels	1	− 0.493	0.169	0.003	0.611
	GCST90277353	Phosphatidylethanolamine (O-18:1_18:2) levels	1	− 0.380	0.120	0.002	0.684
	GCST90277354	Phosphatidylethanolamine (O-18:1_20:4) levels	2	0.296	0.081	2.68E-04	1.345
	GCST90277357	Phosphatidylethanolamine (O-18:2_20:4) levels	2	0.339	0.104	0.001	1.404
	GCST90277367	Phosphatidylinositol (18:1_20:4) levels	2	0.292	0.133	0.028	1.339
	GCST90277387	Triacylglycerol (50:1) levels	2	0.491	0.151	0.001	1.634
	GCST90277400	Triacylglycerol (52:6) levels	3	0.461	0.125	2.28E-04	1.585
	GCST90277407	Triacylglycerol (54:6) levels	2	0.530	0.180	0.003	1.699
	GCST90277408	Triacylglycerol (54:7) levels	3	0.487	0.140	0.001	1.627
	GCST90277409	Triacylglycerol (56:3) levels	3	− 0.259	0.094	0.006	0.772
	GCST90277410	Triacylglycerol (56:4) levels	2	− 0.324	0.131	0.013	0.723
	GCST90277413	Triacylglycerol (56:7) levels	4	0.365	0.098	2.11E-04	1.440

Table 1 (continued)

Exposure	ID.exposure	Trait	nsnp	Beta	Stand error	*P* value	OR
	GCST90277414	Triacylglycerol (56:8) levels	4	0.366	0.142	0.010	1.442
Inflammatory proteome	GCST90274815	Interleukin-6 levels	1	− 0.316	0.090	4.15E-04	0.729
	GCST90274787	Fibroblast growth factor 19 levels	3	− 0.188	0.073	0.010	0.828

Table 2 Directional horizontal pleiotropy evaluation using MR-Egger regression

Exposure	ID.exposure	Trait	Egger_intercept	Standard error	*P* value
Lipidome	GCST90277240	Sterol ester (27:1/16:0) levels	0.012	0.044	0.787
	GCST90277244	Sterol ester (27:1/18:0) levels	0.052	0.024	0.082
	GCST90277246	Sterol ester (27:1/18:2) levels	0.007	0.036	0.851
	GCST90277247	Sterol ester (27:1/18:3) levels	0.016	0.032	0.658
	GCST90277248	Sterol ester (27:1/20:2) levels	− 0.016	0.066	0.849
	GCST90277250	Sterol ester (27:1/20:4) levels	0.005	0.024	0.839
	GCST90277251	Sterol ester (27:1/20:5) levels	− 0.023	0.025	0.529
	GCST90277256	Ceramide (d42:2) levels	− 0.019	0.028	0.530
	GCST90277277	Phosphatidylcholine (16:0_16:0) levels	0.054	0.155	0.752
	GCST90277287	Phosphatidylcholine (16:0_20:4) levels	− 0.019	0.041	0.694
	GCST90277298	Phosphatidylcholine (17:0_20:4) levels	− 0.007	0.048	0.903
	GCST90277304	Phosphatidylcholine (18:0_20:4) levels	− 0.022	0.013	0.161
	GCST90277311	Phosphatidylcholine (18:1_20:2) levels	0.058	0.024	0.245
	GCST90277313	Phosphatidylcholine (18:1_20:4) levels	0.006	0.027	0.827
	GCST90277317	Phosphatidylcholine (18:2_20:4) levels	− 0.073	0.049	0.380
	GCST90277323	Phosphatidylcholine (O-16:0_20:4) levels	− 0.029	0.017	0.341
	GCST90277346	Phosphatidylethanolamine (16:0_20:4) levels	− 0.028	0.028	0.396
	GCST90277349	Phosphatidylethanolamine (18:1_18:1) levels	− 0.049	0.027	0.147
	GCST90277400	Triacylglycerol (52:6) levels	− 0.100	0.120	0.558
	GCST90277408	Triacylglycerol (54:7) levels	− 0.110	0.091	0.441
	GCST90277409	Triacylglycerol (56:3) levels	− 0.017	0.136	0.921
	GCST90277413	Triacylglycerol (56:7) levels	− 0.073	0.059	0.342
	GCST90277414	Triacylglycerol (56:8) levels	− 0.158	0.081	0.189
Inflammatory protein	GCST90274787	Fibroblast growth factor 19 levels	− 0.047	0.031	0.368

