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HMGCR as a promising molecular target for therapeutic intervention in aortic aneurisms: a mendelian randomization study

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Abstract

Background Despite the exploration of the connections between serum low-density lipoprotein cholesterol (LDL-C) levels and aneurisms in epidemiological studies, causality remains unclear. Therefore, this study aimed to assess the causal impact of LDL-C-lowering targets (*HMGCR*, *PCSK9*, *NPC1L1*, *CETP*, *APOB*, and *LDLR*) on various forms of aneurisms using Mendelian Randomization (MR) analysis.

Methods Two genetic instruments acted as proxies for exposure to LDL-C-lowering drugs: expression quantitative trait loci of drug target genes and genetic variants linked to LDL-C near drug target genes. Summary-data-based MR (SMR), inverse-variance-weighted MR (IVW-MR), and multivariable MR (MVMR) methods were employed to compute the effect estimates.

Results The SMR analysis revealed substantial associations between increased *HMGCR* expression and a heightened risk of aortic aneurism (odds ratio [OR] = 1.603, 95% confidence interval [CI] = 1.209–2.124), thoracic aortic aneurism (OR = 1.666, 95% CI = 1.122–2.475), and abdominal aortic aneurism (OR = 1.910, 95% CI = 1.278–2.856). Likewise, IVW-MR analysis demonstrated positive correlations between *HMGCR*-mediated LDL-C and aortic aneurism (OR = 2.228, 95% CI = 1.702–2.918), thoracic aortic aneurism (OR = 1.751, 95% CI = 1.191–2.575), abdominal aortic aneurism (OR = 4.784, 95% CI = 3.257–7.028), and cerebral aneurism (OR = 1.993, 95% CI = 1.277–3.110). Furthermore, in the MVMR analysis, accounting for body mass index, smoking, and hypertension, a significant positive relationship was established between *HMGCR*-mediated LDL-C levels and the development of aortic aneurisms, encompassing both thoracic and abdominal subtypes. Similarly, consistent positive associations were observed for *PCSK9* and *CETP* genes, as well as *PCSK9*-mediated and *CETP*-mediated LDL-C levels, with the occurrence of aortic aneurism and abdominal aortic aneurism. Nonetheless, the evidence for potential associations between *APOB*, *NPC1L1* and *LDLR* with specific subtypes of aortic aneurisms lacked consistent support from both SMR and IVW-MR analyses.

Conclusions Our MR analysis offered compelling evidence of a plausible causal link between *HMGCR* and an increased risk of aortic aneurism, encompassing both thoracic and abdominal types. These groundbreaking findings

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further bolster the case for the deployment of *HMGCR* inhibitors in the treatment of aortic aneurisms, including both thoracic and abdominal variants.

Keywords LDL-C-lowering targets, Aneurism, Summary-data-based mendelian randomization, Two-sample mendelian randomization

Background

Arterial aneurisms, specifically cerebral, thoracic, and abdominal aortic aneurisms, are relatively infrequent yet perilous conditions characterised by elevated mortality and incidence rates [1]. Dyslipidaemia, widely recognized as a major risk factor for coronary artery disease [2], has been extensively studied for its close correlation with various arterial aneurisms, including cerebral aneurism [3], abdominal aortic aneurisms [4], and thoracic aortic aneurisms [5]. Recent findings suggest the potential of regulating lipid metabolism-related target genes as novel molecular targets for the management of arterial aneurisms. For instance, Chen et al. unveiled a tenuous connexion between therapeutic triglyceride reduction, achieved by modulating angiopoietin-like 3 (*ANGPTL3*) and lipoprotein lipase (*LPL*) genes, and a decreased risk of aortic and abdominal aortic aneurisms [6]. Furthermore, spearheading the research, Harrison et al. highlighted a significant link between therapeutic LDL-C reduction through the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes, and increased high-density lipoprotein cholesterol (HDL-C) levels via cholesteryl ester transfer protein (*CETP*) gene regulation, leading to a reduced risk of abdominal aortic aneurism [7]. These studies have partially elucidated the substantial potential of lipid-lowering therapy in averting aortic aneurisms, particularly abdominal aortic aneurisms. However, due to LDL-C being a primary risk factor for cardiovascular diseases and one of the most scrutinised lipid types in lipid-lowering therapies [8], there is currently a dearth of systematic investigation into the potential causal relationship between target genes regulating LDL-C levels and different types of arterial aneurisms. Further exploration in this domain will establish a more robust foundation for the application of LDL-C-lowering therapy in the treatment of aneurisms.

Mendelian Randomisation (MR) stands as one of the most prevalent and sturdy methods, commonly utilised to explore causal associations between exposures and outcomes [9–11]. The random allocation of genotypes during conception (Mendel's second law) enables MR analysis, using genotypes as instrumental variables, to effectively minimise the influence of confounding and reverse causality. While MR historically focussed on unravelling causal links between circulating biomarkers and disease phenotypes [12–14], its current application has expanded to further investigate the causal relationships between potential drug targets and diseases [15–17]. In this context, genetic variants within genes encoding potential drug targets serve as instrumental variables to examine the feasibility of targeting specific pathways in distinct disease states [18–20].

