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ORIGINAL ARTICLE

Lipid-lowering and antihypertensive drugs on aortic disease risk: insights from Mendelian randomization analysis and real-world pharmacovigilance data

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Objective To assess the impact of lipid-lowering drugs (LLDs) and antihypertensive drugs on the risk of aortic diseases.

Methods Mendelian randomization was utilized to analyse data from 500 000 participants in the UK Biobank to evaluate the effects of statins, PCSK9 inhibitors (PCSK9i), β-blockers, and calcium channel blockers on the risks of thoracic aortic aneurysm, abdominal aortic aneurysm, and aortic dissection (AD) using genetic variants as proxies. Real-world pharmacovigilance data from the FAERS (FDA Adverse Event Reporting System) database were used.

Results PCSK9i and statins significantly reduced the risks of aortic aneurysms and AD, respectively. Furthermore, the two LLDs reduced the risk of aortic diseases through certain metabolites. Meanwhile, real-world pharmacovigilance reports also indicated a low incidence of aortic diseases with PCSK9i and statin treatment.

Conclusion LLDs, particularly statins and PCSK9i, significantly protect against aortic diseases, providing a scientific basis for preventing and treating aortic diseases.

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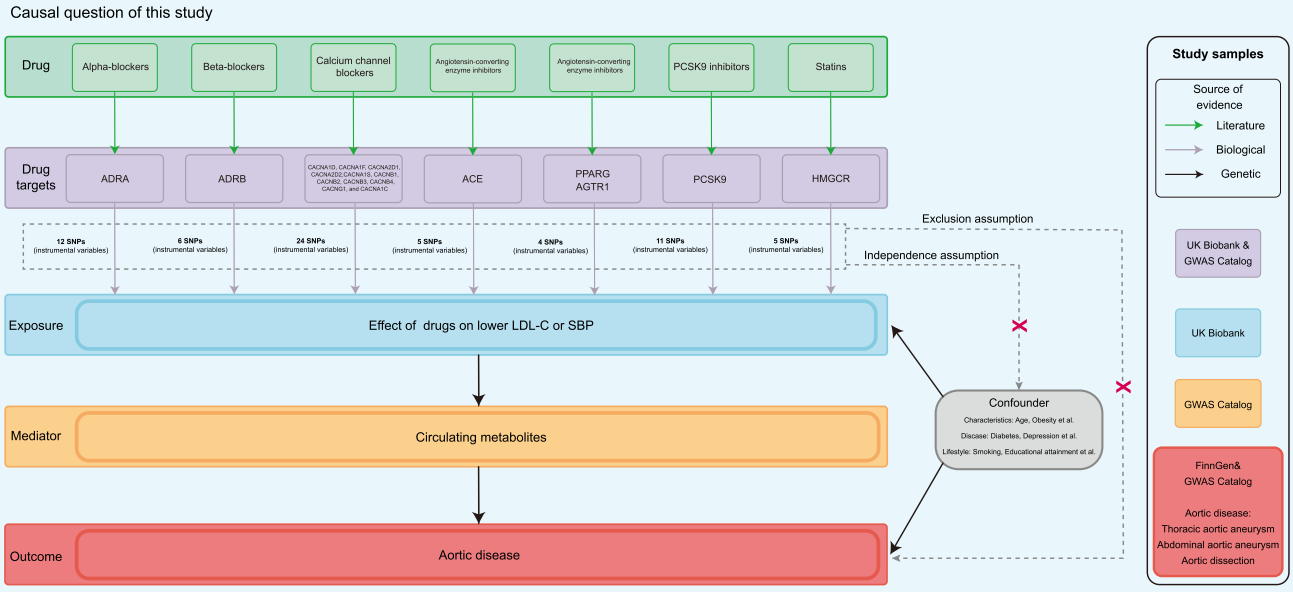
Graphical Abstract



Schematic overview of the causal analysis framework used to investigate the effects of lipid-lowering and antihypertensive drugs on aortic diseases.

Keywords Lipid-lowering drugs • Antihypertensive drugs • Aortic diseases • Mendelian randomization • Metabolites

Abbreviations

AA	aortic aneurysm
AAA	abdominal aortic aneurysm
ABs	α-blockers
ACEIs	angiotensin-converting enzyme inhibitors
AD	aortic dissection
ARBs	angiotensin II receptor blockers
AE	adverse events
BBs	β-blockers
CCBs	calcium channel blockers
CVD	cardiovascular disease
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GWAS	Genome-Wide Association Studies
HDL-C	HDL cholesterol
IVW	inverse variance weighted
LDL-C	LDL cholesterol
MR	Mendelian randomization
OR	odds ratio
PCSK9i	PCSK9 inhibitors
ROR	reporting odds ratio
SNPs	single-nucleotide polymorphisms
TAA	thoracic aortic aneurysm
VLDL-C	very low-density lipoprotein cholesterol

Introduction

Cardiovascular diseases (CVDs), particularly aortic diseases, are the leading cause of death worldwide.[1] Aortic diseases such as thoracic aortic aneurysm (TAA), abdominal aortic aneurysm (AAA), and aortic dissection (AD) represent significant subcategories of CVD with severe health implications.[2–4] Dyslipidaemia and hypertension are the major risk factors associated with these conditions.[5] Lipid-lowering drugs (LLDs) and antihypertensive drugs (AHTDs) are usually recommended, and their roles in reducing cardiovascular events have been extensively researched.[6,7]

LLDs and AHTDs have garnered substantial attention for their potential in preventing and treating aortic diseases.[8–10] However, despite substantial evidence confirming the significant role of these medications in reducing cardiovascular events, their impact on aortic diseases remains elusive.[11,12] Therefore, exploring their precise effects on TAA, AAA, and AD is imperative.

Several studies have explored the relationship between lipid levels and aortic diseases. Allara *et al.*[13] found that lowering LDL cholesterol (LDL-C) prevents ADs. Higher HDL cholesterol (HDL-C) levels reduced aortic aneurysm (AA) risk, while elevated triglyceride levels increased it.[14] PCSK9 inhibitors (PCSK9i) and statins both lower LDL-C, but PCSK9i were less effective at reducing very low-density lipoprotein cholesterol (VLDL-C).[15]

Hypertension is a well-established risk factor for aortic diseases. AHTDs such as α-blockers (ABs) and β-blockers (BBs) can control blood pressure and stress on aortic wall to reduce cardiovascular risk.[16,17] Calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs) can lead to vasodilation and reduced blood pressure.[18,19] Kwok and Schooling[20] suggested that PCSK9i and AHTDs may extend the male lifespan, emphasizing potential benefits in the comprehensive management of aortic diseases.

This study integrates Mendelian randomization (MR) analysis with real-world pharmacovigilance data from the FDA Adverse Event

exposure	outcome	nsnp	method	pval	OR(95% CI)
ABs	Thoracic aortic aneurysm	9	Inverse variance weighted	0.169	0.940 (0.865 to 1.021)
ABs	Abdominal aortic aneurysm	9	Inverse variance weighted	0.298	0.941 (0.846 to 1.048)
ABs	Aortic dissection	9	Inverse variance weighted	0.392	0.890 (0.702 to 1.128)
BBs	Thoracic aortic aneurysm	6	Inverse variance weighted	0.400	0.962 (0.881 to 1.050)
BBs	Abdominal aortic aneurysm	6	Inverse variance weighted	0.636	1.024 (0.927 to 1.131)
BBs	Aortic dissection	6	Inverse variance weighted	0.824	0.983 (0.843 to 1.145)
CCBs	Thoracic aortic aneurysm	22	Inverse variance weighted	**0.016**	0.944 (0.903 to 0.987)
CCBs	Abdominal aortic aneurysm	22	Inverse variance weighted	0.371	0.975 (0.924 to 1.029)
CCBs	Aortic dissection	22	Inverse variance weighted	0.964	1.002 (0.916 to 1.096)
ACEIs	Thoracic aortic aneurysm	4	Inverse variance weighted	0.738	1.017 (0.920 to 1.124)
ACEIs	Abdominal aortic aneurysm	4	Inverse variance weighted	0.810	1.022 (0.852 to 1.226)
ACEIs	Aortic dissection	4	Inverse variance weighted	0.368	0.898 (0.727 to 1.109)
ARBs	Thoracic aortic aneurysm	4	Inverse variance weighted	0.645	1.035 (0.891 to 1.202)
ARBs	Abdominal aortic aneurysm	4	Inverse variance weighted	0.389	0.917 (0.766 to 1.098)
ARBs	Aortic dissection	4	Inverse variance weighted	0.178	1.251 (0.832 to 1.880)
Statins	Thoracic aortic aneurysm	5	Inverse variance weighted	**<0.001**	0.527 (0.442 to 0.629)
Statins	Abdominal aortic aneurysm	5	Inverse variance weighted	**<0.001**	0.228 (0.205 to 0.254)
Statins	Aortic dissection	5	Inverse variance weighted	**0.012**	0.248 (0.190 to 0.324)
PCSK9	Thoracic aortic aneurysm	11	Inverse variance weighted	**0.002**	0.805 (0.720 to 0.901)
PCSK9	Abdominal aortic aneurysm	11	Inverse variance weighted	**<0.001**	0.595 (0.526 to 0.672)
PCSK9	Aortic dissection	11	Inverse variance weighted	0.908	1.023 (0.688 to 1.523)

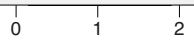


Figure 1 Mendelian randomization analysis for lipid-lowering and antihypertensive drugs with aortic diseases. The analysis utilized the inverse variance-weighted method to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for each metabolite. Significant associations (*P*-value < 0.05) are highlighted. ORs >1 suggest a positive association, while ORs <1 suggest a negative association with aortic diseases.

Reporting System (FAERS) database. MR provides a robust framework for causal inference by leveraging genetic variants as proxies for drug targets, while the FAERS offers comprehensive real-world evidence of adverse drug events. By combining these complementary methodologies, this study aims to fill a critical knowledge gap in aortic disease research, providing both genetic and clinical validation of the effects of antihypertensive and lipid-lowering therapies. This novel approach represents a significant advancement in understanding the interplay between therapeutic interventions and aortic disease risk, offering a framework that can be applied to other complex diseases and drug classes.

Methods

The information about databases and sources used in this study is shown in Supplementary material online, *Table S2*. All systems are accessible to users. Due to the nature of the data sources, informed consent from the original patients was not required for this study. The human-related datasets used in this study were provided by third parties and are available for open use in any research project, with appropriate ethical approval obtained for each study where the data were utilized. Approximately 2 000 000 participants, primarily of European ancestry, were recruited from the UK Biobank (https://www.ukbiobank.ac.uk/), the Genome-Wide Association Studies (GWAS) Catalog (https://www.ebi.ac.uk/gwas/home), and FinnGen (https://www.finngen.fi/en). Additionally, 13 038 441 real-world pharmacovigilance reports were retrieved from the FAERS database, with the majority originating from the United States, Germany, the United Kingdom (UK), and the Netherlands.

See supplementary material online, *Appendix E1* for details.

Results

Validation of genetic instruments for drugs

For LLDs, 5 and 11 genetic variants in the *HMGCR* and *PCSK9* genes, respectively, were selected as proxies for statins and PCSK9i. For AHTDs, 12, 6, 24, 5, and 3 genetic variants were selected as proxies for ABs, BBs, CCBs, ACEIs, and ARBs, respectively (see details in Supplementary material online, *Table S1*).

MR analysis for drug effects on aortic diseases

MR analysis results revealed that different classes of cardiovascular drugs had varying effects on the risk of TAA, AAA, and AD. Unlike AHTDs, LLDs showed exceptional effectiveness in aortic diseases. Statins significantly negatively correlated with the risk of TAA, AAA, and AD [inverse-variance weighted (IVW), odds ratio (OR) $= 0.527$, $P < 0.001$; IVW, OR $= 0.228$, $P < 0.001$; and IVW, OR $= 0.248$, $P = 0.012$, respectively]. Although PCSK9i did not show a statistically significant difference in the risk of AD, they significantly reduced the risk of TAA and AAA (IVW, OR $= 0.805$, $P = 0.002$; and IVW, OR $= 0.595$, $P < 0.001$, respectively) (*Figure 1* and *Table 1*). No statistically significant heterogeneity and pleiotropy were present (*Tables 2* and *3*).

In this study, additional independent datasets were utilized to assess the relationship between LLDs and AHTDs and aortic disease risk. Due to the unavailability of other AD data, only TAA and AAA were reassessed. PCSK9i maintained a low-risk relationship with TAA and AAA (IVW, OR $= 0.562$, $P = 0.039$; and IVW, OR $= 0.718$, $P = 0.030$,