Inflammatory proteins genetically linked to AS

The role of inflammation in the progression of AS is well-documented. To elucidate which specific inflammatory mediators bear a significant genetic linkage to AS, we embark on identifying IVs across a panel of 91 plasma inflammatory proteins. Our criteria for selection ensure that 74 of these proteins have SNPs as IVs suitable for MR analysis, with F-statistic values indicating robust instrument strength, spanning from 29.72 to 1180.19 (Supplementary Table 5). Further analysis, utilizing the IVW/Wald ratio methods, reveals significant causal relationships for two inflammatory proteins: fibroblast growth factor 19 (FGF19) and interleukin-6 (IL-6). Notably, the analysis indicates that reduced levels of FGF19 (OR = 0.830, $P = 0.015$) and IL-6 (OR = 0.729, $P = 1.79E-04$) are significantly associated with an increased risk of developing AS (Fig. 3, Supplementary Table 6). These findings suggest a protective role of higher blood concentrations of these proteins against the disease. Robust RAPS analysis further reinforces the causal link between these inflammatory mediators and AS, offering a consistent and reliable assessment of their impact (Table 1), and the Egger intercept test does not support the presence of pleiotropy ($P > 0.05$) (Table 2).

Identification of inflammatory mediators involved in the lipid-AS causal pathway

To elucidate the potential mediating role of inflammatory proteins in the lipid-induced pathogenesis of AS, we employ a two-step MR approach. This analysis aims