Nevertheless, one of the foremost challenges encountered in MR studies of complex traits, notably lipid fractions, is genetic pleiotropy. This phenomenon pertains to the impact of single nucleotide polymorphisms (SNPs) on the circulating concentrations of multiple lipid fractions. The intricacy of pleiotropy lies in the fact that an SNP, or the combined effect of multiple SNPs, may be associated with various discrete pathways, each potentially displaying different connections with arterial aneurisms. Consequently, such pleiotropic effects may introduce potential bias in MR estimates. To surmount these hurdles, recent strides in the methodology, including Summary-data-based MR (SMR), Inverse-variance-weighted MR (IVW-MR), and multivariable MR (MVMR), have been deployed to enhance precision and mitigate potential bias [21]. Given these methodological advancements, we evaluated the association of LDL-C-lowering targets, including *HMGCR*, *PCSK9*, *CETP*, apolipoprotein B (*APOB*), Niemann-pick C1-like 1 (*NPC1L1*), and low-density lipoprotein receptor (*LDLR*) with distinct types of aneurisms.

Methods

Study design

In this two-sample MR study, we relied on publicly available summary-level data obtained from genome-wide association studies (GWASs) and expression quantitative trait loci studies (eQTLs) (Supplementary Table 1). The relevant codes for SMR analysis, IVW-MR analysis, and MVMR analysis in this study have been presented in Supplementary Table 2. Ethical approval for all original studies was acquired from the respective institutional review boards, and explicit informed consent was obtained from all study participants.

Selection of genetic instruments

Table 1 presents the application of available eQTLs for genes targeted by medicinal compounds, specifically *HMGCR*, *PCSK9*, *NPC1L1*, *LDLR*, *CETP*, and *APOB*, as proxies to evaluate exposure to individual lipid-lowering medications. The summary-level data on eQTLs were sourced from either the eQTLGen

Table 1 Information of genetic instruments

Exposure	Genetic instruments	
	Genetic variants (MAF > 1%, $p < 5.0 \times 10-8$) associated with mRNA expression levels (eQTLs)	**Genetic variants (MAF > 1%) in low linkage disequilibrium (r2 < 0.30), associated with LDL cholesterol ($p < 5.0 \times 10-8$), located within ± 100 kb windows from lipids-related genes region**
HMGCR	Nine hundred and twenty-one common cis-eQTLs in blood for HMGCR gene, top SNP: rs6453133	rs12916, rs3804231, rs10515198, rs10066707, rs12659791, rs72633962, rs3857388
PCSK9	Twenty-four common cis-eQTLs in blood for PCSK9 gene, top SNP: rs472495	rs11591147, rs11206510, rs2479409, rs585131, rs11206514, rs572512, rs2479394, rs12067569, rs10493176, rs4927193, rs11583974, rs2495495
CETP	One hundred and twenty-eight common cis-eQTLs in blood for CETP gene, top SNP: rs1532624	rs12920974, rs1864163, rs12448528, rs247616
LDLR	Eighteen common cis-eQTLs in blood for LDLR gene, top SNP: rs8110515	rs7257769, rs12983316, rs3786722, rs73015030, rs1529711, rs6511720, rs11669133, rs688, rs3786721, rs36005514, rs1010679
NPC1L1	Eleven common cis-eQTLs in adipose subcutaneous tissue for NPC1L1 gene, top SNP: rs41279633	rs2073547, rs217386, rs7791240
APOB	One hundred and sixty-one common cis-eQTLs in adipose subcutaneous tissue for APOB gene, top SNP: rs4665179	rs492399, rs11679386, rs6729410, rs10198175, rs10178381, rs12710745, rs13027175

Consortium (https://www.eqtlgen.org/) or the GTEx Consortium V8 (https://gtexportal.org/), with comprehensive details included in Supplementary Table 1. Our focus was directed towards identifying common eQTL single-nucleotide polymorphisms (SNPs) (minor allele frequency [MAF] > 1%) significantly linked to the expression of *HMGCR*, *CETP*, *LDLR*, or *PCSK9* in blood, and the expression of *NPC1L1* or *APOB* in adipose subcutaneous tissue, applying a significance threshold of $p < 5.0 \times 10^{-8}$. Notably, for *NPC1L1* and *APOB*, no eQTLs in blood or other tissues reached the predetermined significance level. When constructing genetic instruments, only cis-eQTLs were considered, denoting eQTLs located within 1 Mb on both sides of the target gene.