Table 1 **Mendelian randomization results for drug effects on aortic diseases**

Id outcome	Outcome	Exposure	Method	Nsnp	β	SE	*P*-value	OR	OR_lci95	OR_uci95
I9_AORTDIS	Aortic dissection	ABs	MR Egger	9	−0.032	0.524	0.953	1.033	0.357	2.985
I9_AORTDIS	Aortic dissection	ABs	Weighted median	9	0.077	0.160	0.629	0.926	0.693	1.237
I9_AORTDIS	Aortic dissection	ABs	Inverse variance weighted	9	0.116	0.136	0.392	0.890	0.702	1.128
I9_AORTDIS	Aortic dissection	ABs	Simple mode	9	0.086	0.262	0.753	0.918	0.573	1.472
I9_AORTDIS	Aortic dissection	ABs	Weighted mode	9	0.102	0.232	0.670	0.903	0.599	1.360
I9_AORTDIS	Aortic dissection	BBs	MR Egger	6	−0.235	0.265	0.426	1.265	0.655	2.442
I9_AORTDIS	Aortic dissection	BBs	Weighted median	6	−0.014	0.095	0.881	1.014	0.839	1.226
I9_AORTDIS	Aortic dissection	BBs	Inverse variance weighted	6	0.018	0.079	0.824	0.983	0.843	1.145
I9_AORTDIS	Aortic dissection	BBs	Simple mode	6	0.122	0.137	0.413	0.885	0.698	1.122
I9_AORTDIS	Aortic dissection	BBs	Weighted mode	6	−0.005	0.101	0.959	1.006	0.825	1.226
I9_AORTDIS	Aortic dissection	CCBs	MR Egger	22	0.118	0.111	0.299	0.889	0.733	1.077
I9_AORTDIS	Aortic dissection	CCBs	Weighted median	22	0.014	0.064	0.828	0.986	0.871	1.117
I9_AORTDIS	Aortic dissection	CCBs	Inverse variance weighted	22	−0.002	0.046	0.964	1.002	0.916	1.096
I9_AORTDIS	Aortic dissection	CCBs	Simple mode	22	0.044	0.113	0.702	0.957	0.774	1.184
I9_AORTDIS	Aortic dissection	CCBs	Weighted mode	22	0.016	0.085	0.853	0.984	0.835	1.160
I9_AORTDIS	Aortic dissection	ARBs	MR Egger	4	−0.021	0.371	0.960	1.021	0.486	2.146
I9_AORTDIS	Aortic dissection	ARBs	Weighted median	4	−0.215	0.201	0.285	1.239	0.761	2.017
I9_AORTDIS	Aortic dissection	ARBs	Inverse variance weighted	4	−0.224	0.166	0.178	1.251	0.832	1.880
I9_AORTDIS	Aortic dissection	ARBs	Simple mode	4	−0.184	0.285	0.565	1.201	0.614	2.350
I9_AORTDIS	Aortic dissection	ARBs	Weighted mode	4	−0.117	0.267	0.691	1.124	0.625	2.022
I9_AORTDIS	Aortic dissection	ACEIs	MR Egger	4	1.107	0.615	0.214	0.331	0.222	0.492
I9_AORTDIS	Aortic dissection	ACEIs	Weighted median	4	0.163	0.134	0.222	0.849	0.680	1.061
I9_AORTDIS	Aortic dissection	ACEIs	Inverse variance weighted	4	0.108	0.120	0.368	0.898	0.727	1.109
I9_AORTDIS	Aortic dissection	ACEIs	Simple mode	4	0.179	0.195	0.427	0.836	0.607	1.151
I9_AORTDIS	Aortic dissection	ACEIs	Weighted mode	4	0.170	0.161	0.369	0.844	0.647	1.101
I9_AORTDIS	Aortic dissection	Statins	MR Egger	5	−0.673	2.360	0.794	0.510	0.005	1.716
I9_AORTDIS	Aortic dissection	Statins	Weighted median	5	1.382	0.588	0.019	0.251	0.188	0.335
I9_AORTDIS	Aortic dissection	Statins	Inverse variance weighted	5	1.394	0.552	0.012	0.248	0.190	0.324
I9_AORTDIS	Aortic dissection	Statins	Simple mode	5	2.150	0.865	0.068	0.116	0.096	0.142
I9_AORTDIS	Aortic dissection	Statins	Weighted mode	5	1.460	0.647	0.087	0.232	0.173	0.312
I9_AORTDIS	Aortic dissection	PCSK9	MR Egger	11	0.358	0.294	0.254	0.699	0.467	1.046
I9_AORTDIS	Aortic dissection	PCSK9	Weighted median	11	0.157	0.237	0.507	0.854	0.575	1.270
I9_AORTDIS	Aortic dissection	PCSK9	Inverse variance weighted	11	−0.023	0.198	0.908	1.023	0.688	1.523
I9_AORTDIS	Aortic dissection	PCSK9	Simple mode	11	−0.114	0.460	0.810	1.120	0.408	3.072

Table I Continued

Id outcome	Outcome	Exposure	Method	Nsnp	β	SE	*P*-value	OR	OR_lci95	OR_uci95
I9_AORTDIS	Aortic dissection	PCSK9	Weighted mode	11	0.155	0.244	0.539	0.856	0.568	1.289
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	MR Egger	9	0.067	0.175	0.713	0.935	0.679	1.289
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	Weighted median	9	0.085	0.057	0.136	0.919	0.829	1.018
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	Inverse variance weighted	9	0.062	0.045	0.169	0.940	0.865	1.021
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	Simple mode	9	0.098	0.087	0.292	0.907	0.777	1.058
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	Weighted mode	9	0.093	0.073	0.237	0.911	0.800	1.038
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	MR Egger	6	0.239	0.139	0.162	0.788	0.635	0.977
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	Weighted median	6	0.046	0.039	0.236	0.955	0.888	1.027
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	Inverse variance weighted	6	0.039	0.047	0.400	0.962	0.881	1.050
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	Simple mode	6	−0.080	0.100	0.459	1.083	0.876	1.340
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	Weighted mode	6	0.086	0.044	0.110	0.917	0.847	0.994
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	MR Egger	22	0.099	0.059	0.111	0.906	0.816	1.006
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	Weighted median	22	0.082	0.024	0.001	0.921	0.882	0.963
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	Inverse variance weighted	22	0.057	0.024	0.016	0.944	0.903	0.987
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	Simple mode	22	0.099	0.036	0.013	0.906	0.849	0.967
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	Weighted mode	22	0.085	0.027	0.005	0.919	0.875	0.965
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	MR Egger	4	0.170	0.133	0.329	0.844	0.677	1.051
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	Weighted median	4	−0.090	0.076	0.235	1.094	0.930	1.286
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	Inverse variance weighted	4	−0.034	0.074	0.645	1.035	0.891	1.202
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	Simple mode	4	−0.094	0.115	0.471	1.099	0.859	1.407
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	Weighted mode	4	−0.114	0.102	0.347	1.121	0.895	1.403
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	MR Egger	4	0.380	0.220	0.226	0.684	0.509	0.918
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	Weighted median	4	−0.001	0.053	0.986	1.001	0.902	1.111
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	Inverse variance weighted	4	−0.017	0.050	0.738	1.017	0.920	1.124
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	Simple mode	4	0.064	0.078	0.474	0.938	0.812	1.083
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	Weighted mode	4	−0.012	0.060	0.851	1.012	0.899	1.140
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	MR Egger	5	0.749	0.791	0.413	0.473	0.227	0.984
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	Weighted median	5	0.747	0.200	0.000	0.474	0.394	0.571
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	Inverse variance weighted	5	0.640	0.170	0.000	0.527	0.442	0.629
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	Simple mode	5	0.745	0.302	0.069	0.475	0.358	0.628
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	Weighted mode	5	0.745	0.211	0.024	0.475	0.390	0.577
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	MR Egger	11	0.188	0.105	0.107	0.828	0.698	0.983
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	Weighted median	11	0.223	0.087	0.011	0.800	0.698	0.917

Table I Continued

Id outcome	Outcome	Exposure	Method	Nsnp	β	SE	*P*-value	OR	OR_lci95	OR_uci95
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	Inverse variance weighted	11	0.217	0.071	0.002	0.805	0.720	0.901
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	Simple mode	11	0.359	0.174	0.066	0.698	0.550	0.886
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	Weighted mode	11	0.236	0.090	0.025	0.789	0.687	0.907
GCST90027266	Thoracic aortic aneurysm	ABs	MR Egger	11	0.334	0.470	0.495	1.397	0.556	3.509
GCST90027266	Thoracic aortic aneurysm	ABs	Weighted median	11	0.162	0.128	0.206	1.176	0.915	1.511
GCST90027266	Thoracic aortic aneurysm	ABs	Inverse variance weighted	11	0.031	0.136	0.817	1.032	0.791	1.346
GCST90027266	Thoracic aortic aneurysm	ABs	Simple mode	11	0.187	0.215	0.404	1.206	0.791	1.838
GCST90027266	Thoracic aortic aneurysm	ABs	Weighted mode	11	0.206	0.151	0.202	1.229	0.914	1.652
GCST90027266	Thoracic aortic aneurysm	BBs	MR Egger	6	−0.128	0.373	0.749	0.880	0.424	1.826
GCST90027266	Thoracic aortic aneurysm	BBs	Weighted median	6	−0.023	0.095	0.811	0.978	0.811	1.178
GCST90027266	Thoracic aortic aneurysm	BBs	Inverse variance weighted	6	0.046	0.106	0.664	1.047	0.851	1.288
GCST90027266	Thoracic aortic aneurysm	BBs	Simple mode	6	0.148	0.164	0.409	1.159	0.841	1.598
GCST90027266	Thoracic aortic aneurysm	BBs	Weighted mode	6	−0.126	0.102	0.272	0.881	0.721	1.077
GCST90027266	Thoracic aortic aneurysm	CCBs	MR Egger	24	0.191	0.098	0.064	1.210	0.999	1.467
GCST90027266	Thoracic aortic aneurysm	CCBs	Weighted median	24	0.123	0.050	0.014	1.131	1.025	1.248
GCST90027266	Thoracic aortic aneurysm	CCBs	Inverse variance weighted	24	0.046	0.041	0.265	1.047	0.966	1.135
GCST90027266	Thoracic aortic aneurysm	CCBs	Simple mode	24	0.101	0.087	0.260	1.106	0.932	1.312
GCST90027266	Thoracic aortic aneurysm	CCBs	Weighted mode	24	0.131	0.059	0.037	1.140	1.015	1.280
GCST90027266	Thoracic aortic aneurysm	ARBs	MR Egger	4	0.033	0.351	0.934	1.034	0.520	2.056
GCST90027266	Thoracic aortic aneurysm	ARBs	Weighted median	4	−0.201	0.180	0.263	0.818	0.575	1.163
GCST90027266	Thoracic aortic aneurysm	ARBs	Inverse variance weighted	4	−0.155	0.149	0.299	0.857	0.640	1.147
GCST90027266	Thoracic aortic aneurysm	ARBs	Simple mode	4	−0.209	0.236	0.441	0.811	0.511	1.289
GCST90027266	Thoracic aortic aneurysm	ARBs	Weighted mode	4	−0.233	0.218	0.364	0.792	0.517	1.215
GCST90027266	Thoracic aortic aneurysm	ACEIs	MR Egger	4	0.890	0.754	0.359	2.436	0.555	10.687
GCST90027266	Thoracic aortic aneurysm	ACEIs	Weighted median	4	0.015	0.135	0.915	1.015	0.779	1.322
GCST90027266	Thoracic aortic aneurysm	ACEIs	Inverse variance weighted	4	0.041	0.155	0.792	1.042	0.769	1.410
GCST90027266	Thoracic aortic aneurysm	ACEIs	Simple mode	4	−0.076	0.207	0.739	0.927	0.618	1.392
GCST90027266	Thoracic aortic aneurysm	ACEIs	Weighted mode	4	0.013	0.147	0.936	1.013	0.760	1.351
GCST90027266	Thoracic aortic aneurysm	Statins	MR Egger	5	−2.450	1.640	0.232	0.086	0.003	2.149
GCST90027266	Thoracic aortic aneurysm	Statins	Weighted median	5	0.121	0.484	0.803	1.128	0.437	2.914
GCST90027266	Thoracic aortic aneurysm	Statins	Inverse variance weighted	5	0.247	0.417	0.554	1.280	0.565	2.900
GCST90027266	Thoracic aortic aneurysm	Statins	Simple mode	5	0.424	0.791	0.620	1.528	0.324	7.203
GCST90027266	Thoracic aortic aneurysm	Statins	Weighted mode	5	−0.001	0.486	0.999	0.999	0.386	2.590
GCST90027266	Thoracic aortic aneurysm	PCSK9	MR Egger	11	−0.022	0.451	0.963	0.979	0.404	2.370
GCST90027266	Thoracic aortic aneurysm	PCSK9	Weighted median	11	−0.357	0.275	0.193	0.700	0.408	1.198

Table 1 Continued

Id outcome	Outcome	Exposure	Method	Nsnp	β	SE	P-value	OR	OR_lci95	OR_uci95
GCST90027266	Thoracic aortic aneurysm	PCSK9	Inverse variance weighted	11	−0.576	0.279	0.039	0.562	0.325	0.971
GCST90027266	Thoracic aortic aneurysm	PCSK9	Simple mode	11	−0.477	0.447	0.312	0.621	0.258	1.492
GCST90027266	Thoracic aortic aneurysm	PCSK9	Weighted mode	11	−0.396	0.306	0.225	0.673	0.369	1.227
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	MR Egger	9	−0.054	0.212	0.805	1.056	0.682	1.636
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	Weighted median	9	0.049	0.075	0.513	0.952	0.829	1.095
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	Inverse variance weighted	9	0.060	0.058	0.298	0.941	0.846	1.048
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	Simple mode	9	0.098	0.115	0.417	0.906	0.739	1.111
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	Weighted mode	9	0.015	0.111	0.897	0.985	0.795	1.222
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	MR Egger	6	0.249	0.128	0.124	0.779	0.641	0.948
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	Weighted median	6	−0.029	0.048	0.539	1.030	0.935	1.134
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	Inverse variance weighted	6	−0.024	0.050	0.636	1.024	0.927	1.131
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	Simple mode	6	−0.099	0.084	0.291	1.104	0.920	1.325
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	Weighted mode	6	−0.032	0.060	0.616	1.033	0.914	1.166
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	MR Egger	22	0.011	0.071	0.873	0.989	0.862	1.134
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	Weighted median	22	0.025	0.035	0.474	0.975	0.912	1.043
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	Inverse variance weighted	22	0.025	0.028	0.371	0.975	0.924	1.029
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	Simple mode	22	0.083	0.070	0.249	0.920	0.810	1.044
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	Weighted mode	22	0.032	0.044	0.471	0.968	0.891	1.052
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	MR Egger	4	0.406	0.191	0.167	0.666	0.519	0.855
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	Weighted median	4	−0.047	0.113	0.676	1.048	0.831	1.322
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	Inverse variance weighted	4	0.086	0.100	0.389	0.917	0.766	1.098
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	Simple mode	4	−0.044	0.174	0.817	1.045	0.732	1.493
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	Weighted mode	4	−0.056	0.141	0.720	1.057	0.789	1.417
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	MR Egger	4	0.761	0.315	0.137	0.467	0.350	0.623
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	Weighted median	4	0.017	0.076	0.823	0.983	0.849	1.139
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	Inverse variance weighted	4	−0.022	0.091	0.810	1.022	0.852	1.226
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	Simple mode	4	0.028	0.092	0.781	0.972	0.816	1.158
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	Weighted mode	4	0.026	0.080	0.768	0.974	0.836	1.136
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	MR Egger	5	2.095	1.012	0.130	0.123	0.096	0.157
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	Weighted median	5	1.436	0.293	9.61931785122871e-07	0.238	0.208	0.273
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	Inverse variance weighted	5	1.476	0.241	8.51241082535659e-10	0.228	0.205	0.254
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	Simple mode	5	1.051	0.435	0.073	0.350	0.260	0.471
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	Weighted mode	5	1.462	0.331	0.012	0.232	0.199	0.270
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	MR Egger	11	0.535	0.161	0.009	0.586	0.487	0.704
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	Weighted median	11	0.539	0.131	3.88843556333233e-05	0.584	0.502	0.678
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	Inverse variance weighted	11	0.520	0.105	8.2441761169892e-07	0.595	0.526	0.672