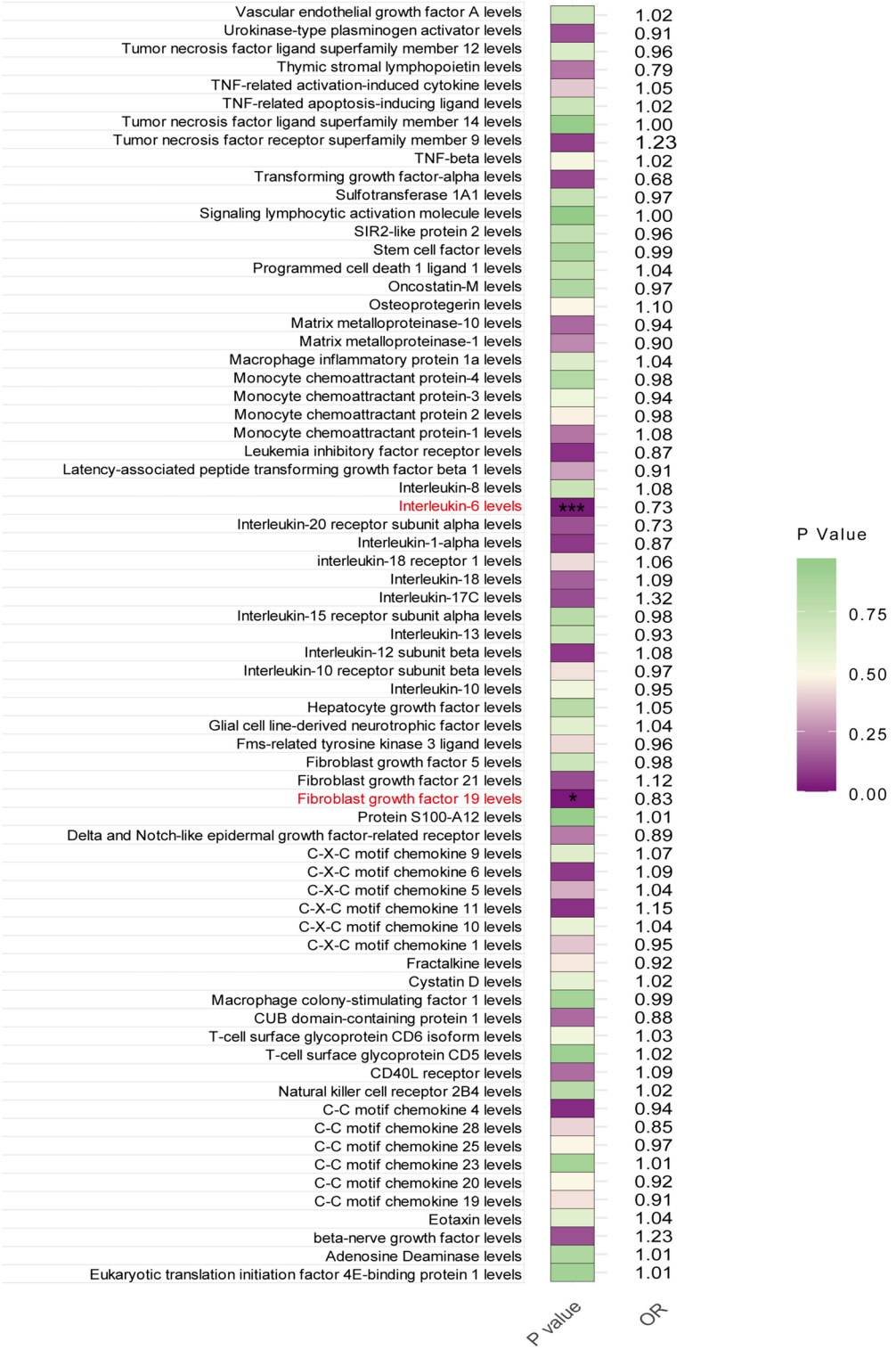

Fig. 3 Heatmap of the Mendelian randomization results for the inflammatory proteome and aortic stenosis. Two significant inflammatory proteins are labeled in red. *$P < 0.05$, ***$P < 0.001$

to discern any mediated correlations between 50 lipid species and the levels of FGF19 and IL-6, which are previously identified as causally associated with AS. Our general and robust MR estimates for the relationship between these lipids and FGF19 levels do not reveal any significant mediated correlations, suggesting that FGF19 does not act as a mediator in the lipid-AS effector pathway (Fig. 4, Supplementary Table 7). Similarly, the MR analysis investigating the causal link between lipids associated with AS and IL-6 levels yields null causal estimates. This finding implies that, within the scope of our analysis, IL-6 levels do not mediate the effect of lipids on AS risk (Fig. 5, Supplementary Table 8).

Discussion

Our study begins to explore the genetic basis of AS, focusing on the causal roles of the lipidome and inflammatory proteins. Our investigation into the causal relationships between specific lipid types and AS provides important insights, clarifying complex relationships beyond traditional cardiovascular risk factors. We identified 54 lipid species with significant causal relationships to AS, 38 of which are associated with increased risk, and 12 associated with decreased risk, highlighting the complicated role of lipid metabolism in the pathogenesis of AS [24]. Specifically, the observed significant OR for Sterol ester (27:1/17:1) highlights the potential of certain lipid profiles as pivotal biomarkers or drivers of AS [24]. Notably, our analysis also indicates that lower levels of FGF19 and IL-6 are associated with increased AS risk. Nevertheless, subsequent research into the potential mediating roles of these inflammatory proteins in the lipid-AS pathway yielded null results, indicating more complex interactions.

The identification of lipids causally linked to AS reinforces the critical role of lipid metabolism in the pathogenesis of disease. This aligns with increasing literature suggesting that, in addition to traditional risk factors, specific lipid profiles may have a direct impact on the cardiovascular system, thereby influencing the development of AS [3, 7, 12, 13, 25, 26]. The identification of 54 lipids causally related to AS not only reinforces the lipid hypothesis in the pathogenesis of AS but also expands our understanding of lipid involvement beyond traditional lipid markers like low-density lipoprotein cholesterol [14, 15, 27]. The significant risk association with Sterol ester levels suggests that certain lipid molecules may contribute to valvular calcification or inflammation, two key processes in the development of AS, through specific pathways [3, 5, 12]. This granularity in the involvement of lipids in AS offers a more refined perspective for potential therapeutic targets. Traditionally, lipid-lowering therapies, especially statins, have shown varied outcomes in AS treatment, which could be due to their broad target spectrum [28–30]. However, recent studies suggest the potential for more targeted lipid-modifying strategies. Combination lipid-lowering therapy as a first-line strategy in very high-risk patients has been discussed, emphasizing the importance of intensive LDL-C lowering [31]. Furthermore, the dawn of a new era of targeted lipid-lowering therapies has been heralded, with novel biological and therapeutic discoveries offering insight into innovative targeting strategies that have increased efficacy and improved tolerability [32]. Our findings suggest the possibility of more targeted lipid-modifying strategies that could more effectively mitigate AS progression, tailored to the specific lipid profiles causally linked to the disease. This approach aligns with the current shift toward precision medicine, where treatment is customized based on individual genetic, environmental, and lifestyle factors. The exploration of lipid-modifying drug targets has highlighted the potential for personalized interventions in lipid management [33].