To further affirm the observed associations using eQTLs as instrumental variables, we also introduced an additional instrument by selecting specific SNPs within 100 kb windows from the target gene of each medication. These SNPs exhibited an association with LDL-C levels at a genome-wide significance level ($p < 5.0 \times 10^{-8}$) and were utilised as proxies for exposure to lipid-lowering drugs. The GWAS summary data for LDL-C levels were obtained from the Global Lipids Genetics Consortium (GLGC), featuring an extensive sample size of 173,082 individuals [22] (Supplementary Table 1). Throughout the selection process, only common SNPs (MAF > 1%) were taken into account. Amongst the identified SNPs, seven were found within 100 kb regions of the *HMGCR* gene. Additionally, twelve SNPs were identified from the *PCSK9* gene, and three SNPs were carefully chosen from the *NPC1L1* gene. Moreover, four SNPs were identified from the *CETP* gene, while eleven SNPs were selected from the *LDLR* gene, and seven SNPs were chosen from the *APOB* gene (Table 1). To ensure the robustness and validity of each instrumental variable, we meticulously assessed the selected SNPs for weak linkage disequilibrium (r2 < 0.30) with one another.

Outcome sources

GWAS summary-level data pertaining to outcomes of arterial aneurisms, involving aortic aneurism (7395 cases and 349539 controls), thoracic aortic aneurism (3510 cases and 349539 controls), abdominal aortic aneurism (3548 cases and 349539 controls), other aneurisms (1530 cases and 349539 controls), and nonruptured cerebral aneurism (2582 cases and 342673 controls), were acquired from FinnGen Round 9. Comprehensive links for downloading these GWAS datasets can be found in Supplementary Table 1.

MR analyses

In the primary MR analysis, we employed the SMR method, utilising eQTLs as instrumental variables to estimate effect sizes. This approach evaluated the association between gene expression levels and the outcome of interest by leveraging summary-level data from both GWAS and eQTL investigations [23].We utilised SMR software, version 1.03, available at https://cnsgenomics.com/software/smr/#Overview, for allele harmonisation and analysis. Furthermore, the IVW-MR method was adopted to amalgamate effect estimates in the analysis that incorporated genetic variants linked to LDL-C levels as instrumental variables. This method facilitates the exploration of causal relationships with the outcome of interest. Allele harmonisation and analysis for this segment of the study were carried out using the "TwoSampleMR" package [24] in R software, version 4.3.0.

Sensitivity analyses

The robustness of SNPs employed as instrumental variables was appraised thru the *F*-statistic, and SNPs with an *F*-statistic exceeding 10 were included to mitigate potential weak instrument bias [25]. Positive control analyses were carried out to corroborate both genetic instruments. Given that reducing LDL-C levels is a well-established effect of lipid-lowering medications, we scrutinised the association of our areas of interest with LDL-C levels, serving as a positive control study for the instrument derived from eQTLs. As lowering LDL cholesterol levels is a well-established effect of lipid-lowering drugs, we examined the association of exposures of interest with LDL levels as a positive control study for the instrumental variables derived from eQTLs. Additionally, for the instrument derived from LDL cholesterol GWAS, we performed a positive control study by investigating the association of exposures of interest with coronary heart disease, given that it represents the primary indication for lipid-lowering drugs.

Employing the SMR method, we employed the heterogeneity in dependant instruments (HEIDI) test to scrutinise whether the observed association between gene expression and the outcome could be attributed to a linkage scenario. This analytical investigation was executed using the SMR software [23], and a p-value of <0.01 in the HEIDI test indicates potential linkage [26]. It is imperative to acknowledge that a single SNP might be associated with the expression of multiple genes, giving rise to the potential of horizontal pleiotropy. To assess the risk of horizontal pleiotropy, we identified other nearby genes (within a 1 Mb window) demonstrating a substantial association with the genetic instrumental variant. Subsequently, we conducted SMR analysis to explore whether the expression of these genes correlated with arterial aneurism outcomes.

In the context of the IVW-MR method, we performed a Cochran Q test to examine heterogeneity, where $p<0.05$ would signify evidence of heterogeneity [27]. To evaluate potential horizontal pleiotropy of the SNPs used as instrument variants, two methodologies were employed: MR-Egger regression and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis. In MR Egger regression, the intercept term was scrutinised for directional horizontal pleiotropy, with $p<0.05$ indicating evidence of such pleiotropy [28]. Moreover, MR-PRESSO analysis allowed us to pinpoint horizontal pleiotropic outliers and provide adjusted estimates, with $p<0.05$ for the Global test indicating the presence of such outliers [29]. Additionally, a MVMR study was conducted to probe the directness of the observed association. Initially, we examined the association of *HMGCR*-mediated LDL-C with common risk factors, encompassing body mass index, diabetes, hypertension, and smoking. Subsequently, a MVMR study was undertaken, incorporating adjustments for factors displaying significant associations, to investigate the correlation between *HMGCR*-mediated LDL-C levels and aortic aneurism. All analyses were conducted using R software, version 4.3.0.

