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Relationship of Apolipoprotein B to Aortic Aneurysm: Frailty Index as a Partial Mediator – a Mendelian Randomization Study

Aim	Aortic aneurysm is characterized by localized expansion and damage to the vessel wall. While apolipoprotein B (ApoB) has been linked to atherosclerosis, its causal relationship with aortic aneurysm remains unclear. This study used a Mendelian randomization (MR) approach to explore the causal relationships between ApoB, aortic aneurysm, and potential mediators.
Material and methods	Single nucleotide polymorphism (SNP) data related to ApoB, apolipoprotein A1 (ApoA1), triglycerides, frailty index, and aortic aneurysm were obtained from large-scale genome-wide association studies. MR analysis was conducted to evaluate causal relationships, using inverse variance weighting (IVW) as the primary statistical method. Additionally, we assessed whether the frailty index mediates the relationship between ApoB and aortic aneurysm.
Results	Univariate MR analysis revealed that ApoB is significantly associated with aortic aneurysm (IVW odds ratio (OR) = 1.443, 95% confidence interval (CI) = 1.273–1.637, p < 0.001). Multivariable MR (MVMR) analysis, adjusted for ApoA1 and triglycerides, confirmed these results. In mediation analysis, the frailty index was found to partially mediate the effect of ApoB on aortic aneurysm (mediation contribution: 20.1%–23.1%). The ORs for ApoB and the frailty index with respect to aortic aneurysm were 1.325 (95% CI = 1.168–1.505) and 4.188 (95% CI = 1.859–9.435), respectively.
Conclusion	ApoB has a causal relationship with aortic aneurysm, with the frailty index acting as a partial mediator in this pathway.

Keywords	Apolipoprotein B; frailty index; aortic aneurysm; Mendelian randomization; mediation effect
For citations	Tongxue Zhang, Yajing Li, Xiaoyu Liu, Jinfeng Wang, Danlei Chen, Hanyu Lei et all. Relationship of Apolipoprotein B to Aortic Aneurysm: Frailty Index as a Partial Mediator – a Mendelian Randomization Study. Kardiologiia. 2025;65(2):57–63. [Russian: Тунсюэ Чжан, Яцзин Ли, Сяоюй Лю, Цзиньфэн Ван, Данлей Чэнь, Ханьюй Лэй и др. Связь между аполипопротеином В и аневризмой аорты: индекс хрупкости как частичный опосредующий фактор – исследование с использованием Менделевской рандомизации. Кардиология. 2025;65(2):57–63].

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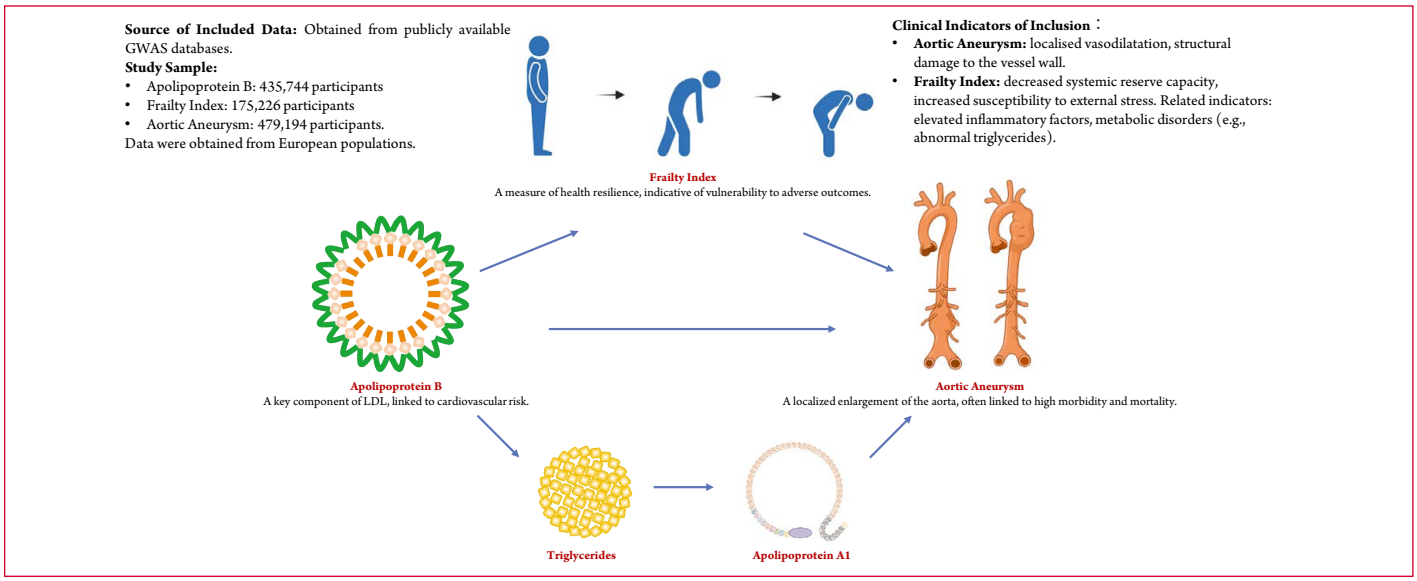
Introduction