Furthermore, the causal association between lower levels of FGF19 and IL-6 and increased AS risk provides insights into the protective roles these inflammatory mediators may play in the disease's pathology. While inflammation is a recognized contributor to AS, our findings suggest that specific proteins might alleviate the disease's progression. These results prompt a reevaluation of the inflammation hypothesis in AS, pointing out the differential impacts of inflammatory mediators on cardiovascular health [8, 9]. Although our research on the mediated roles of inflammatory proteins did not demonstrate a direct pathway through which lipids influence AS via inflammation, it does not diminish the potential relevance of the lipid-inflammation relationship in AS pathology. The complex interplay between lipid levels and inflammatory processes remains an area ripe for further exploration, particularly considering the diverse roles of various lipid types and inflammatory mediators. Understanding this dynamic could reveal new insights into AS mechanisms, offering new avenues for interventions that address both lipid dysregulation and inflammation.

Given the complexity of AS, our study emphasizes the need for further research to untangle the intricate web of genetic, metabolic, and inflammatory factors leading to its pathogenesis. Future studies should explore potential interactions between different lipid types, a broader range of inflammatory mediators, and their cumulative impact on AS. Additionally, integrating advanced omics technologies could illuminate the molecular mechanisms driving these associations, providing a more comprehensive understanding of AS etiology and identifying novel therapeutic targets. Interventional studies targeting specific