Results

Genetic instruments selection

Tables 1and Supplementary Table 3 delineate a total of 921, 24, 128, 18, 11, and 161 cis-eQTLs identified from eQTLGen or the GTEx Consortium for the genes *HMGCR*, *PCSK9*, *CETP*, *LDLR*, *NPC1L1*, and *APOB*, respectively. The most significant cis-eQTL SNP was chosen as the genetic instrument for each respective target gene. Additionally, we meticulously selected 7, 12, 4, 11, 3, and 7 SNPs within or in close proximity to genes *HMGCR*, *PCSK9*, *CETP*, *LDLR*, *NPC1L1*, and *APOB*, respectively, from a GWAS summary dataset on LDL-C levels obtained from the GLGC. Notably, all instrument variants manifested *F*-Statistics surpassing 20, thereby ensuring effective mitigation of any potential bias arising from weak instruments in our study (Supplementary Table 4). Substantiating the robustness of the selected genetic instruments, positive control analyses established significant associations between exposures, including genes *HMGCR*, *PCSK9*, *CETP*, *LDLR*, *NPC1L1*, *APOB* and LDL-C levels when utilising proposed eQTL-based instruments (Supplementary Table 5), as well as between exposures and coronary heart disease when employing LDL-C GWAS-proposed instruments (Supplementary Table 6).

Primary analysis

The results depicted in Fig. 1 and Supplementary Table 7 unveil substantial associations between augmented expression of *HMGCR* and an escalated risk of aortic aneurism (odds ratio [OR] = 1.603, 95% confidence interval [CI] = 1.209–2.124; $p=0.0008$), thoracic aortic aneurism (OR = 1.666, 95% CI = 1.122–2.475; $p=0.0103$), and abdominal aortic aneurism (OR = 1.910, 95% CI = 1.278–2.856; $p=0.0013$). Similarly, heightened expression of *PCSK9* exhibited an association with an elevated risk of aortic aneurism (OR = 1.290, 95% CI = 1.064–1.564; $p=0.0058$) and abdominal aortic aneurism (OR = 1.498, 95% CI = 1.132–1.983; $p=0.0023$), while amplified expression of *CETP* was related to a higher risk of aortic aneurism (OR = 1.417, 95% CI = 1.088–1.847; $p=0.0089$) and abdominal aortic aneurism (OR = 2.138, 95% CI = 1.453–3.147; $p=0.0001$). These findings suggest potential advantages of *HMGCR* inhibitors in reducing the risk of aortic aneurism, encompassing both abdominal and thoracic subtypes. Furthermore, *PCSK9* and *CETP* inhibitors might also contribute to a reduced risk of abdominal aortic aneurism. Encouragingly, there were suggestive

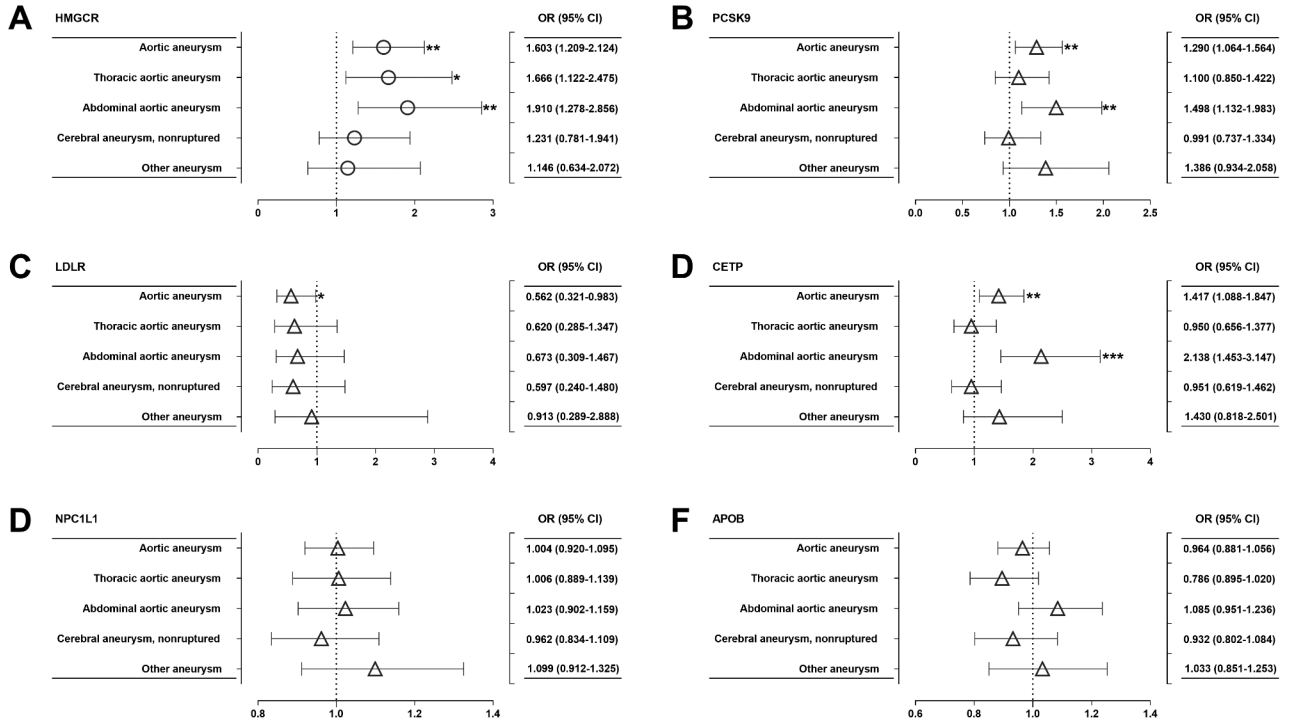

Fig. 1 Summary-data-based Mendelian randomization (SMR) analysis illustrating the correlation between the expression of genes *HMGCR*, *PCSK9*, *LDLR*, *CETP*, *NPC1L1*, and *APOB*, and various types of aneurisms

findings of a negative association between *LDLR* expression and the risk of aortic aneurism (OR=0.562, 95% CI=0.321–0.983; p=0.0359). However, no significant association was discerned between the expression of *NPC1L1*, *APOB*, and various types of arterial aneurisms.