Table 1 Continued

Id outcome	Outcome	Exposure	Method	Nsnp	β	SE	P-value	OR	OR_lci95	OR_uci95
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	Simple mode	11	0.415	0.230	0.101	0.660	0.490	0.889
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	Weighted mode	11	0.535	0.142	0.004	0.586	0.498	0.689
GCST90399672	Abdominal aortic aneurysm	ABs	MR Egger	11	0.021	0.128	0.871	0.979	0.765	1.252
GCST90399672	Abdominal aortic aneurysm	ABs	Weighted median	11	0.086	0.047	0.065	0.917	0.843	0.998
GCST90399672	Abdominal aortic aneurysm	ABs	Inverse variance weighted	11	0.075	0.037	0.044	0.928	0.868	0.993
GCST90399672	Abdominal aortic aneurysm	ABs	Simple mode	11	0.097	0.081	0.256	0.908	0.786	1.047
GCST90399672	Abdominal aortic aneurysm	ABs	Weighted mode	11	0.094	0.069	0.207	0.910	0.804	1.031
GCST90399672	Abdominal aortic aneurysm	BBs	MR Egger	6	0.104	0.099	0.355	0.902	0.757	1.074
GCST90399672	Abdominal aortic aneurysm	BBs	Weighted median	6	0.032	0.038	0.403	0.969	0.901	1.041
GCST90399672	Abdominal aortic aneurysm	BBs	Inverse variance weighted	6	0.021	0.030	0.488	0.979	0.924	1.038
GCST90399672	Abdominal aortic aneurysm	BBs	Simple mode	6	0.026	0.055	0.660	0.975	0.877	1.083
GCST90399672	Abdominal aortic aneurysm	BBs	Weighted mode	6	0.036	0.046	0.475	0.965	0.884	1.053
GCST90399672	Abdominal aortic aneurysm	CCBs	MR Egger	19	−0.049	0.057	0.406	1.050	0.933	1.182
GCST90399672	Abdominal aortic aneurysm	CCBs	Weighted median	19	−0.024	0.025	0.328	1.025	0.975	1.077
GCST90399672	Abdominal aortic aneurysm	CCBs	Inverse variance weighted	19	−0.018	0.019	0.333	1.018	0.981	1.057
GCST90399672	Abdominal aortic aneurysm	CCBs	Simple mode	19	−0.018	0.042	0.685	1.018	0.935	1.107
GCST90399672	Abdominal aortic aneurysm	CCBs	Weighted mode	19	−0.015	0.035	0.674	1.015	0.946	1.089
GCST90399672	Abdominal aortic aneurysm	ARBs	MR Egger	4	0.094	0.139	0.570	0.911	0.710	1.167
GCST90399672	Abdominal aortic aneurysm	ARBs	Weighted median	4	0.005	0.077	0.949	0.995	0.856	1.157
GCST90399672	Abdominal aortic aneurysm	ARBs	Inverse variance weighted	4	0.015	0.064	0.809	0.985	0.870	1.114
GCST90399672	Abdominal aortic aneurysm	ARBs	Simple mode	4	−0.006	0.105	0.958	1.006	0.818	1.237
GCST90399672	Abdominal aortic aneurysm	ARBs	Weighted mode	4	−0.022	0.105	0.849	1.022	0.828	1.262
GCST90399672	Abdominal aortic aneurysm	ACEIs	MR Egger	4	0.308	0.255	0.351	0.735	0.509	1.062
GCST90399672	Abdominal aortic aneurysm	ACEIs	Weighted median	4	0.138	0.060	0.021	0.871	0.787	0.965
GCST90399672	Abdominal aortic aneurysm	ACEIs	Inverse variance weighted	4	0.148	0.049	0.003	0.862	0.793	0.937
GCST90399672	Abdominal aortic aneurysm	ACEIs	Simple mode	4	0.139	0.081	0.185	0.870	0.758	0.999
GCST90399672	Abdominal aortic aneurysm	ACEIs	Weighted mode	4	0.130	0.068	0.152	0.878	0.781	0.987
GCST90399672	Abdominal aortic aneurysm	Statins	MR Egger	5	1.044	0.749	0.258	0.352	0.210	0.590
GCST90399672	Abdominal aortic aneurysm	Statins	Weighted median	5	0.939	0.237	7.25250935679555e-05	0.391	0.326	0.469
GCST90399672	Abdominal aortic aneurysm	Statins	Inverse variance weighted	5	0.851	0.188	6.02619662548934e-06	0.427	0.365	0.500
GCST90399672	Abdominal aortic aneurysm	Statins	Simple mode	5	0.948	0.345	0.051	0.387	0.298	0.503
GCST90399672	Abdominal aortic aneurysm	Statins	Weighted mode	5	0.988	0.269	0.021	0.372	0.306	0.453
GCST90399672	Abdominal aortic aneurysm	PCSK9	MR Egger	7	1.157	0.673	0.146	0.314	0.208	0.476
GCST90399672	Abdominal aortic aneurysm	PCSK9	Weighted median	7	0.164	0.175	0.350	0.849	0.634	1.136
GCST90399672	Abdominal aortic aneurysm	PCSK9	Inverse variance weighted	7	0.331	0.153	0.030	0.718	0.579	0.890
GCST90399672	Abdominal aortic aneurysm	PCSK9	Simple mode	7	0.122	0.251	0.644	0.885	0.572	1.369
GCST90399672	Abdominal aortic aneurysm	PCSK9	Weighted mode	7	0.131	0.212	0.559	0.877	0.610	1.262

Table 2 Heterogeneity analyses of Mendelian randomization studies on aortic diseases

Id outcome	Outcome	Exposure	Method	Q	Q_*df*	Q_*P*-value
I9_AORTDIS	Aortic dissection	ABs	MR Egger	11.263	7	0.128
I9_AORTDIS	Aortic dissection	ABs	Inverse variance weighted	11.403	8	0.180
I9_AORTDIS	Aortic dissection	BBs	MR Egger	4.442	4	0.350
I9_AORTDIS	Aortic dissection	BBs	Inverse variance weighted	5.545	5	0.353
I9_AORTDIS	Aortic dissection	CCBs	MR Egger	23.506	20	0.265
I9_AORTDIS	Aortic dissection	CCBs	Inverse variance weighted	25.169	21	0.240
I9_AORTDIS	Aortic dissection	ARBs	MR Egger	0.920	2	0.631
I9_AORTDIS	Aortic dissection	ARBs	Inverse variance weighted	1.294	3	0.731
I9_AORTDIS	Aortic dissection	ACEIs	MR Egger	0.352	2	0.838
I9_AORTDIS	Aortic dissection	ACEIs	Inverse variance weighted	3.088	3	0.378
I9_AORTDIS	Aortic dissection	Statins	MR Egger	4.208	3	0.240
I9_AORTDIS	Aortic dissection	Statins	Inverse variance weighted	5.351	4	0.253
I9_AORTDIS	Aortic dissection	PCSK9	MR Egger	3.665	9	0.932
I9_AORTDIS	Aortic dissection	PCSK9	Inverse variance weighted	6.748	10	0.749
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	MR Egger	9.815	7	0.199
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	Inverse variance weighted	9.816	8	0.278
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	MR Egger	9.641	4	0.047
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	Inverse variance weighted	15.059	5	0.010
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	MR Egger	52.189	20	0.000
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	Inverse variance weighted	53.708	21	0.000
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	MR Egger	1.677	2	0.432
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	Inverse variance weighted	4.627	3	0.201
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	MR Egger	0.848	2	0.654
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	Inverse variance weighted	4.230	3	0.238
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	MR Egger	3.724	3	0.293
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	Inverse variance weighted	3.749	4	0.441
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	MR Egger	6.177	9	0.722
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	Inverse variance weighted	6.309	10	0.789
GCST90027266	Thoracic aortic aneurysm	ABs	MR Egger	25.025	9	0.003
GCST90027266	Thoracic aortic aneurysm	ABs	Inverse variance weighted	26.289	10	0.003
GCST90027266	Thoracic aortic aneurysm	BBs	MR Egger	12.605	4	0.013
GCST90027266	Thoracic aortic aneurysm	BBs	Inverse variance weighted	13.361	5	0.020
GCST90027266	Thoracic aortic aneurysm	CCBs	MR Egger	29.653	22	0.127
GCST90027266	Thoracic aortic aneurysm	CCBs	Inverse variance weighted	33.198	23	0.078
GCST90027266	Thoracic aortic aneurysm	ARBs	MR Egger	0.402	2	0.818
GCST90027266	Thoracic aortic aneurysm	ARBs	Inverse variance weighted	0.750	3	0.861
GCST90027266	Thoracic aortic aneurysm	ACEIs	MR Egger	3.307	2	0.191
GCST90027266	Thoracic aortic aneurysm	ACEIs	Inverse variance weighted	5.488	3	0.139
GCST90027266	Thoracic aortic aneurysm	Statins	MR Egger	1.181	3	0.758
GCST90027266	Thoracic aortic aneurysm	Statins	Inverse variance weighted	4.068	4	0.397
GCST90027266	Thoracic aortic aneurysm	PCSK9	MR Egger	13.999	9	0.122
GCST90027266	Thoracic aortic aneurysm	PCSK9	Inverse variance weighted	17.541	10	0.063
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	MR Egger	2.466	7	0.930
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	Inverse variance weighted	2.784	8	0.947
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	MR Egger	3.433	4	0.488
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	Inverse variance weighted	8.405	5	0.135
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	MR Egger	36.712	20	0.013
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	Inverse variance weighted	36.795	21	0.018
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	MR Egger	0.636	2	0.727
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	Inverse variance weighted	4.146	3	0.246
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	MR Egger	0.323	2	0.851
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	Inverse variance weighted	6.756	3	0.080

Table 2 Continued

Id outcome	Outcome	Exposure	Method	Q	Q_*df*	Q_*P*-value
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	MR Egger	1.712	3	0.634
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	Inverse variance weighted	2.108	4	0.716
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	MR Egger	4.321	9	0.889
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	Inverse variance weighted	4.337	10	0.931
GCST90399672	Abdominal aortic aneurysm	ABs	MR Egger	5.031	9	0.832
GCST90399672	Abdominal aortic aneurysm	ABs	Inverse variance weighted	5.219	10	0.876
GCST90399672	Abdominal aortic aneurysm	BBs	MR Egger	2.681	4	0.612
GCST90399672	Abdominal aortic aneurysm	BBs	Inverse variance weighted	3.446	5	0.632
GCST90399672	Abdominal aortic aneurysm	CCBs	MR Egger	8.052	17	0.965
GCST90399672	Abdominal aortic aneurysm	CCBs	Inverse variance weighted	8.375	18	0.973
GCST90399672	Abdominal aortic aneurysm	ARBs	MR Egger	0.620	2	0.733
GCST90399672	Abdominal aortic aneurysm	ARBs	Inverse variance weighted	1.020	3	0.796
GCST90399672	Abdominal aortic aneurysm	ACEIs	MR Egger	0.475	2	0.788
GCST90399672	Abdominal aortic aneurysm	ACEIs	Inverse variance weighted	0.881	3	0.830
GCST90399672	Abdominal aortic aneurysm	Statins	MR Egger	2.693	3	0.441
GCST90399672	Abdominal aortic aneurysm	Statins	Inverse variance weighted	2.763	4	0.598
GCST90399672	Abdominal aortic aneurysm	PCSK9	MR Egger	5.194	5	0.393
GCST90399672	Abdominal aortic aneurysm	PCSK9	Inverse variance weighted	6.835	6	0.336

Table 3 Pleiotropy analyses of Mendelian randomization studies on aortic diseases

ID outcome	Outcome	Exposure	Egger_intercept	SE	*P*-value
I9_AORTDIS	Aortic dissection	ABs	0.027	0.090	0.777
I9_AORTDIS	Aortic dissection	BBs	0.096	0.096	0.375
I9_AORTDIS	Aortic dissection	CCBs	−0.042	0.036	0.248
I9_AORTDIS	Aortic dissection	ARBs	−0.045	0.074	0.603
I9_AORTDIS	Aortic dissection	ACEIs	−0.272	0.165	0.240
I9_AORTDIS	Aortic dissection	Statins	0.128	0.142	0.433
I9_AORTDIS	Aortic dissection	PCSK9	−0.049	0.028	0.113
I9_THAORTANEUR	Thoracic aortic aneurysm	ABs	−0.001	0.030	0.977
I9_THAORTANEUR	Thoracic aortic aneurysm	BBs	−0.076	0.051	0.208
I9_THAORTANEUR	Thoracic aortic aneurysm	CCBs	−0.014	0.019	0.454
I9_THAORTANEUR	Thoracic aortic aneurysm	ARBs	−0.045	0.026	0.228
I9_THAORTANEUR	Thoracic aortic aneurysm	ACEIs	−0.108	0.059	0.207
I9_THAORTANEUR	Thoracic aortic aneurysm	Statins	−0.007	0.048	0.896
I9_THAORTANEUR	Thoracic aortic aneurysm	PCSK9	0.004	0.010	0.725
GCST90027266	Thoracic aortic aneurysm	ABs	−0.056	0.084	0.517
GCST90027266	Thoracic aortic aneurysm	BBs	0.067	0.137	0.650
GCST90027266	Thoracic aortic aneurysm	CCBs	−0.052	0.032	0.119
GCST90027266	Thoracic aortic aneurysm	ARBs	−0.040	0.068	0.615
GCST90027266	Thoracic aortic aneurysm	ACEIs	−0.227	0.198	0.370
GCST90027266	Thoracic aortic aneurysm	Statins	0.164	0.097	0.188
GCST90027266	Thoracic aortic aneurysm	PCSK9	−0.054	0.036	0.166
I9_ABAORTANEUR	Abdominal aortic aneurysm	ABs	0.021	0.036	0.590
I9_ABAORTANEUR	Abdominal aortic aneurysm	BBs	−0.104	0.047	0.090
I9_ABAORTANEUR	Abdominal aortic aneurysm	CCBs	0.005	0.023	0.834
I9_ABAORTANEUR	Abdominal aortic aneurysm	ARBs	−0.071	0.038	0.202
I9_ABAORTANEUR	Abdominal aortic aneurysm	ACEIs	−0.213	0.084	0.127
I9_ABAORTANEUR	Abdominal aortic aneurysm	Statins	−0.039	0.061	0.574
I9_ABAORTANEUR	Abdominal aortic aneurysm	PCSK9	−0.002	0.015	0.904
GCST90399672	Abdominal aortic aneurysm	ABs	0.010	0.022	0.675
GCST90399672	Abdominal aortic aneurysm	BBs	−0.031	0.035	0.431