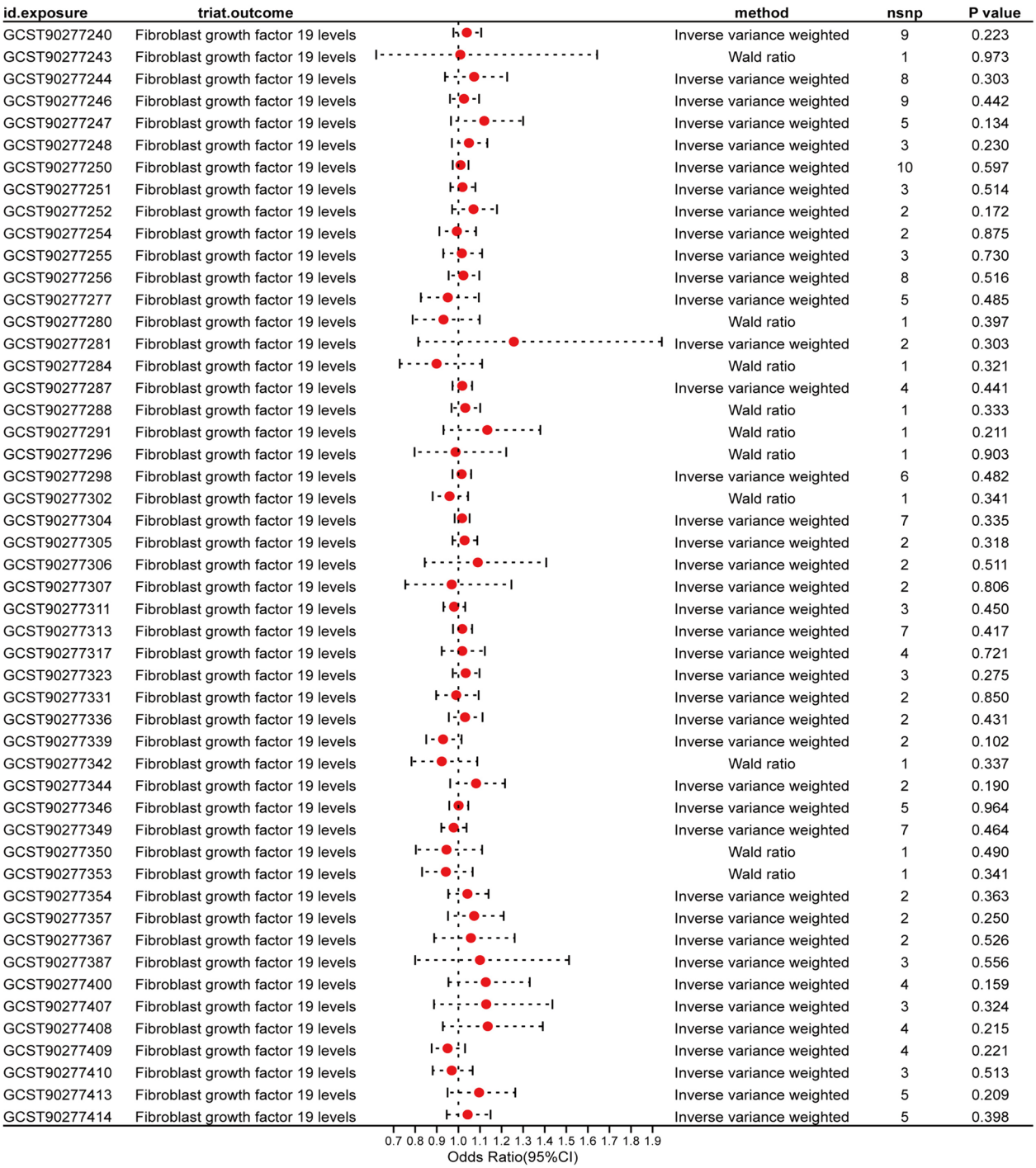

Fig. 4 Mediated Mendelian randomization results of lipidome causally associated with aortic stenosis and fibroblast growth factor 19 levels. nsnp, number of single nucleotide polymorphisms

lipid molecules could provide empirical evidence of their role in AS pathogenesis and their potential therapeutic value.

Our research delves into the lipidome and proteome, offering a comprehensive analysis of the causal relationships between lipid types, inflammatory proteins, and AS. This dual focus enriches our understanding and presents the subtleties of AS pathogenesis, where both lipid metabolism and inflammatory processes play significant roles. The study's strengths