Fig. 2 and Supplementary Table 8 illustrate the IVW-MR analysis, offering suggestive evidence for the link between *HMGCR*-mediated LDL-C (equivalent to a 1 mmol/l increase) and an augmented risk of aortic aneurism (OR=2.228, 95% CI=1.702–2.918; p=5.75E-09), thoracic aortic aneurism (OR=1.751, 95% CI=1.191–2.575; p=0.0044), abdominal aortic aneurism (OR=4.784, 95% CI=3.257–7.028; p=1.48E-15), and nonruptured aortic aneurism (OR=1.993, 95% CI=1.277–3.110; p=0.0024). These findings further bolster the potential protective impact of *HMGCR* inhibitors against various types of arterial aneurisms. Additionally, a robust positive correlation surfaced between *PCSK9*-mediated LDL-C and the risk of aortic aneurism (OR=1.226, 95% CI=1.095–1.464; p=0.0015), abdominal aortic aneurism (OR=1.631, 95% CI=1.318–2.018; p=6.61E-06), and other aneurism (OR=1.813, 95% CI=1.319–2.491; p=0.0002). Furthermore, *CETP*-mediated LDL-C was positively related to the risk of aortic aneurism (OR=2.928, 95% CI=1.863–4.600; p=3.18E-06) and abdominal aortic aneurism (OR=7.867, 95% CI=4.115–15.040; p=4.42E-10). Moreover, *LDLR*-mediated LDL-C was favourably associated with the risk of abdominal aortic aneurism (OR=2.217, 95% CI=1.750–2.809; p=4.16E-11), while exhibiting an unfavourable association with the risk of thoracic aortic aneurism (OR=0.634, 95% CI=0.504–0.797; p=9.67E-05). However, the IVW-MR analysis failed to furnish any corroboration for the association between *NPC1L1*-mediated LDL-C, *APOB*-mediated LDL-C, and various types of arterial aneurisms. Furthermore, all causal inferences obtained through the IVW-MR method exhibit statistical power exceeding 0.8, with a Type I error rate of 0.05 (Supplementary Table 8). In addition, the results of the MVMR analysis (Fig. 3), controlling for conventional aneurysm risk factors, including hypertension, BMI, and smoking, further underscore the independent impact of *HMGCR*-mediated LDL-C levels on the heightened risk of aortic aneurysm (OR = 1.920, 95% CI = 1.450–2.542; p = 5.20E-06), thoracic aortic aneurysm (OR = 1.519, 95% CI = 1.026–2.249; p = 0.036) and abdominal aortic aneurysm (OR = 3.697, 95% CI = 2.542–5.378; p = 8.05E-12).

Sensitivity analysis

In the SMR analysis, the HEIDI test indicated that all observed associations remained uninfluenced by potential linkage scenarios (p>0.01) (Supplementary Table 7). To delve further into the prospective presence of horizontal pleiotropy in the association between *HMGCR* expression and different types of arterial aneurisms, we probed whether any link existed between the