Table 3 Continued

ID outcome	Outcome	Exposure	Egger_intercept	SE	*P*-value
GCST90399672	Abdominal aortic aneurysm	CCBs	0.010	0.017	0.577
GCST90399672	Abdominal aortic aneurysm	ARBs	−0.018	0.028	0.592
GCST90399672	Abdominal aortic aneurysm	ACEIs	−0.043	0.068	0.589
GCST90399672	Abdominal aortic aneurysm	Statins	−0.012	0.044	0.808
GCST90399672	Abdominal aortic aneurysm	PCSK9	−0.049	0.039	0.264

exposure	outcome	nsnp	method	pval	OR(95% CI)
5–hydroxylysine levels	Thoracic aortic aneurysm	29	Inverse variance weighted	**0.022**	1.092 (1.013 to 1.178)
4–guanidinobutanoate levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.044**	1.067 (1.002 to 1.136)
Campesterol levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.003**	1.119 (1.039 to 1.204)
1–stearoyl–GPG (18:0) levels	Thoracic aortic aneurysm	26	Inverse variance weighted	**0.019**	0.901 (0.826 to 0.983)
Hexanoylglycine levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.032**	1.064 (1.005 to 1.125)
Octadecanedioate levels	Thoracic aortic aneurysm	25	Inverse variance weighted	**0.017**	0.896 (0.819 to 0.981)
5alpha–androstan–3beta,17alpha–diol disulfate levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.019**	1.092 (1.015 to 1.176)
13–HODE + 9–HODE levels	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.005**	0.852 (0.762 to 0.952)
2R,3R–dihydroxybutyrate levels	Thoracic aortic aneurysm	29	Inverse variance weighted	**0.047**	0.933 (0.870 to 0.999)
4–hydroxyglutamate levels	Thoracic aortic aneurysm	25	Inverse variance weighted	**0.044**	0.916 (0.841 to 0.998)
S–methylcysteine levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.028**	0.914 (0.844 to 0.991)
2–stearoyl–GPE (18:0) levels	Thoracic aortic aneurysm	31	Inverse variance weighted	**0.013**	0.907 (0.840 to 0.979)
Sphingomyelin (d18:1/14:0, d16:1/16:0) levels	Thoracic aortic aneurysm	28	Inverse variance weighted	**0.006**	0.948 (0.913 to 0.984)
Eugenol sulfate levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.029**	0.913 (0.842 to 0.991)
Octadecanedioylcarnitine (C18–DC) levels	Thoracic aortic aneurysm	27	Inverse variance weighted	**0.033**	0.927 (0.864 to 0.994)
Sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2) levels	Thoracic aortic aneurysm	25	Inverse variance weighted	**0.008**	0.902 (0.836 to 0.974)
Sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2) levels	Thoracic aortic aneurysm	18	Inverse variance weighted	**0.028**	0.879 (0.784 to 0.986)
Lignoceroyl sphingomyelin (d18:1/24:0) levels	Thoracic aortic aneurysm	25	Inverse variance weighted	**0.049**	1.107 (1.000 to 1.225)
Nonanoylcarnitine (C9) levels	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.033**	1.094 (1.007 to 1.187)
Sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0) levels	Thoracic aortic aneurysm	17	Inverse variance weighted	**0.013**	0.893 (0.816 to 0.977)
Behenoyl dihydrosphingomyelin (d18:0/22:0) levels	Thoracic aortic aneurysm	36	Inverse variance weighted	**0.009**	1.101 (1.025 to 1.183)
1–(1–enyl–palmitoyl)–2–linoleoyl–GPC (p–16:0/18:2) levels	Thoracic aortic aneurysm	21	Inverse variance weighted	**0.030**	0.848 (0.730 to 0.984)
N–palmitoyl–sphinganine (d18:0/16:0) levels	Thoracic aortic aneurysm	22	Inverse variance weighted	**0.044**	1.121 (1.003 to 1.253)
1–(1–enyl–palmitoyl)–2–linoleoyl–GPE (p–16:0/18:2) levels	Thoracic aortic aneurysm	22	Inverse variance weighted	**0.011**	0.892 (0.817 to 0.974)
1–stearoyl–2–oleoyl–GPI (18:0/18:1) levels	Thoracic aortic aneurysm	24	Inverse variance weighted	**0.010**	1.110 (1.025 to 1.203)
Linoleoylcholine levels	Thoracic aortic aneurysm	21	Inverse variance weighted	**0.006**	0.843 (0.746 to 0.953)
Cerotoylcarnitine (C26) levels	Thoracic aortic aneurysm	27	Inverse variance weighted	**0.012**	1.097 (1.021 to 1.178)
3–hydroxyphenylacetoylglutamine levels	Thoracic aortic aneurysm	17	Inverse variance weighted	**0.049**	0.925 (0.856 to 1.000)
Octadecenedioate (C18:1–DC) levels	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.020**	0.926 (0.867 to 0.988)
Hydroxyasparagine levels	Thoracic aortic aneurysm	21	Inverse variance weighted	**0.009**	0.844 (0.743 to 0.959)
3–carboxy–4–methyl–5–pentyl–2–furanpropionate (3–CMPFP) levels	Thoracic aortic aneurysm	25	Inverse variance weighted	**0.021**	1.102 (1.015 to 1.196)
Sulfate of piperine metabolite C18H21NO3 (1) levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.007**	0.877 (0.798 to 0.965)
Palmitoyl–sphingosine–phosphoethanolamine (d18:1/16:0) levels	Thoracic aortic aneurysm	27	Inverse variance weighted	**0.014**	1.130 (1.025 to 1.246)
5–hydroxymethyl–2–furoylcarnitine levels	Thoracic aortic aneurysm	24	Inverse variance weighted	**0.021**	1.095 (1.014 to 1.183)
Deoxycholic acid 12–sulfate levels	Thoracic aortic aneurysm	21	Inverse variance weighted	**0.014**	0.945 (0.904 to 0.989)
Tetrahydrocortisol glucuronide levels	Thoracic aortic aneurysm	27	Inverse variance weighted	**0.008**	0.886 (0.810 to 0.970)
4–acetamidobutanoate levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.018**	1.099 (1.016 to 1.189)
Gamma–glutamylhistidine levels	Thoracic aortic aneurysm	22	Inverse variance weighted	**0.013**	0.893 (0.816 to 0.977)
Quinolinate levels	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.017**	1.122 (1.021 to 1.233)
Histidine levels	Thoracic aortic aneurysm	22	Inverse variance weighted	**0.021**	0.921 (0.859 to 0.988)
Salicylate levels	Thoracic aortic aneurysm	23	Inverse variance weighted	0.050	1.123 (1.000 to 1.261)
X–12221 levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.025**	0.900 (0.820 to 0.987)
X–12100 levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.018**	1.130 (1.021 to 1.250)
X–17325 levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.038**	1.088 (1.005 to 1.177)
X–22509 levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.018**	1.072 (1.012 to 1.135)
Bilirubin (E,Z or Z,E) levels	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.042**	0.949 (0.903 to 0.998)
Glycochenodeoxycholate glucuronide (1) levels	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.004**	0.888 (0.818 to 0.964)
Inosine 5'–monophosphate (IMP) to phosphate ratio	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.012**	1.102 (1.021 to 1.189)
Phosphate to N–acetylneuraminate ratio	Thoracic aortic aneurysm	31	Inverse variance weighted	**0.047**	1.088 (1.001 to 1.182)
Creatine to carnitine ratio	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.030**	1.093 (1.009 to 1.185)
Spermidine to N–acetylputrescine ratio	Thoracic aortic aneurysm	21	Inverse variance weighted	**0.026**	0.908 (0.834 to 0.988)
Adenosine 5'–diphosphate (ADP) to aspartate ratio	Thoracic aortic aneurysm	26	Inverse variance weighted	**0.018**	1.064 (1.011 to 1.120)
Citrate to oxalate (ethanedioate) ratio	Thoracic aortic aneurysm	14	Inverse variance weighted	**0.043**	1.126 (1.004 to 1.262)
Cortisone to 4–cholesten–3–one ratio	Thoracic aortic aneurysm	31	Inverse variance weighted	0.050	0.949 (0.900 to 1.000)
Glycerol to palmitoylcarnitine (C16) ratio	Thoracic aortic aneurysm	21	Inverse variance weighted	**0.005**	0.851 (0.760 to 0.953)
Succinate to proline ratio	Thoracic aortic aneurysm	15	Inverse variance weighted	**0.037**	1.119 (1.007 to 1.243)
Choline phosphate to choline ratio	Thoracic aortic aneurysm	19	Inverse variance weighted	**0.042**	0.903 (0.818 to 0.996)
Serine to threonine ratio	Thoracic aortic aneurysm	23	Inverse variance weighted	**0.012**	1.103 (1.022 to 1.190)
3–methyl–2–oxovalerate to 3–methyl–2–oxobutyrate ratio	Thoracic aortic aneurysm	20	Inverse variance weighted	**0.002**	1.216 (1.075 to 1.375)

Figure 2 Circulating metabolites and risk of thoracic aortic aneurysm (TAA) using Mendelian randomization analysis. The analysis utilized the inverse variance-weighted method to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for each metabolite. Significant associations (*P*-value < 0.05) are highlighted. ORs >1 suggest a positive association, while ORs <1 suggest a negative association with TAA.

exposure	outcome	nsnp	method	pval	OR(95% CI)
Benzoate levels	Abdominal aortic aneurysm	18	Inverse variance weighted	**0.017**	1.113 (1.019 to 1.215)
5–hydroxylysine levels	Abdominal aortic aneurysm	29	Inverse variance weighted	**0.015**	1.144 (1.027 to 1.275)
Kynurenine levels	Abdominal aortic aneurysm	24	Inverse variance weighted	**0.035**	1.134 (1.009 to 1.275)
Isovalerate (i5:0) levels	Abdominal aortic aneurysm	17	Inverse variance weighted	**0.018**	0.806 (0.674 to 0.964)
Cysteine s–sulfate levels	Abdominal aortic aneurysm	16	Inverse variance weighted	**0.045**	1.191 (1.004 to 1.413)
5–hydroxyhexanoate levels	Abdominal aortic aneurysm	17	Inverse variance weighted	**0.044**	1.173 (1.005 to 1.369)
1–methyl–4–imidazoleacetate levels	Abdominal aortic aneurysm	28	Inverse variance weighted	**0.012**	1.137 (1.028 to 1.257)
Campesterol levels	Abdominal aortic aneurysm	19	Inverse variance weighted	**0.004**	1.200 (1.059 to 1.360)
Stachydrine levels	Abdominal aortic aneurysm	24	Inverse variance weighted	**0.042**	0.862 (0.747 to 0.995)
Cysteine–glutathione disulfide levels	Abdominal aortic aneurysm	27	Inverse variance weighted	**0.024**	0.889 (0.802 to 0.985)
Pregnenediol sulfate (C21H34O5S) levels	Abdominal aortic aneurysm	30	Inverse variance weighted	**0.017**	0.863 (0.764 to 0.974)
2s,3R–dihydroxybutyrate levels	Abdominal aortic aneurysm	23	Inverse variance weighted	**0.020**	0.831 (0.712 to 0.971)
Cysteinylglycine disulfide levels	Abdominal aortic aneurysm	18	Inverse variance weighted	**0.007**	1.172 (1.044 to 1.316)
Sphingomyelin (d18:1/14:0, d16:1/16:0) levels	Abdominal aortic aneurysm	28	Inverse variance weighted	**<0.001**	0.919 (0.876 to 0.963)
Sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2) levels	Abdominal aortic aneurysm	25	Inverse variance weighted	**0.023**	0.881 (0.790 to 0.983)
1–(1–enyl–palmitoyl)–2–linoleoyl–GPE (p–16:0/18:2) levels	Abdominal aortic aneurysm	22	Inverse variance weighted	**0.011**	0.834 (0.724 to 0.960)
1–myristoyl–2–arachidonoyl–GPC (14:0/20:4) levels	Abdominal aortic aneurysm	24	Inverse variance weighted	**0.001**	1.172 (1.063 to 1.292)
Furaneol sulfate levels	Abdominal aortic aneurysm	15	Inverse variance weighted	**0.009**	0.838 (0.734 to 0.957)
Linoleoylcholine levels	Abdominal aortic aneurysm	20	Inverse variance weighted	**0.034**	0.821 (0.685 to 0.985)
3–hydroxyphenylacetoylglutamine levels	Abdominal aortic aneurysm	17	Inverse variance weighted	**0.029**	0.884 (0.791 to 0.988)
Ascorbic acid 3–sulfate levels	Abdominal aortic aneurysm	20	Inverse variance weighted	**0.037**	0.907 (0.828 to 0.994)
Methyl vanillate sulfate levels	Abdominal aortic aneurysm	22	Inverse variance weighted	**0.003**	0.853 (0.767 to 0.949)
11beta–hydroxyandrosterone glucuronide levels	Abdominal aortic aneurysm	27	Inverse variance weighted	**0.033**	1.137 (1.011 to 1.280)
Erucate (22:1n9) levels	Abdominal aortic aneurysm	19	Inverse variance weighted	**0.045**	1.215 (1.005 to 1.469)
Trans–4–hydroxyproline levels	Abdominal aortic aneurysm	25	Inverse variance weighted	**0.003**	0.781 (0.663 to 0.921)
N–acetylputrescine levels	Abdominal aortic aneurysm	23	Inverse variance weighted	**0.029**	1.097 (1.010 to 1.193)
Leucine levels	Abdominal aortic aneurysm	18	Inverse variance weighted	**0.041**	1.221 (1.008 to 1.478)
Plasma free proline levels	Abdominal aortic aneurysm	32	Inverse variance weighted	**0.009**	0.847 (0.747 to 0.960)
Glutamate levels	Abdominal aortic aneurysm	21	Inverse variance weighted	**<0.001**	1.299 (1.117 to 1.511)
Tryptophan levels	Abdominal aortic aneurysm	21	Inverse variance weighted	**0.036**	0.855 (0.738 to 0.989)
X–11381 levels	Abdominal aortic aneurysm	25	Inverse variance weighted	**0.017**	0.934 (0.883 to 0.988)
X–12410 levels	Abdominal aortic aneurysm	27	Inverse variance weighted	**0.041**	1.117 (1.004 to 1.241)
X–16935 levels	Abdominal aortic aneurysm	25	Inverse variance weighted	**0.018**	0.883 (0.797 to 0.979)
X–18901 levels	Abdominal aortic aneurysm	28	Inverse variance weighted	**0.001**	1.208 (1.075 to 1.356)
X–21285 levels	Abdominal aortic aneurysm	29	Inverse variance weighted	**0.047**	0.913 (0.835 to 0.999)
X–24565 levels	Abdominal aortic aneurysm	32	Inverse variance weighted	**0.012**	1.061 (1.013 to 1.110)
X–25271 levels	Abdominal aortic aneurysm	16	Inverse variance weighted	**0.017**	0.784 (0.641 to 0.958)
X–25519 levels	Abdominal aortic aneurysm	19	Inverse variance weighted	**0.049**	1.160 (1.000 to 1.344)
Carnitine C4 levels	Abdominal aortic aneurysm	37	Inverse variance weighted	**0.026**	1.117 (1.013 to 1.231)
5–acetylamino–6–formylamino–3–methyluracil levels	Abdominal aortic aneurysm	21	Inverse variance weighted	**<0.001**	1.130 (1.056 to 1.209)
Bilirubin (z,z) levels	Abdominal aortic aneurysm	32	Inverse variance weighted	**0.019**	0.925 (0.867 to 0.987)
Aspartate to asparagine ratio	Abdominal aortic aneurysm	19	Inverse variance weighted	**0.010**	0.854 (0.758 to 0.962)
Phosphate to phosphoethanolamine ratio	Abdominal aortic aneurysm	14	Inverse variance weighted	**0.035**	1.208 (1.014 to 1.440)
Spermidine to N–acetylputrescine ratio	Abdominal aortic aneurysm	21	Inverse variance weighted	**0.013**	0.858 (0.760 to 0.968)
Citrate to oxalate (ethanedioate) ratio	Abdominal aortic aneurysm	14	Inverse variance weighted	**0.048**	1.179 (1.001 to 1.389)
Adenosine 5'–monophosphate (AMP) to glutamine ratio	Abdominal aortic aneurysm	18	Inverse variance weighted	0.050	0.848 (0.719 to 1.000)
Adenosine 5'–monophosphate (AMP) to threonine ratio	Abdominal aortic aneurysm	22	Inverse variance weighted	**0.045**	0.897 (0.806 to 0.998)
Phosphate to oleoyl–linoleoyl–glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	31	Inverse variance weighted	**0.018**	0.840 (0.727 to 0.970)
Retinol (Vitamin A) to linoleoyl–arachidonoyl–glycerol (18:2 to 20:4) [2] ratio	Abdominal aortic aneurysm	24	Inverse variance weighted	**0.011**	0.847 (0.746 to 0.963)
Retinol (Vitamin A) to oleoyl–linoleoyl–glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	32	Inverse variance weighted	**0.008**	0.819 (0.707 to 0.949)
Succinate to proline ratio	Abdominal aortic aneurysm	15	Inverse variance weighted	**0.019**	1.196 (1.029 to 1.391)
Leucine to N–palmitoyl–sphingosine (d18:1 to 16:0) ratio	Abdominal aortic aneurysm	22	Inverse variance weighted	**0.006**	0.804 (0.689 to 0.938)
Cholesterol to linoleoyl–arachidonoyl–glycerol (18:2 to 20:4) [1] ratio	Abdominal aortic aneurysm	20	Inverse variance weighted	**0.031**	0.865 (0.759 to 0.987)
Cholesterol to oleoyl–linoleoyl–glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	33	Inverse variance weighted	**0.042**	0.858 (0.741 to 0.994)
Benzoate to oleoyl–linoleoyl–glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	30	Inverse variance weighted	**0.001**	0.802 (0.703 to 0.915)
Benzoate to linoleoyl–arachidonoyl–glycerol (18:2 to 20:4) [2] ratio	Abdominal aortic aneurysm	26	Inverse variance weighted	**0.008**	0.897 (0.828 to 0.972)
Androsterone glucuronide to etiocholanolone glucuronide ratio	Abdominal aortic aneurysm	25	Inverse variance weighted	**0.023**	1.122 (1.016 to 1.238)
Paraxanthine to 5–acetylamino–6–formylamino–3–methyluracil ratio	Abdominal aortic aneurysm	25	Inverse variance weighted	**0.022**	0.922 (0.860 to 0.988)