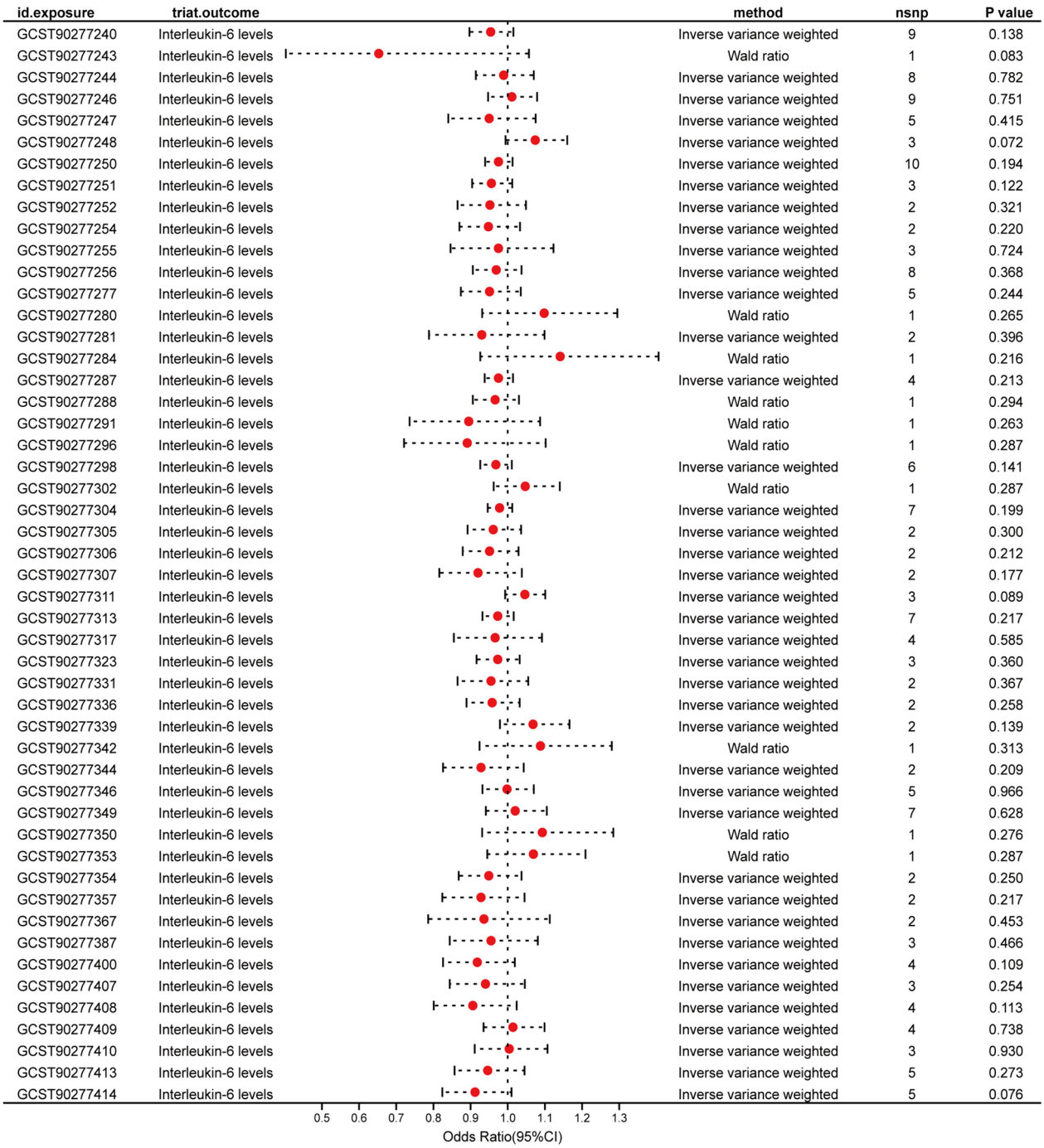

Fig. 5 Mediated Mendelian randomization results of lipidome causally associated with aortic stenosis and interleukin-6 levels

include the robust methodology of MR, which clarifies causal pathways using genetic proxies, and a wide-ranging analysis including various lipids and proteins, highlighting potential therapeutic targets. However, while MR is a powerful tool for inferring causality, it is subject to certain biases, such as pleiotropy, where genetic variants influence multiple traits, potentially confounding the results. We attempted to mitigate this using robust statistical methods like MR-Egger and MR-RAPS, but some residual bias may remain. The cross-sectional nature of GWAS data also limits our ability to infer temporal relationships. Although MR can help establish causality, it cannot fully address the directionality of the relationships between lipids, inflammatory proteins,

and AS. Other challenges, such as the generalizability of the study across different populations, the complex interactions between metabolic and inflammatory pathways, and translating these genetic insights into practical clinical interventions, remain. Additionally, the data sources themselves also introduce potential sources of bias. For example, measurement bias in the lipidomic and proteomic data could affect the reliability of our findings [23]. Lipid and protein levels can be influenced by various pre-analytical and analytical factors, leading to measurement variability. This variability can introduce noise into the data, potentially obscuring true associations or creating spurious ones. Despite these obstacles, our integrated approach to studying the lipidome and proteome emphasizes the complexity of AS and paves the way for new diagnostic and therapeutic strategies, highlighting the importance of a multifaceted understanding of cardiovascular diseases.

Conclusion

Our investigation provides novel insights into the genetic and molecular landscape of AS, identifying key lipid and inflammatory proteins that influence the disease. We found certain lipids that increase AS risk and others that may protect against it, along with evidence that proteins like FGF19 and IL-6 could lower AS risk. Although we did not find direct links between these proteins and how lipids affect AS, our results opened up new avenues for targeted treatments. By deepening our understanding of AS's underlying causes, we pave the way for personalized approaches to managing this condition, offering hope for better prevention and therapy options in future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02014-z.

Additional file 1: Table S1. Detailed information on the genome-wide association studies (GWAS) of 179 lipids. Table S2. Detailed information on the GWAS of 91 inflammatory proteins. Table S3. Genetic instrumental variables for lipid groups. Table S4. Mendelian randomization estimates of lipidome and aortic stenosis. Table S5. Genetic instrumental variables of inflammatory proteomes. Table S6. Mendelian randomization estimates of inflammatory proteomes and aortic stenosis. Table S7. Mediated Mendelian randomization results of lipid groups and fibroblast growth factor 19 levels assessed using robust adjusted profile score (RAPS) approach. Table S8. Mediated Mendelian randomization results of lipid groups and interleukin-6 levels assessed using robust adjusted profile score (RAPS) approach.

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None

Author contributions
L. Z. and N. L. Conceptualization, Data interpretation, Writing-Original draft preparation, Software, Resources. L. S. and G. S. Conceptualization, Writing-review & editing, Funding acquisition. L. Z. and H. S. Methodology, Investigation, Supervision.

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Availability of data and materials
All data supporting the findings of this study are included in this article and its supplementary materials.

Declarations

Ethics approval and consent to participate
All datasets complied with the ethical guidelines established in their original studies, so no additional ethical approval was required for this reanalysis.

Consent for publication
All authors approved the final version and agreed to be responsible for the study.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiovascular Surgery, Lihuili Hospital Affiliated to Ningbo University, Ningbo 315041, Zhejiang, China. [2]Institute of Pharmaceutics, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China.

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