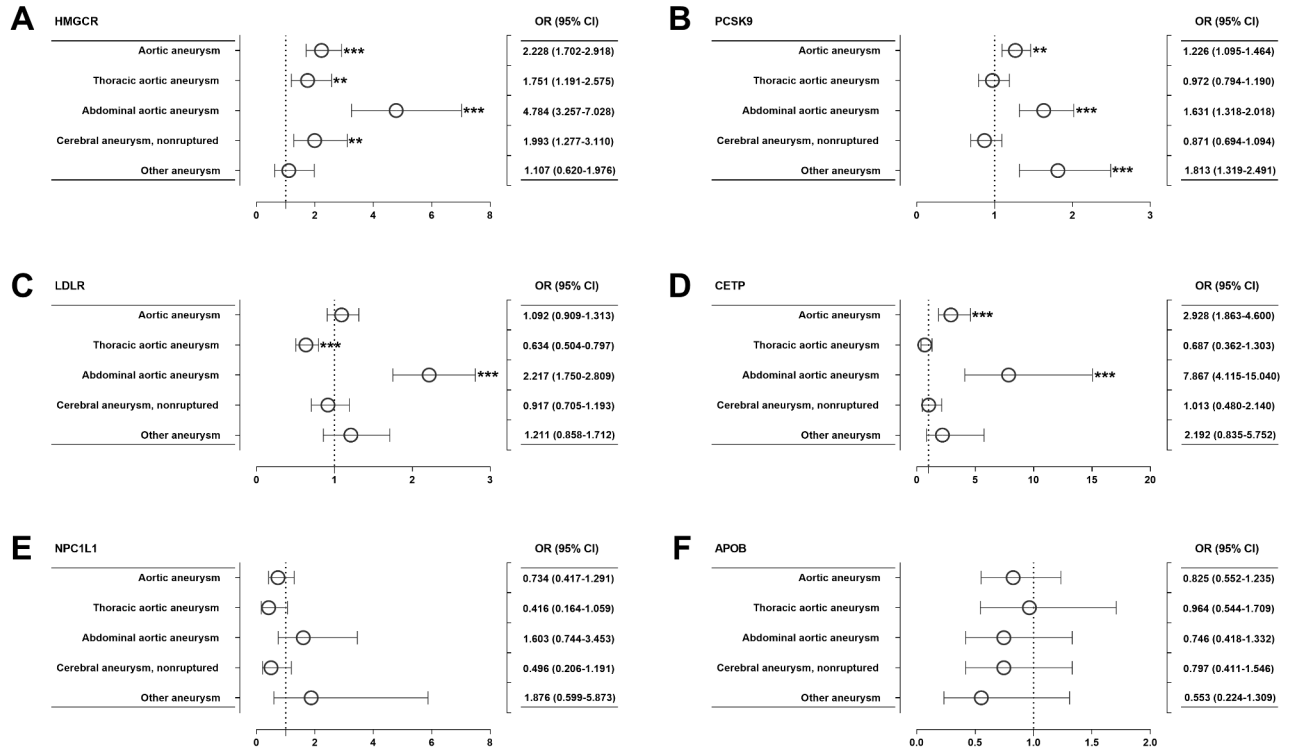

Fig. 2 Inverse-variance-weighted Mendelian randomization (IVW-MR) analysis delineating the connexion between LDL-C levels influenced by genes *HMGCR*, *PCSK9*, *LDLR*, *CETP*, *NPC1L1*, or *APOB* and diverse forms of aneurisms

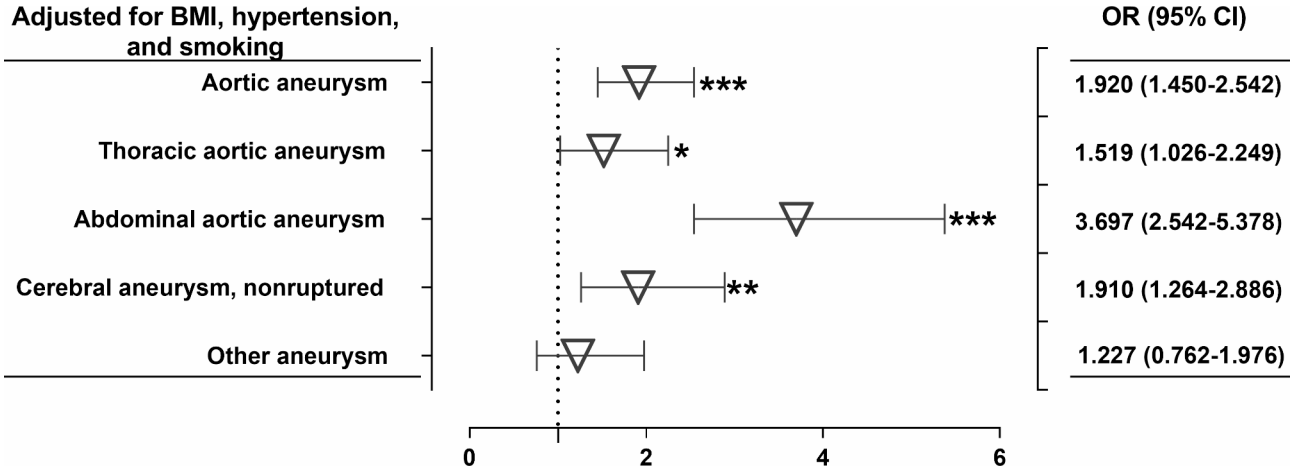

Fig. 3 Relationship between LDL-C levels modulated by the gene *HMGCR* and diverse forms of aneurisms, adjusted for BMI, hypertension, and smoking in multivariable MR (MVMR) analysis

expression of neighbouring genes significantly associated with the top eQTL SNP (rs6453133) of *HMGCR* and various types of arterial aneurisms. Amongst the six identified genes, including POC5 centriolar protein (*POC5*), ankyrin repeat and death domain containing 1B (*ANKDD1B*), ceramide transporter 1 (*CERT1*, also known as *COL4A3BP)*, DNA polymerase kappa (*POLK*), ankyrin repeat domain 31 (*ANKRD31*), and *HMGCR*, whose expression was linked to the instrument variant of rs6453133 (Supplementary Table 9), only *HMGCR*, *ANKDD1B*, *POLK* and *POC5* displayed available eQTLs at a genome-wide significance level ($p<5.0\times10^{-8}$). Significantly, amongst these genes, solely *HMGCR* expression portrayed a significant relationship with aortic aneurisms, comprising both thoracic and abdominal subtypes, thus suggesting a delimited role of horizontal pleiotropy in the observed associations (Supplementary Table 10).