Figure 3 Mendelian randomization analysis of circulating metabolites on abdominal aortic aneurysm (AAA) risk. The analyses utilize the inverse variance-weighted method, presenting odds ratios (ORs) with 95% confidence intervals (CIs) for each metabolite.

respectively) but statins were only significantly negatively correlated with AAA risk (IVW, OR = 0.427, $P < 0.001$), with no statistical difference in TAA. Furthermore, CCBs were not statistically significantly associated with TAA risk. No statistically significant heterogeneity and pleiotropy were present (see Supplementary material online, *Figures 1* and 2; *Tables 1–3*).

MR analysis of circulating metabolites and aortic diseases

MR and IVW methods were applied to assess the relationships between different metabolite levels and various single-nucleotide polymorphisms (SNPs) in aortic disease populations to further explore whether the effects of LLDs in the body are mediated through metabolites (see Supplementary material online, *Table S6*).

Fifty-nine metabolites were associated with TAA risk (*Figure 2*; see Supplementary material online, *Table S7*). 4-Guanidinobutanoate (OR = 1.197, $P = 0.044$), octadecadienoate (18:2) (OR = 1.196, $P = 0.009$), palmitoyl-sphingosine-1-phosphate (d18:1/16:0) (OR = 1.098, $P = 0.041$), and 1-linoleoyl-glycerol (18:2) (OR = 1.071, $P = 0.044$) levels were significantly positively associated with the risk of TAA. Conversely, 5-hydroxyindole (OR = 0.972, $P = 0.022$), hexadecanedioate (C16-DC) (OR = 0.872, $P = 0.042$), tetradecanedioate (OR = 0.862, $P = 0.017$), and sulfo-3-methylthiopropyl cysteine (OR = 0.841, $P = 0.018$) levels were inversely associated with TAA risk, suggesting a protective effect. No statistically significant heterogeneity or pleiotropy was observed (see Supplementary material online, *Table S8*).

Moreover, significant associations were found between specific circulating metabolites and AAA risk. Fifty-eight metabolites had

exposure	outcome	nsnp	method	pval	OR(95% CI)
Kynurenine levels	Aortic dissection	24	Inverse variance weighted	**0.003**	1.423 (1.127 to 1.795)
1–methyl–4–imidazoleacetate levels	Aortic dissection	28	Inverse variance weighted	**0.046**	1.203 (1.003 to 1.444)
Hyocholate levels	Aortic dissection	20	Inverse variance weighted	**0.014**	0.829 (0.714 to 0.962)
4–hydroxyhippurate levels	Aortic dissection	19	Inverse variance weighted	**0.020**	1.411 (1.056 to 1.886)
Gamma–glutamylisoleucine levels	Aortic dissection	16	Inverse variance weighted	**0.047**	1.263 (1.003 to 1.590)
Docosapentaenoate (n6 DPA; 22:5n6) levels	Aortic dissection	14	Inverse variance weighted	**0.039**	0.655 (0.438 to 0.979)
Carnitine C5:1 levels	Aortic dissection	25	Inverse variance weighted	**<0.001**	0.628 (0.490 to 0.806)
Tetradecanedioate (C14–DC) levels	Aortic dissection	18	Inverse variance weighted	**0.046**	0.858 (0.738 to 0.997)
Hexadecanedioate (C16–DC) levels	Aortic dissection	22	Inverse variance weighted	**0.042**	0.842 (0.713 to 0.994)
Tryptophan betaine levels	Aortic dissection	34	Inverse variance weighted	**0.002**	0.742 (0.616 to 0.894)
5alpha–pregnan–3beta,20alpha–diol disulfate levels	Aortic dissection	29	Inverse variance weighted	**0.043**	0.817 (0.671 to 0.994)
Androstenediol (3alpha, 17alpha) monosulfate (3) levels	Aortic dissection	30	Inverse variance weighted	**0.043**	1.112 (1.003 to 1.232)
5–(galactosylhydroxy)–L–lysine levels	Aortic dissection	13	Inverse variance weighted	**0.049**	0.750 (0.563 to 0.999)
2,3–dihydroxyisovalerate levels	Aortic dissection	23	Inverse variance weighted	**0.013**	1.343 (1.063 to 1.697)
S–methylcysteine sulfoxide levels	Aortic dissection	21	Inverse variance weighted	**0.011**	1.453 (1.091 to 1.936)
Margaroylcarnitine (C17) levels	Aortic dissection	25	Inverse variance weighted	**0.047**	1.310 (1.003 to 1.711)
3–methyl catechol sulfate (1) levels	Aortic dissection	27	Inverse variance weighted	**0.043**	0.793 (0.634 to 0.993)
Sphingomyelin (d18:1/14:0, d16:1/16:0) levels	Aortic dissection	28	Inverse variance weighted	**0.003**	0.876 (0.802 to 0.957)
Etiocholanolone glucuronide levels	Aortic dissection	20	Inverse variance weighted	**0.027**	0.796 (0.650 to 0.975)
Octadecenedioylcarnitine (C18:1–DC) levels	Aortic dissection	14	Inverse variance weighted	**0.008**	0.797 (0.674 to 0.941)
Eugenol sulfate levels	Aortic dissection	23	Inverse variance weighted	**0.043**	0.776 (0.608 to 0.992)
Octadecanedioylcarnitine (C18–DC) levels	Aortic dissection	27	Inverse variance weighted	**0.045**	0.853 (0.730 to 0.996)
Sphingomyelin (d18:1/20:0, d16:1/22:0) levels	Aortic dissection	20	Inverse variance weighted	**0.046**	0.796 (0.636 to 0.996)
Taurodeoxycholic acid 3–sulfate levels	Aortic dissection	22	Inverse variance weighted	**0.003**	0.800 (0.691 to 0.928)
Glycodeoxycholate 3–sulfate levels	Aortic dissection	30	Inverse variance weighted	**0.003**	0.840 (0.750 to 0.942)
1–stearoyl–2–oleoyl–gpc (18:0/18:1) levels	Aortic dissection	33	Inverse variance weighted	**0.036**	0.784 (0.624 to 0.984)
Tricosanoyl sphingomyelin (d18:1/23:0) levels	Aortic dissection	27	Inverse variance weighted	**0.049**	1.310 (1.001 to 1.716)
1–stearoyl–2–docosahexaenoyl–gpc (18:0/22:6) levels	Aortic dissection	27	Inverse variance weighted	**0.010**	0.764 (0.622 to 0.938)
1,2–dilinoleoyl–GPE (18:2/18:2) levels	Aortic dissection	28	Inverse variance weighted	**0.003**	1.358 (1.111 to 1.660)
1–oleoyl–2–docosahexaenoyl–GPC (18:1/22:6) levels	Aortic dissection	31	Inverse variance weighted	**0.020**	0.731 (0.561 to 0.952)
Furaneol sulfate levels	Aortic dissection	15	Inverse variance weighted	**0.006**	0.705 (0.550 to 0.904)
Linoleoyl–arachidonoyl–glycerol (18:2/20:4) [2] levels	Aortic dissection	33	Inverse variance weighted	**0.021**	0.821 (0.695 to 0.971)
Palmitoleoylcarnitine (C16:1) levels	Aortic dissection	19	Inverse variance weighted	**0.029**	1.417 (1.036 to 1.937)
Arachidoylcarnitine (C20) levels	Aortic dissection	29	Inverse variance weighted	**0.037**	1.201 (1.011 to 1.426)
Lignoceroylcarnitine (C24) levels	Aortic dissection	26	Inverse variance weighted	**0.020**	1.233 (1.034 to 1.472)
Nervonoylcarnitine (C24:1) levels	Aortic dissection	24	Inverse variance weighted	**0.004**	1.349 (1.098 to 1.658)
3–hydroxyoleoylcarnitine levels	Aortic dissection	26	Inverse variance weighted	**0.046**	1.284 (1.004 to 1.642)
Octadecenedioate (C18:1–DC) levels	Aortic dissection	20	Inverse variance weighted	**0.009**	0.785 (0.654 to 0.942)
N–acetyl–2–aminooctanoate levels	Aortic dissection	24	Inverse variance weighted	**0.033**	1.204 (1.015 to 1.429)
3–indoleglyoxylic acid levels	Aortic dissection	20	Inverse variance weighted	**0.034**	1.237 (1.016 to 1.506)
Sulfate of piperine metabolite C18H21NO3 (3) levels	Aortic dissection	22	Inverse variance weighted	**0.011**	0.718 (0.556 to 0.927)
Deoxycholic acid 12–sulfate levels	Aortic dissection	21	Inverse variance weighted	**0.029**	0.859 (0.750 to 0.984)
3,5–dichloro–2,6–dihydroxybenzoic acid levels	Aortic dissection	20	Inverse variance weighted	**0.017**	0.719 (0.548 to 0.943)
Vanillic acid glycine levels	Aortic dissection	23	Inverse variance weighted	**0.010**	1.268 (1.058 to 1.520)
Erucate (22:1n9) levels	Aortic dissection	19	Inverse variance weighted	**0.018**	1.447 (1.065 to 1.967)
Butyrate/isobutyrate (4:0) levels	Aortic dissection	20	Inverse variance weighted	**0.001**	0.623 (0.467 to 0.832)
Cortisone levels	Aortic dissection	17	Inverse variance weighted	**0.026**	1.461 (1.047 to 2.038)
Betaine levels	Aortic dissection	25	Inverse variance weighted	**0.045**	0.819 (0.673 to 0.996)
X–11787 levels	Aortic dissection	20	Inverse variance weighted	**0.027**	0.818 (0.684 to 0.977)
X–17685 levels	Aortic dissection	21	Inverse variance weighted	**0.006**	1.486 (1.123 to 1.967)
X–17351 levels	Aortic dissection	17	Inverse variance weighted	**0.019**	0.709 (0.532 to 0.945)
X–18913 levels	Aortic dissection	19	Inverse variance weighted	**0.038**	1.319 (1.016 to 1.713)
X–21310 levels	Aortic dissection	21	Inverse variance weighted	**0.048**	0.763 (0.584 to 0.997)
X–24241 levels	Aortic dissection	24	Inverse variance weighted	**0.019**	1.335 (1.049 to 1.699)
X–24328 levels	Aortic dissection	34	Inverse variance weighted	**0.038**	1.290 (1.014 to 1.642)
X–26111 levels	Aortic dissection	21	Inverse variance weighted	**0.001**	0.679 (0.538 to 0.857)
X–26109 levels	Aortic dissection	26	Inverse variance weighted	**0.013**	0.815 (0.694 to 0.958)
Carnitine C4 levels	Aortic dissection	37	Inverse variance weighted	**0.008**	1.259 (1.062 to 1.494)
Deoxycholic acid glucuronide levels	Aortic dissection	24	Inverse variance weighted	**0.047**	0.829 (0.689 to 0.998)
Spermidine to 5–methylthioadenosine (MTA) ratio	Aortic dissection	17	Inverse variance weighted	**0.022**	1.395 (1.048 to 1.856)
Adenosine 5'–monophosphate (AMP) to inosine 5'–monophosphate (IMP) ratio	Aortic dissection	23	Inverse variance weighted	**0.007**	0.773 (0.642 to 0.931)
Adenosine 5'–monophosphate (AMP) to phenylalanine ratio	Aortic dissection	22	Inverse variance weighted	**0.034**	1.363 (1.023 to 1.814)
Palmitate (16:0) to myristate (14:0) ratio	Aortic dissection	17	Inverse variance weighted	**0.022**	1.506 (1.062 to 2.136)
Uridine to pseudouridine ratio	Aortic dissection	26	Inverse variance weighted	**0.047**	1.291 (1.004 to 1.660)
Glutamate to kynurenine ratio	Aortic dissection	24	Inverse variance weighted	**0.039**	0.754 (0.576 to 0.986)
Adenosine 5'–diphosphate (ADP) to sulfate ratio	Aortic dissection	23	Inverse variance weighted	**0.002**	0.716 (0.579 to 0.885)
Phosphate to linoleoyl–arachidonoyl–glycerol (18:2 to 20:4) [2] ratio	Aortic dissection	26	Inverse variance weighted	**0.002**	1.350 (1.119 to 1.627)
Retinol (Vitamin A) to linoleoyl–arachidonoyl–glycerol (18:2 to 20:4) [1] ratio	Aortic dissection	24	Inverse variance weighted	**0.006**	1.345 (1.090 to 1.660)
Adenosine 5'–diphosphate (ADP) to EDTA ratio	Aortic dissection	25	Inverse variance weighted	**0.015**	0.780 (0.639 to 0.953)
Adenosine 5'–monophosphate (AMP) to urate ratio	Aortic dissection	23	Inverse variance weighted	0.050	1.292 (1.001 to 1.669)
Arachidonate (20:4n6) to paraxanthine ratio	Aortic dissection	22	Inverse variance weighted	**0.021**	0.768 (0.614 to 0.961)
Caffeine to paraxanthine ratio	Aortic dissection	27	Inverse variance weighted	**0.026**	0.794 (0.648 to 0.973)
Cholesterol to linoleoyl–arachidonoyl–glycerol (18:2 to 20:4) [2] ratio	Aortic dissection	29	Inverse variance weighted	**0.031**	1.238 (1.020 to 1.502)

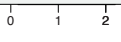


Figure 4 Circulating metabolites and risk of aortic dissection (AD) using Mendelian randomization analysis. The analysis utilized the inverse variance-weighted method to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for each metabolite. Significant associations (*P*-value < 0.05) are highlighted. ORs >1 suggest a positive association, while ORs <1 suggest a negative association with AD.

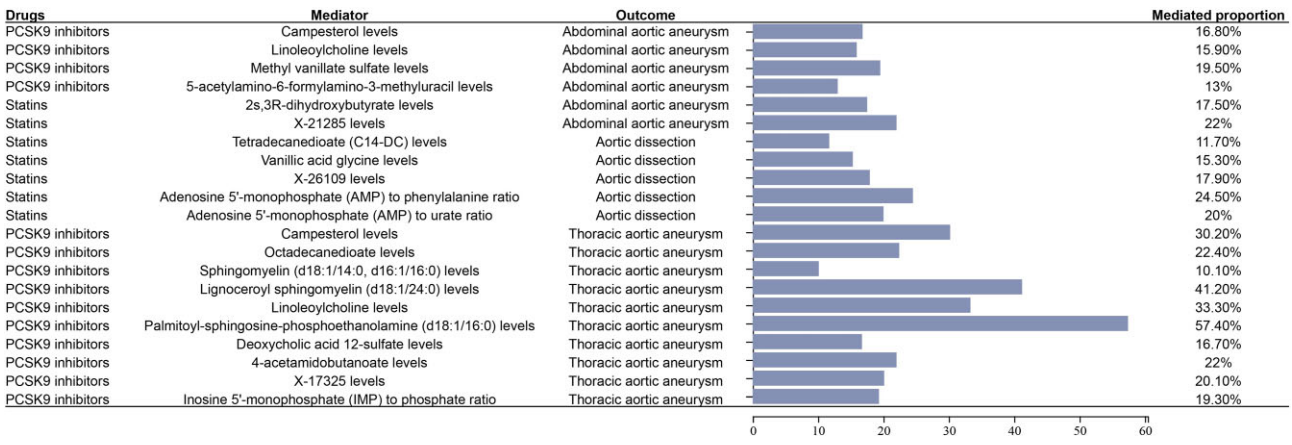


Figure 5 Mediated effects of metabolites on the outcomes of aortic diseases influenced by PCSK9 inhibitors and statins.

Table 4 Mediated effects of metabolites on the outcomes of aortic diseases influenced by drugs

Drugs	Metabolite	Outcome	Mediated	Mediated proportion
PCSK9 inhibitors	Campesterol levels	Abdominal aortic aneurysm	0.0363 (−0.0146, 0.0873)	16.80%
PCSK9 inhibitors	Sphingomyelin (d18:1/14:0, d16:1/16:0) levels	Abdominal aortic aneurysm	−0.0197 (−0.0551, 0.0158)	3.04%
PCSK9 inhibitors	Sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2) levels	Abdominal aortic aneurysm	−0.0332 (−0.0762, 0.00988)	1.90%
PCSK9 inhibitors	Linoleoylcholine levels	Abdominal aortic aneurysm	0.0403 (−0.00218, 0.0827)	15.90%
PCSK9 inhibitors	Methyl vanillate sulfate levels	Abdominal aortic aneurysm	0.0397 (−0.0222, 0.102)	19.50%
PCSK9 inhibitors	X-25271 levels	Abdominal aortic aneurysm	−0.0554 (−0.106, −0.00518)	−1.00%
PCSK9 inhibitors	5-acetylamino-6-formylamino-3-methyluracil levels	Abdominal aortic aneurysm	0.0271(-0.0133, 0.0675)	13%
PCSK9 inhibitors	Phosphate to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	−0.0357 (−0.0762, 0.0049)	0.94%
PCSK9 inhibitors	Retinol (vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	−0.0444 (−0.09, 0.00109)	0.21%
PCSK9 inhibitors	Cholesterol to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	−0.05 (−0.104, 0.00415)	0.80%
PCSK9 inhibitors	Benzoate to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	Abdominal aortic aneurysm	−0.0359 (−0.08, 0.00819)	1.58%
PCSK9 inhibitors	Paraxanthine to 5-acetylamino-6-formylamino-3-methyluracil ratio	Abdominal aortic aneurysm	0.0151 (−0.0172, 0.0474)	9.13%
Statins	Benzoate levels	Abdominal aortic aneurysm	−0.0366 (−0.153, 0.0802)	5.43%
Statins	5-hydroxyhexanoate levels	Abdominal aortic aneurysm	−0.0593 (−0.192, 0.0738)	5%
Statins	Cysteine-glutathione disulfide levels	Abdominal aortic aneurysm	−0.0639 (−0.247, 0.119)	8.09%
Statins	2s,3R-dihydroxybutyrate levels	Abdominal aortic aneurysm	0.09 (−0.0785, 0.258)	17.50%
Statins	1-myristoyl-2-arachidonoyl-GPC (14:0/20:4) levels	Abdominal aortic aneurysm	−0.05 (−0.155, 0.0547)	3.70%
Statins	11β-hydroxyandrosterone glucuronide levels	Abdominal aortic aneurysm	−0.0382 (−0.132, 0.0561)	3.80%
Statins	X-21285 levels	Abdominal aortic aneurysm	0.0674 (−0.189, 0.324)	22%
Statins	Phosphate to phosphoethanolamine ratio	Abdominal aortic aneurysm	−0.11 (−0.297, 0.0767)	5.19%
Statins	Adenosine 5′-monophosphate (AMP) to glutamine ratio	Abdominal aortic aneurysm	−0.0872 (−0.255, 0.0804)	5.45%
Statins	Adenosine 5′-monophosphate (AMP) to threonine ratio	Abdominal aortic aneurysm	−0.051 (−0.2, 0.0975)	6.60%
Statins	Tetradecanedioate (C14-DC) levels	Aortic dissection	0.0522 (−0.0585, 0.163)	11.70%
Statins	5-(galactosyl hydroxy)-L-lysine levels	Aortic dissection	−0.143 (−0.328, 0.0433)	3.11%

Table 4 Continued

Drugs	Metabolite	Outcome	Mediated	Mediated proportion
Statins	Vanillic acid glycine levels	Aortic dissection	0.0801 (−0.0525, 0.213)	15.30%
Statins	X-18913 levels	Aortic dissection	−0.121 (−0.279, 0.0366)	2.63%
Statins	X-26109 levels	Aortic dissection	0.0912 (−0.0677, 0.25)	17.90%
Statins	Adenosine 5′-monophosphate (AMP) to phenylalanine ratio	Aortic dissection	0.16 (−0.0225, 0.342)	24.50%
	Adenosine 5′-monophosphate (AMP) to urate ratio	Aortic dissection	0.121(−0.0362, 0.279)	20%
PCSK9 inhibitors	Campesterol levels	Thoracic aortic aneurysm	0.0223(−0.0208, 0.0654)	30.20%
PCSK9 inhibitors	Octadecanedioate levels	Thoracic aortic aneurysm	0.0186(−0.0113, 0.0486)	22.40%
PCSK9 inhibitors	2R,3R-dihydroxybutyrate levels	Thoracic aortic aneurysm	−0.0107(−0.0356, 0.0143)	6.61%
PCSK9 inhibitors	Sphingomyelin (d18:1/14:0, d16:1/16:0) levels	Thoracic aortic aneurysm	−0.0124(−0.0466, 0.0218)	10.10%
PCSK9 inhibitors	Sphingomyelin (d18:1/20:2, d18:2/20:1, d16:1/22:2) levels	Thoracic aortic aneurysm	−0.0269(−0.0685, 0.0147)	6.79%
PCSK9 inhibitors	Sphingomyelin (d18:1/22:2, d18:2/22:1, d16:1/24:2) levels	Thoracic aortic aneurysm	−0.0357(−0.0794, 0.00809)	3.74%
PCSK9 inhibitors	Lignoceroyl sphingomyelin (d18:1/24:0) levels	Thoracic aortic aneurysm	0.0358(−0.0175, 0.0891)	41.20%
PCSK9 inhibitors	Sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0) levels	Thoracic aortic aneurysm	−0.0301(−0.0705, 0.0104)	4.79%
PCSK9 inhibitors	Linoleoylcholine levels	Thoracic aortic aneurysm	0.0333(−0.00544, 0.0721)	33.30%
PCSK9 inhibitors	Palmitoyl-sphingosine-phosphoethanolamine (d18:1/16:0) levels	Thoracic aortic aneurysm	0.0455(−0.0331, 0.124)	57.40%
PCSK9 inhibitors	Deoxycholic acid 12-sulfate levels	Thoracic aortic aneurysm	0.00912(−0.018, 0.0362)	16.70%
PCSK9 inhibitors	4-acetamidobutanoate levels	Thoracic aortic aneurysm	0.0177(−0.0122, 0.0476)	22%
PCSK9 inhibitors	X-17325 levels	Thoracic aortic aneurysm	0.0139(−0.0155, 0.0434)	20.10%
PCSK9 inhibitors	Inosine 5′-monophosphate (IMP) to phosphate ratio	Thoracic aortic aneurysm	−0.0367(−0.115, 0.0418)	19.30%

significant associations (*Figure 3*; see Supplementary material online, *Table S9*). Benzoate (OR = 1.113, $P = 0.017$), 5-hydroxyindole (OR = 1.144, $P = 0.015$), and linoelaidylcarnitine (OR = 1.134, $P = 0.035$) levels were significantly positively associated with an increased risk of AAA. No statistically significant heterogeneity or pleiotropy was found (see Supplementary material online, *Table S10*).

Seventy-three circulating metabolites were significantly associated with AD risk (*Figure 4*; see Supplementary material online, *Table S11*). Tyrosine (OR = 1.420, $P = 0.003$), 1-methyl-4-imidazoleacetate (OR = 1.220, $P = 0.046$), hexadecanedioate (C16-DC) (OR = 2.742, $P = 0.007$), γ-glutamyltyrosine (OR = 1.411, $P = 0.018$), and androstenediol (3α, 17α) monosulfate (3) (OR = 0.712, $P = 0.025$) levels were significantly positively associated with the risk of AD. No statistically significant heterogeneity or pleiotropy was detected (see Supplementary material online, *Table S12*).

Mediation effect analysis

In the mediation analysis (*Figure 5* and *Table 4*), PCSK9i, lignoceroyl sphingomyelin (d18:1/24:0) exhibited the highest mediation effect on TAA, with 57.4% of the mediation effects of PCSK9i. Campesterol and deoxycholic acid 12-sulfate levels also showed substantial mediation effects on TAA, with 30.2% and 16.7% mediation effects of PCSK9i, respectively.

For statins, the adenosine 5′-monophosphate (AMP) to urate ratio had a 24% mediation effect on AD, suggesting a strong influence through purine metabolism pathways. Tetradecanedioate (C14-DC) levels mediate 17.5% of statin effects on AAA, indicating the relevance of fatty acid metabolism in statin action.

Characteristics of real-world drug reports

The FAERS database was utilized to explore the relationship between LLDs and aortic diseases. The FAERS database received 14 931 458 reports between the first quarter of 2015 and the first quarter of 2024. After excluding duplicates and outliers based on the data cleaning criteria of the FAERS, 13 038 441 reports were retained. A total of 152 284 reports for PCSK9i, 675 511 for statins, and 1 838 035 or 2 140 233 for control group drugs, with at least one PCSK9i, statin, and control group drug as a suspect or concomitant medication, respectively, were identified (*Figure 6*). Over 39% of patients were 65 years or older, with fewer males than females taking PCSK9i (39.2% vs. 53.4%). Most reports came from healthcare professionals, with the United States leading in report numbers across all groups (*Table 5*).

Disproportionality analysis of LLDs and aortic diseases

The proportion of reports identifying AA as an adverse event (AE) was significantly lower in the PCSK9i group than in the control group, with a reporting odds ratio (ROR) of 0.631 ($P < 0.05$) and an IC_{025} of −2.298 (*Figure 7* and *Table 6*). This indicates an abnormally

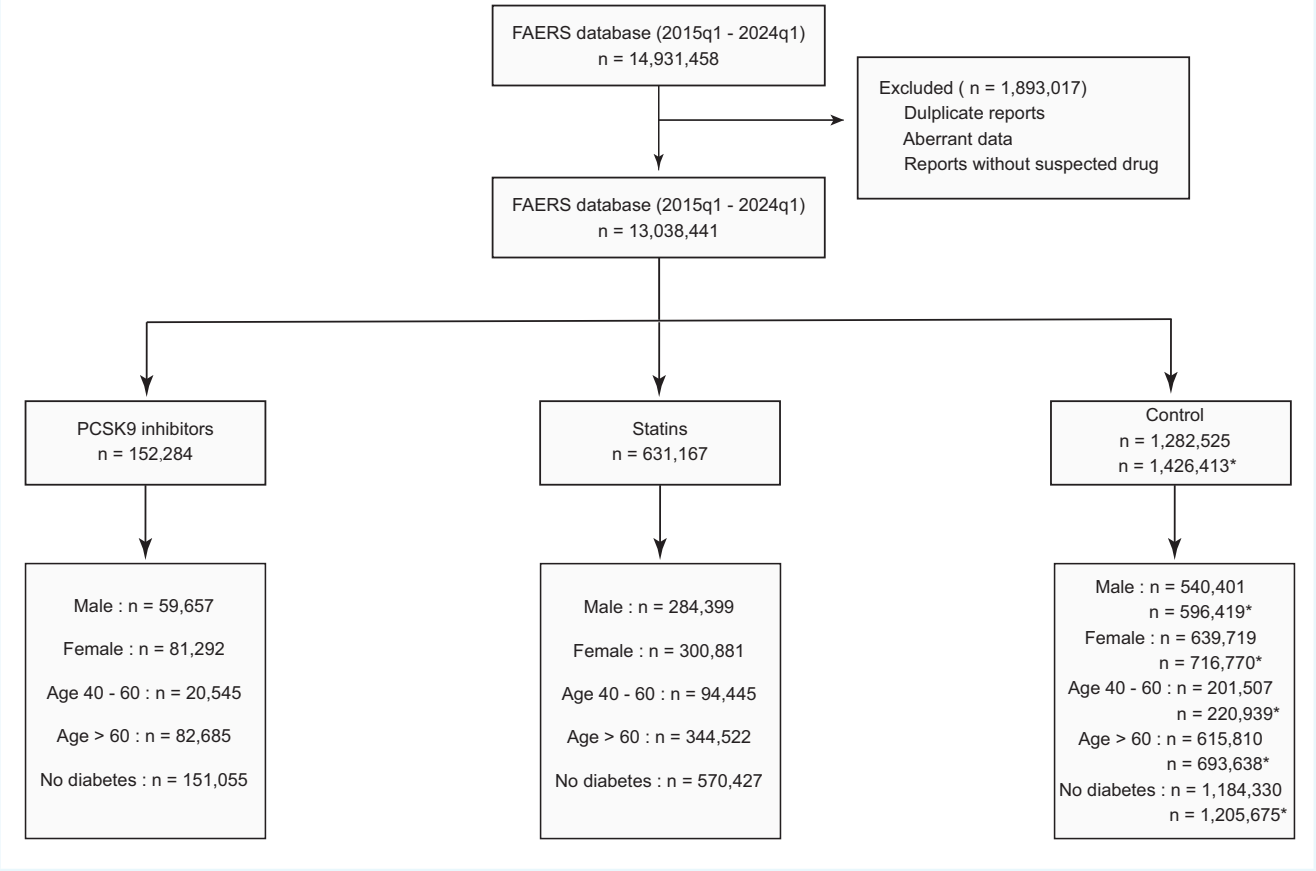


Figure 6 Study flow chart. A series of interconnected analyses is reported, with progressive exclusions. FAERS, FDA Adverse Event Reporting System. Moreover, we applied an algorithm to further detect suspected duplicate reports by screening for identical values in four key fields: age, sex, event date, and country of occurrence. Numbers are referred to the total number or reports in each analysis (*with the PCSK9 inhibitor).