In the IVW-MR analysis, the Cochran Q test did not yield any evidence of heterogeneity for all reported results (all $p>0.05$; Supplementary Table 8). Likewise, both the intercept term in MR-Egger regression and MR-PRESSO analysis suggested no significant overall horizontal pleiotropy (all $p>0.05$; Supplementary Table 8). Furthermore, traditional risk factors, encompassing smoking, hypertension, and body mass index (BMI), showcased notable positive correlations with various types of arterial aneurisms (Supplementary Table 11). Moreover, in the MVMR analysis, on accounting for BMI, smoking, and hypertension, a substantial positive relationship was established between *HMGCR*-mediated LDL-C levels and the development of aortic aneurisms, comprising both thoracic and abdominal subtypes (Supplementary Table 12).

Discussion

Aortic aneurism, encompassing both thoracic and abdominal types, ranks as the second most prevalent aortic disorder following atherosclerosis and has the potential to impact any segment of the aorta [30]. The estimated number of annual aortic aneurism-related mortalities worldwide stands at approximately 200,000 deaths [31]. Given the absence of effective pharmacological treatments, surgical repair remains the primary approach for managing aortic aneurisms. Therefore, investigating drugs that could be repurposed for the treatment of aortic aneurisms carries significant practical significance in reducing their incidence and mortality rates and alleviating the burden of surgical interventions. Furthermore, repurposing existing drugs presents a more cost-effective and time-saving approach compared to developing novel therapies.

The pivotal role of lipid metabolism disorders, particularly elevated LDL-C levels, in the pathophysiological process of aortic aneurism has garnered increasing scholarly attention. Kanaoka et al., in a clinical study involving 166 patients diagnosed with abdominal aortic aneurisms, observed that achieving a postoperative reduction in the LDL-C/HDL-C ratio to <1.5 significantly correlated with reduced risk of late cardiovascular events following surgical treatment for abdominal aortic aneurisms [32]. Similarly, Chen et al. conducted an extensive investigation exploring the relationship between blood lipid levels and various types of arterial aneurisms, unveiling a positive association between high LDL-C levels and the risk of both aortic and abdominal aortic aneurisms. Despite these efforts, their analysis on the causal relationship between LDL-C metabolism-related target genes (*HMGCR*, *NPC1L1*, *PCSK9*, *CETP*, and *LDLR*) and arterial aneurisms did not yield significant findings [6].

Furthermore, Harrison et al. proposed that elevated LDL-C levels were linked to an increased risk of abdominal aortic aneurism and suggested that LDL-C metabolism-related genes *PCSK9* and *HMGCR* could serve as potential molecular targets for effective treatment of abdominal aortic aneurism. However, they did not explore whether these LDL-C metabolism-related genes hold significant potential for treating thoracic aortic aneurism [7]. Despite its lower incidence rate compared to abdominal aortic aneurism, thoracic aortic aneurism exhibits a poorer prognosis, with notably higher mortality rates attributed to its rupture [33, 34]. Therefore, deeper exploration of the potential causal relationship between LDL-C metabolism-related genes and thoracic aortic aneurisms can provide a robust theoretical foundation for the application of LDL-C-lowering drugs in their treatment, ultimately reducing incidence and mortality rates associated with this condition.

In this study, we employed the SMR method, utilising blood eQTLs as instrumental variables to investigate the causal relationship between LDL-C metabolism-related genes, specifically *HMGCR*, *NPC1L1*, *PCSK9*, *CETP*, *APOB*, and *LDLR*, and various types of arterial aneurisms, such as aortic aneurism, thoracic aortic aneurism, abdominal aortic aneurism, cerebral aneurism, and other aneurisms. Our investigation revealed a significant association between increased *HMGCR* expression and a higher risk of aortic aneurisms, including both thoracic and abdominal subtypes. Additionally, elevated expression of *PCSK9* and *CETP* demonstrated a strong correlation with an increased risk of aortic aneurism and abdominal aortic aneurism. Notably, our findings represent a novel contribution [7], being the first to suggest the potential benefits of *HMGCR* inhibitors in reducing the risk of aortic aneurisms, comprising both thoracic and abdominal subtypes. Nevertheless, *PCSK9* and *CETP* inhibitors may primarily contribute to lowering the risk of abdominal aortic aneurism, consistent with previous studies [7]. Furthermore, our results were further validated by IVW-MR analysis, employing SNP variants located in the LDL-C metabolism-related genetic region, which were selected from GWAS summary data associated with LDL-C levels in the GLGC as instrumental variables. One of the primary challenges encountered in MR studies of complex traits, particularly lipid fractions, is genetic pleiotropy. Thus, in this study, we explored the possibility of horizontal pleiotropy in the relationship between *HMGCR* expression and arterial aneurisms. To investigate these associations, we examined the relationships between nearby genes (*HMGCR* and *POC5*) linked to the top eQTL SNP (rs6453133), and arterial aneurisms. Amongst the identified genes, only *HMGCR* expression exhibited a significant relationship with aortic aneurisms, implying limited horizontal pleiotropy in the observed associations. Furthermore, in the IVW-MR analysis, additional investigations utilising MR-Egger regression