low incidence of AA with PCSK9i compared with control group drugs, consistent with results from MR analyses. Diabetes is often accompanied with dyslipidaemia, increasing their likelihood of taking LLDs. Since diabetes is a negative factor for AA, this may lead to inaccuracies in the results. Intriguingly, the PCSK9i group still showed a considerably low incidence of AA (ROR = 0.569, $P < 0.01$) even after excluding reports from patients with diabetes. This disproportionality was consistently high in the female gender and age >60 subgroups (*Figure 7* and *Table 6*).

MR analysis showed that statins had the same protective effect in AAA as PCSK9i but not in TAA. However, the FAERS database does not distinguish between TAA and AAA but groups them as AA. PCSK9i are often used as an alternative for inadequate response to statins. A comparison of AA incidence between PCSK9i and statins revealed that the PCSK9i group showed a lower AA incidence (ROR = 0.631, $P < 0.001$) than the statins group. This consistency was maintained in gender, age >60, and no diabetes subgroups (*Figure 7* and *Table 6*). Collectively, these results demonstrate that PCSK9i exhibit superior efficacy in reducing AA incidence compared with other drugs (*Figure 7* and *Table 6*).

Unlike AA, MR analysis revealed a significant negative correlation between statins and the risk of AD (*Figure 1*). The proportion of reports identifying AD as an AE was significantly lower in the statin than in the control group, with an ROR of 0.620 ($P < 0.05$) and an IC_{025} of −2.127. This indicates an abnormally low AD incidence with statins compared with control group drugs, confirming previous findings. Subgroup analyses also revealed that statins maintained a lower AD incidence under conditions of male gender, age >60, and no diabetes subgroups (*Figure 8* and *Table 7*), highlighting the exceptional performance of statins in reducing AD risk.

Discussion

Surgery is the preferred treatment for aortic diseases but it is not effective in all patients. Therefore, new interventions should be developed. Hypertension, hyperlipaemia, smoking, gender, and age are crucial factors to consider when assessing aortic disease risk in a patient. The underlying mechanisms of aortic diseases likely involve an interplay between genetic predispositions and these acquired risk factors.[21] Studies have shown that LLDs can prevent AAs and aortic valve stenosis.[22–24] However, reports on the relationship between LLDs and the risk of various aortic diseases remain limited and inconclusive.

This study employed multiple MR methods to evaluate the effects of cardiovascular drugs, including LLDs (mediated by statins or PCSK9i) and blood pressure-lowering agents (mediated by ABs, BBs, CCBs, ACEIs, or ARBs), on the risk of aortic diseases. Results showed that PCSK9i exhibited significant protective effects in reducing the risk of AA. Additionally, statins significantly reduced AD risk.

The distinct origins of smooth muscle cells in the thoracic aorta (neural crest and somitic mesoderm) compared with those in the abdominal aorta (splanchnic mesoderm) may underlie the differing

Table 5 Baseline statistics of the population in real-world drug reports

	PCSK9 inhibitors (*N* = 152 284)	Statins (*N* = 631 167)	Control (*N* = 1 282 525)	Control* (*N* = 1 426 413)
Reporting region				
United States	146 138 (96.0%)	382 410 (60.6%)	724 577 (56.5%)	863 816 (60.6%)
Japan	855 (0.6%)	16 021 (2.5%)	41 576 (3.2%)	42 273 (3.0%)
Germany	759 (0.5%)	23 401 (3.7%)	55 548 (4.3%)	56 016 (3.9%)
Great Britain (UK)	614 (0.4%)	48 084 (7.6%)	74 128 (5.8%)	74 616 (5.2%)
Netherlands	375 (0.2%)	—	—	—
France	—	27 010 (4.3%)	58 343 (4.5%)	58 456 (4.1%)
Reporter				
Consumer/lawyer	75 269 (49.4%)	263 077 (41.7%)	542 315 (42.3%)	613 889 (43.0%)
Health professional	75 904 (49.8%)	342 575 (54.3%)	700 217 (54.6%)	771 538 (54.1%)
Event year				
2015–2019	78 551 (48.4%)	344 621 (54.6%)	693 253 (54.1%)	767 531 (53.8%)
2020–2024	73 733 (51.6%)	286 546 (45.4%)	589 272 (45.9%)	658 882 (46.2%)
Age, years				
<18	81 (0.1%)	703 (0.1%)	8 924 (0.7%)	9 005 (0.6%)
18–64	38 161 (25.1%)	161 735 (25.6%)	345 944 (27.0%)	382 044 (26.8%)
65–85	63 756 (41.9%)	260 068 (41.2%)	453 187 (35.3%)	513 115 (36.0%)
>85	2 350 (1.5%)	25 197 (4.0%)	54 930 (4.3%)	57 161 (4.0%)
Missing	47 936 (31.5%)	183 464 (29.1%)	419 540 (32.7%)	465 088 (32.6%)
Sex				
Female	81 292 (53.4%)	300 881 (47.7%)	639 719 (49.9%)	716 770 (50.2%)
Male	59 657 (39.2%)	284 399 (45.1%)	540 401 (42.1%)	596 419 (41.8%)
Missing	11 335 (7.4%)	45 887 (7.3%)	102 405 (8.0%)	113 224 (7.9%)

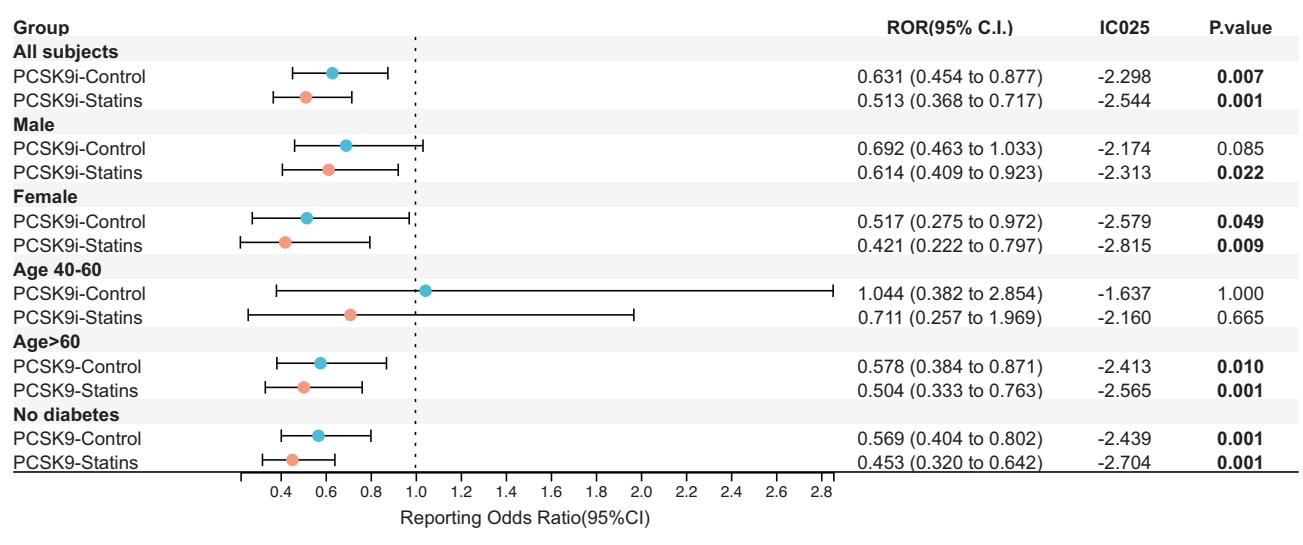


Figure 7 Disproportionality analysis. The forest plot shows reporting odds ratio (ROR) with 95% confidence intervals (CIs) for aortic aneurysm (AA) in reports for PCSK9 inhibitors (PCSK9i) vs. control drugs. An ROR <1.0 indicates a disproportional lower rate of AA among reports for PCSK9i.

Table 6 Aortic aneurysm adverse events that were treated with PCSK9 inhibitors (PCSK9i)

Group	ROR	ROR (95% CI)	IC_{025}	*P*-value
All subjects				
PCSK9i—control	0.631	0.631 (0.454 to 0.877)	−2.298	0.007
PCSK9i—statins	0.513	0.513 (0.368 to 0.717)	−2.544	0.000
Male				
PCSK9i—control	0.692	0.692 (0.463 to 1.033)	−2.174	0.085
PCSK9i—statins	0.614	0.614 (0.409 to 0.923)	−2.313	0.022
Female				
PCSK9i—control	0.517	0.517 (0.275 to 0.972)	−2.579	0.049
PCSK9i—statins	0.421	0.421 (0.222 to 0.797)	−2.815	0.009
Age 40–60				
PCSK9i—control	1.044	1.044 (0.382 to 2.854)	−1.637	1.000
PCSK9i—statins	0.711	0.711 (0.257 to 1.969)	−2.160	0.665
Age >60				
PCSK9i—control	0.578	0.578 (0.384 to 0.871)	−2.413	0.010
PCSK9i—statins	0.504	0.504 (0.333 to 0.763)	−2.565	0.001
No diabetes				
PCSK9i—control	0.569	0.569 (0.404 to 0.802)	−2.439	0.001
PCSK9i—statins	0.453	0.453 (0.320 to 0.642)	−2.704	0.000

pathogenic mechanisms between AD and AAA. Additionally, AD exhibits notable differences from AAA in terms of population prevalence, patterns of inheritance, and the specific genes associated with predisposition.[25] Statin ameliorates endothelial dysfunction via up-regulation of endothelial nitric oxide synthase (eNOS) and endothelium-derived nitric oxide production, inhibition of Rho prenylation, and other antioxidant effects.[26] Endothelial dysfunction plays an important role in the pathogenesis of vascular remodelling, including thoracic AD.[27] PCSK9i primarily influence cholesterol metabolism by regulating the degradation of LDL receptors.[15] Lowering systemic inflammation and slowing atherosclerosis progression may protect against AA development. PCSK9i, often used when conventional LLDs are ineffective, have stronger lipid-lowering effects and more effectively reduce arterial wall inflammation.[28] AD may be characterized by a tear in the intima, primarily induced by arteriosclerosis and abnormal matrix metalloproteinases (MMP) activity. Unlike PCSK9i, statins also improve endothelial function and provide antioxidant benefits.[29,30] Endothelial cells form the arterial intima, so statins may lower AD risk by improving endothelial function. This may explain the differing effects of PCSK9i and statins on these two diseases.[16] Real-world drug reports also indicated that except in the male gender and age 40–60 subgroups, PCSK9i displayed a lower rate of AA reports in other subgroups than in the control or the statin group. Compared with the control group, statins maintained a lower reporting ratio in all subgroups, except for the female gender and age 40–60 subgroups, in reports with AD as the major disease.

The use of genetic proxies enhances causal inferences by minimizing confounding factors. Unlike traditional observational studies, MR provides more reliable insights. Real-world drug data further highlight the roles of PCSK9i and statins in reducing aortic diseases, supporting future personalized medicine and prevention strategies.[31] Nonetheless, this study has some limitations including use of genetic tools that explain only a small proportion of phenotypes,[32] focus on cardiovascular drugs, excluding other non-drug factors that affect aortic disease risk,[33] and possibility of other confounding genetic pathways.[31,34] Although real-world drug reports were used to enhance the accuracy of the results, these reports were from subjects with a history of medication use and diseases other than the target disease. The effect of all potential confounding factors could not be excluded in the analyses.

Study limitations

This study had some limitations that need to be considered in the interpretation of the findings. First, it was an observational study based on multiple sources; therefore, reverse causality might exist. However, the study rigorously adjusted for confounding factors and validated the association through MR analysis, thereby addressing this issue to the best extent possible. Second, we acknowledge that the FAERS

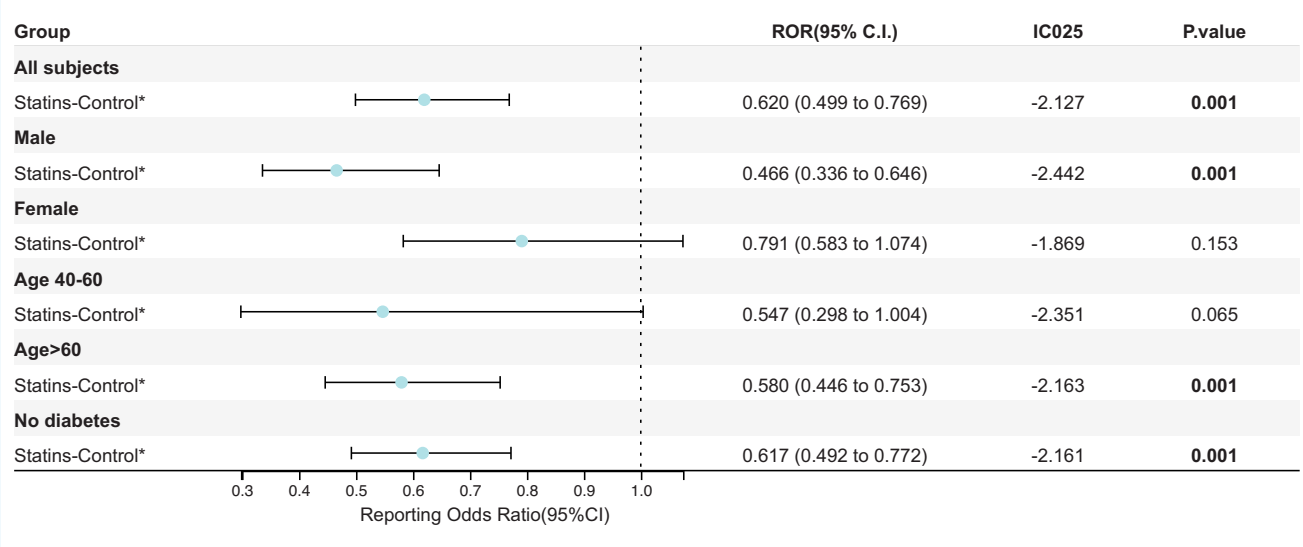


Figure 8 Disproportionality analysis. The forest plot shows reporting odds ratio (ROR) with 95% confidence intervals (CIs) for aortic dissection (AD) in reports for statins vs. control drugs. An ROR <1.0 indicates a disproportional lower rate of AD among reports for statins. (*with the PCSK9 inhibitor).

Table 7 Aortic dissection adverse events that were treated with statins

Group	ROR	ROR (95% CI)	IC_{025}	*P*-value
All subjects				
Statins—control	0.620	0.620 (0.499 to 0.769)	−2.127	1.48E-05
Male				
Statins—control	0.466	0.466 (0.336 to 0.646)	−2.442	3.90E-06
Female				
Statins—control	0.791	0.791 (0.583 to 1.074)	−1.869	0.153
Age 40–60				
Statins—control	0.547	0.547 (0.298 to 1.004)	−2.351	0.065
Age > 60				
Statins—control	0.580	0.580 (0.446 to 0.753)	−2.163	4.63E-05
No diabetes				
Statins—control	0.617	0.617 (0.492 to 0.772)	−2.161	2.66E-05

database inherently includes subjects with comorbidities unrelated to the target disease. To minimize confounding, we carefully excluded subjects with conditions that significantly influence aortic disease risk. However, it remains challenging to identify a population exclusively affected by the target disease, given the nature of real-world pharmacovigilance data. Third, there was a chance of misclassification of antihypertensive agents used in the UK Biobank data during follow-up because the antihypertensive agent use was only evaluated once at baseline. Fourth, our study included the largest set of real-world data for PCSK9i spanning nearly a decade; the inherent limitations of the FAERS database, including its spontaneous reporting nature and the relatively short post-marketing period of PCSK9i, must be acknowledged. These factors may limit the ability to detect rare or long-term AEs associated with these medications. To further validate these findings, long-term cohort studies and clinical trials with extended follow-up periods are needed to better assess the safety profile and clinical impact of PCSK9i on aortic disease risk.

Conclusions

In summary, this study highlights the potential value of genetic information in the prevention and treatment of aortic diseases. Specifically, statins and PCSK9i offer new perspectives in the development of new drugs and the design of precision medicine strategies. Elevated levels of lipoprotein(a) [Lp(a)] are causally associated with an increased risk of AAs, as well as AD, through pathways involving pro-atherogenic, pro-inflammatory, and pro-thrombotic mechanisms.[35,36] This study would provide a roadmap for continuing investigations into the connections between more risk factors, emerging drugs, and their impact on aortic disease risk.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Acknowledgements

The acknowledgments to GWAS consortia were described in detail in Supplementary material online, *Tables S1* and S2. This study conforms to the principles outlined in the Declaration of Helsinki.

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Conflict of interest: none declared.

Data availability

All data used in this study are publicly available, and the source of the data is described in the main text.

Author contributions

H.N. and W. Zhao conceived the original conception, designed the experiment plan, carried out data analysis, and drafted the manuscript. Q.W revised the manuscript. W. Zhou reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, Decleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes De Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;**76**:2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010
2. Akhmerov A, Parimon T. Extracellular vesicles, inflammation, and cardiovascular disease. *Cells* 2022;**11**:2229. https://doi.org/10.3390/cells11142229
3. Kori M, Cig D, Arga KY, Kasavi C. Multiomics data integration identifies new molecular signatures for abdominal aortic aneurysm and aortic occlusive disease: implications for early diagnosis, prognosis, and therapeutic targets. *OMICS* 2022;**26**:290–304. https://doi.org/10.1089/omi.2022.0021
4. Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, Bura-Rivière A, De Backer J, Deglise S, Della Corte A, Heiss C, Kałużna-Oleksy M, Kurpas D, Mceniery CM, Mirault T, Pasquet AA, Pitcher A, Schaubroeck HAI, Schlager O, Sirnes PA, Sprynger MG, Stabile E, Steinbach F, Thielmann M, Van Kimmenade RRJ, Venermo M, Rodriguez-Palomares JF, ESC Scientific Document Group. 2024 ESC guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J* 2024;**45**:3538–3700. https://doi.org/10.1093/eurheartj/ehae179
5. Lewis JR, Wong G, Taverniti A, Vucak-Dzumhur M, Elder GJ. Association between aortic calcification, cardiovascular events, and mortality in kidney and Pancreas-kidney transplant recipients. *Am J Nephrol* 2019;**50**:177–186. https://doi.org/10.1159/000502328
6. Mc Namara K, Alzubaidi H, Jackson JK. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? *Integr Pharm Res Pract* 2019;**8**:1–11. https://doi.org/10.2147/iprp.S133088
7. Mcevoy JW, Mccarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, Christodorescu RM, Daskalopoulou SS, Ferro CJ, Gerdts E, Hanssen H, Harris J, Lauder L, Mcmanus RJ, Molloy GJ, Rahimi K, Regitz-Zagrosek V, Rossi GP, Sandset EC, Scheenaerts B, Staessen JA, Uchmanowicz I, Volterrani M, Touyz RM; ESC Scientific Document Group. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024;**45**:3912–4018. https://doi.org/10.1093/eurheartj/ehae178
8. Gallego-Colon E, Daum A, Yosefy C. Statins and PCSK9 inhibitors: a new lipid-lowering therapy. *Eur J Pharmacol* 2020;**878**:173114. https://doi.org/10.1016/j.ejphar.2020.173114
9. Nicholls SJ. PCSK9 inhibitors and reduction in cardiovascular events: current evidence and future perspectives. *Kardiol Pol* 2023;**81**:115–122. https://doi.org/10.33963/KP.a2023.0030

10. Alkhalil M. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, reality or dream in managing patients with cardiovascular disease. *Curr Drug Metab* 2019;**20**:72–82. https://doi.org/10.2174/1389200219666180816141827
11. Schmidt AF, Carter J-PL, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas J. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2020;**10**:Cd011748. https://doi.org/10.1002/14651858.CD011748.pub3
12. Koutsogianni AD, Liamis G, Liberopoulos E, Adamidis PS, Florentin M. Effects of lipid-modifying and other drugs on lipoprotein(a) levels-potent clinical implications. *Pharmaceuticals (Basel)* 2023;**16**:750. https://doi.org/10.3390/ph16050750
13. Allara E, Morani G, Carter P, Gkatzionis A, Zuber V, Foley CN, Rees JMB, Mason AM, Bell S, Gill D, Lindström S, Butterworth AS, Di Angelantonio E, Peters J, Burgess S; INVENT consortium. Genetic determinants of lipids and cardiovascular disease outcomes: a wide-angled mendelian randomization investigation. *Circ Genom Precis Med* 2019;**12**:e002711. https://doi.org/10.1161/circgen.119.002711
14. Chen Y, Huang M, Xuan Y, Li K, Xu X, Wang L, Sun Y, Xiao L, Xu P, Kong W, Wang DW. Association between lipid levels and risk for different types of aneurysms: a mendelian randomization study. *J Pers Med* 2021;**11**:1171. https://doi.org/10.3390/jpm11111171
15. Sliz E, Kettunen J, Holmes MV, Williams CO, Boachie C, Wang Q, Männikkö M, Sebert S, Walters R, Lin K, Millwood IY, Clarke R, Li L, Rankin N, Welsh P, Delles C, Jukema JW, Trompet S, Ford I, Perola M, Salomaa V, Järvelin M-R, Chen Z, Lawlor DA, Ala-Korpela M, Danesh J, Davey Smith G, Sattar N, Butterworth A, Würtz P. Metabolomic consequences of genetic inhibition of PCSK9 compared with statin treatment. *Circulation* 2018;**138**:2499–2512. https://doi.org/10.1161/circulationaha.118.034942
16. Silva IVG, de Figueiredo RC, Rios DRA. Effect of different classes of antihypertensive drugs on endothelial function and inflammation. *Int J Mol Sci* 2019;**20**:3458. https://doi.org/10.3390/ijms20143458
17. Rethy LB, Feinstein MJ, Achenbach CJ, Townsend RR, Bress AP, Shah SJ, Cohen JB. Antihypertensive class and cardiovascular outcomes in patients with HIV and hypertension. *Hypertension* 2021;**77**:2023–2033. https://doi.org/10.1161/hypertensionaha.120.16263
18. Zheng Y, Li D, Zeng N, Guo H, Li H, Shen S. Trends of antihypertensive agents in patients with hypertension and coronary artery disease in a tertiary hospital of China. *Intl J Clin Pharm* 2020;**42**:482–488. https://doi.org/10.1007/s11096-020-00986-6
19. Ohishi M, Yoshida T, Oh A, Hiroi S, Takeshima T, Otsuka Y, Iwasaki K, Shimasaki Y. Analysis of antihypertensive treatment using real-world Japanese data-the retrospective study of antihypertensives for lowering blood pressure (REAL) study. *Hypertens Res* 2019;**42**:1057–1067. https://doi.org/10.1038/s41440-019-0238-2
20. Kwok MK, Schooling CM. Unraveling potential sex-specific effects of cardiovascular medications on longevity using mendelian randomization. *J Am Heart Assoc* 2023;**12**:e030943. https://doi.org/10.1161/jaha.123.030943
21. Mukherjee D. Unraveling the genetic predisposition for aortic aneurysms: is it time for tailored medicine? *Am J Hypertens* 2008;**21**:967. https://doi.org/10.1038/ajh.2008.232
22. Preiss D, Tobert JA, Hovingh GK, Reith C. Lipid-modifying agents, from statins to PCSK9 inhibitors: JACC Focus seminar. *J Am Coll Cardiol* 2020;**75**:1945–1955. https://doi.org/10.1016/j.jacc.2019.11.072
23. Bergmark BA, O'donoghue ML, Murphy SA, Kuder JF, Ezhov MV, Ceška R, Gouni-Berthold I, Jensen HK, Tokgozoglu SL, Mach F, Huber K, Gaciong Z, Lewis BS, Schiele F, Jukema JW, Pedersen TR, Giugliano RP, Sabatine MS. An exploratory analysis of proprotein convertase subtilisin/kexin type 9 inhibition and aortic stenosis in the FOURIER trial. *JAMA Cardiol* 2020;**5**:709–713. https://doi.org/10.1001/jamacardio.2020.0728
24. Cupido AJ, Reeskamp LF, Hingorani AD, Finan C, Asselbergs FW, Hovingh GK, Schmidt AF. Joint genetic inhibition of PCSK9 and CETP and the association with coronary artery disease: a factorial mendelian randomization study. *JAMA Cardiol* 2022;**7**:955–964. https://doi.org/10.1001/jamacardio.2022.2333
25. Zhang L, Issa Bhaloo S, Chen T, Zhou B, Xu Q. Role of resident stem cells in vessel formation and arteriosclerosis. *Circ Res* 2018;**122**:1608–1624. https://doi.org/10.1161/circresaha.118.313058
26. Yoshida O, Kondo T, Kureishi-Bando Y, Sugiura T, Maeda K, Okumura K, Murohara T. Pitavastatin, an HMG-CoA reductase inhibitor, ameliorates endothelial function in chronic smokers. *Circ J* 2010;**74**:195–202. https://doi.org/10.1253/circj.cj-09-0345
27. Jia L-X, Zhang W-M, Li T-T, Liu Y, Piao C-M, Ma Y-C, Lu Y, Wang Y, Liu T-T, Qi Y-F, Du J. ER stress dependent microparticles derived from smooth muscle cells promote endothelial dysfunction during thoracic aortic aneurysm and dissection. *Clin Sci (Lond)* 2017;**131**:1287–1299. https://doi.org/10.1042/cs20170252
28. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol* 2019;**16**:155–165. https://doi.org/10.1038/s41569-018-0107-8
29. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. *Atherosclerosis* 2009;**203**:325–330. https://doi.org/10.1016/j.atherosclerosis.2008.08.022
30. Tousoulis D, Simopoulou C, Papageorgiou N, Oikonomou E, Hatzis G, Siasos G, Tsiamis E, Stefanadis C. Endothelial dysfunction in conduit arteries and in microcirculation. Novel therapeutic approaches. *Pharmacol Ther* 2014;**144**:253–267. https://doi.org/10.1016/j.pharmthera.2014.06.003
31. Gala H, Tomlinson I. The use of mendelian randomisation to identify causal cancer risk factors: promise and limitations. *J Pathol* 2020;**250**:541–554. https://doi.org/10.1002/path.5421
32. Gill D, Georgakis MK, Walker VM, Schmidt AF, Gkatzionis A, Freitag DF, Finan C, Hingorani AD, Howson JMM, Burgess S, Swerdlow DI, Davey Smith G, Holmes MV, Dichgans M, Scott RA, Zheng J, Psaty BM, Davies NM. Mendelian randomization for studying the effects of perturbing drug targets. *Wellcome Open Res* 2021;**6**:16. https://doi.org/10.12688/wellcomeopenres.16544.2
33. Schmidt AF, Finan C, Gordillo-Marañón M, Asselbergs FW, Freitag DF, Patel RS, Tyl B, Chopade S, Faraway R, Zwierzyna M, Hingorani AD. Genetic drug target validation using mendelian randomisation. *Nat Commun* 2020;**11**:3255. https://doi.org/10.1038/s41467-020-16969-0
34. Yuan S, Mason AM, Burgess S, Larsson SC. Genetic liability to insomnia in relation to cardiovascular diseases: a Mendelian randomisation study. *Eur J Epidemiol* 2021;**36**:393–400. https://doi.org/10.1007/s10654-021-00737-5
35. Wang S, Zha L, Chen J, Du D, Liu D, Zhong M, Shang R, Sun D, Sun C, Jin E. The relationship between lipoprotein(a) and risk of cardiovascular disease: a mendelian randomization analysis. *Eur J Med Res* 2022;**27**:211. https://doi.org/10.1186/s40001-022-00825-6
36. Thomas PE, Vedel-Krogh S, Nielsen SF, Nordestgaard BG, Kamstrup PR. Lipoprotein(a) and risks of peripheral artery disease, abdominal aortic aneurysm, and major adverse limb events. *J Am Coll Cardiol* 2023;**82**:2265–2276. https://doi.org/10.1016/j.jacc.2023.10.009