and MR-PRESSO analysis provided further evidence that the causal association between *HMGCR*-related LDL-C levels and aortic aneurisms remains unaffected by potential horizontal pleiotropy. In addition, the MVMR analysis, with adjustment for BMI, smoking, and hypertension, consistently showed a significant positive correlation between *HMGCR*-mediated LDL-C levels and the risk of aortic aneurisms, comprising both thoracic and abdominal subtypes. These robust findings underscored the potential of *HMGCR* as a promising molecular target for therapeutic intervention in aortic aneurisms. Notably, statins, the well-known *HMGCR* inhibitors, might also exhibit an unique role in the prevention and treatment of aortic aneurisms, extending beyond their established efficacy in managing atherosclerosis.

Several limitations existed in this study. Firstly, the lack of available eQTLs in blood for *NPC1L1* and *APOB* limited the comprehensive exploration of their associations with different types of arterial aneurisms. Moreover, the scarcity of accessible eQTLs for these target genes within the liver, a pivotal tissue intricately involved in lipid metabolism, might have provided more convincing evidence for the observed associations. Secondly, the unavailability of specific datasets restricted the comprehensive evaluation of *HMGCR*'s role in the progression and rupture of aortic aneurisms. Thirdly, the usage of summary-level data constrained the potential for subgroup analyses, necessitating individual-level data for more comprehensive MR investigations. Fourthly, despite conducting various sensitivity analyses, the potential for residual confounding and/or horizontal pleiotropy cannot be entirely dismissed. Lastly, the study's primary reliance on eQTL and GWAS data from European populations warrants cautious extrapolation of these findings to other ethnic groups.

Conclusion

In conclusion, our MR analysis provided robust evidence suggesting a rational causal link between the LDL-C metabolism target gene *HMGCR* and an elevated risk of aortic aneurisms, including both thoracic and abdominal variants. These groundbreaking discoveries established a solid theoretical foundation for the utilisation of *HMGCR* inhibitors, such as statins, as potential therapeutic agents for aortic aneurisms.

Abbreviations

LDL-C	Low-density lipoprotein cholesterol
MR	Mendelian randomization
IVW-MR	Inverse-variance-weighted mendelian randomization
SMR	Summary-data-based mendelian randomization
OR	Odds ratio
CI	Confidence interval
ANGPTL3	Angiopoietin-like 3
LPL	Lipoprotein lipase
HMGCR	3-hydroxy-3-methylglutaryl coenzyme A reductase
PCSK9	Proprotein convertase subtilisin/kexin type 9
HDL-C	High-density lipoprotein cholesterol
CETP	Cholesteryl ester transfer protein
SNPs	Single nucleotide polymorphisms
APOB	Apolipoprotein B
NPC1L1	Niemann-pick C1-like 1
LDLR	Low-density lipoprotein receptor
eQTLs	Expression quantitative trait loci studies
GWASs	Genome-wide association studies
MAF	Minor allele frequency
GLGC	Global Lipids Genetics Consortium
HEIDI	Heterogeneity in dependent instruments
MR-PRESSO	MR-Egger regression and Mendelian Randomization Pleiotropy RESidual Sum and Outlier
BMI	Body mass index
POC5	POC5 centriolar protein
ANKDD1B	Ankyrin repeat and death domain containing 1B
COL4A3BP/CERT1, POLK	DNA polymerase kappa
ANKRD31	Aankyrin repeat domain 31

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00849-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

Supplementary Material 12

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Author contributions

P.-F. Z. conceived the study, participated in the design, performed the statistical analyses, and drafted the manuscript. J.-J.R. and H.-W.P. conceived the study, participated in the design and helped to draft the manuscript. Z.-F.Z., H.J., and Z.-Y. L. contributed to the acquisition of genetic association data. All authors read and approved the final manuscript.

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Data availability
Individual-level data cannot be provided but the raw data of the eQTLGen Consortium, GTEx, Global Lipids Genetics Consortium, CARDIoGRAMplusC4D Consortium and FinnGen study can be acessed at https://www.eqtlgen.org/, https://gtexportal.org/, http://csg.sph.umich.edu/willer/public/lipids2013/, http://www.cardiogramplusc4d.org/, and https://console.cloud.google.com/storage/browser/finngen-public-data-r9/summary_stats;=objects?pli=1&prefix=&forceOnObjectsSortingFiltering=false, respectively. The detailed information about the IVs used in the analysis of this study can be obtained from **Supplementary Tables 3** and **4**.

Declarations

Ethics approval and consent to participate
This two-sample MR study is based on publicly available summary-level data from genome-wide association studies (GWASs) and expression quantitative trait loci (eQTLs) studies. All these studies had been approved by the relevant institutional review boards and participants had provided informed consents.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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