Aortic aneurysm is a vascular disease characterized pathologically by localized dilation and structural damage to the vessel wall. It can occur in the thoracic aorta, abdominal aorta, or other parts of the aorta [1]. A strong inflammatory response is a hallmark of the aneurysm process, with macrophages, neutrophils, T cells, and B cells participating in the inflammatory response involved in the development of the aneurysm [2]. Lipid components in the blood also play a role in certain vascular diseases, such as atherosclerosis. Studies have shown that elevated plasma apolipoprotein B (ApoB) is associated with an increase in angiotensin II-induced abdominal aortic aneurysms [3], suggesting a potential causal relationship between ApoB and aneurysm development. Adipose tissue exhibits strong metabolic activity, with a significant number of macrophages producing a range of signaling molecules that can activate various stress pathways. This includes an increase in oxidative stress pathways that promote the release of more reactive oxygen species and pro-inflammatory factors. This in turn increases catabolic processes while diminishing anabolic processes. The resulting imbalance in these processes can lead to vascular muscle damage and a decline in muscle mass, ultimately resulting in vascular wall weakness [4]. Additionally, higher amounts of remnant cholesterol are associated with an increased risk of fragility in middle-aged and older adults [5].

Central illustration. Relationship of Apolipoprotein B to Aortic Aneurysm: Frailty Index as a Partial Mediator – a Mendelian Randomization Study



Research has also shown that patients with sarcopenia or frailty have a significantly higher risk of mortality following endovascular aneurysm repair (EVAR) [6].

As reviewed above, previous studies have suggested a potentially causal relationship between ApoB, frailty, and aortic aneurysms. Therefore, we used genetic variations in ApoB, apolipoprotein A1 (ApoA1), triglycerides, the frailty index, and aortic aneurysms as instrumental variables in applying Mendelian randomization (MR) to simulate the conditions of a randomized experiment, and, thus, to explore the possible relationships among these variables.

Material and methods

Data sources

Single nucleotide polymorphisms (SNPs) data related to ApoB, ApoA1, triglycerides, frailty index, and aortic aneurysms were sourced from the open genome-wide association study (GWAS) database of the Integrative Epidemiology Unit (IEU). The basic information for each GWAS dataset is provided in tabular form in the results section (Table 1). Data on ApoB, Apo1, triglycerides, aortic aneurysm, and frailty index were derived from European samples with sizes of 435744, 398508, 94595, 479194, and 175226, respectively. This study selected ApoB as the exposure, with ApoA1 and triglycerides considered potentially confounding factors. SNP from GWAS data were used as instrumental variables to conduct a two-sample Mendelian randomization analysis for assessing the causal relationship between ApoB and aortic aneurysms. We performed mediation analysis using the frailty index as an intermediate to estimate the proportion of the effect of ApoB on aortic aneurysms mediated by the frailty index.

Selection of instrumental variables

SNPs were used as instrumental variables. To ensure independence and remove linkage disequilibrium, the following threshold conditions were set: linkage disequilibrium parameter $r^2 = 0.001$, genetic distance 10000 kb, $p < 1 \times 10^{-8}$, and SNPs with incompatible alleles and palindromic SNPs with intermediate allele frequencies were deleted. In the GWAS dataset of the outcome variable, significant SNPs associated with the exposure factors were extracted to obtain the final instrumental variable, and information such as the effect allele, non-effect allele, allele effect value (β), standard error (SE), and p-value were recorded. The F-statistic was used to test the strength of the instrumental variables. An F-value >10 indicates that there is no weak instrumental variable bias [7, 8].

Table 1. Data source information

Variable	Number of participants	Number of SNP	First author	Year of publication	PubMed ID
ApoB	435,744	4,231,412	Barton	2021	29875488
ApoA1	398,508	4,218,115	Barton	2021	34226706
Triglycerides	94,595	2,410,057	Willer	2013	24097068
Aortic aneurysm	479,194	24,191,825	Sakaue	2021	34594039
Frailty index	175,226	7,589,717	Atkins	2021	3443159

Ancestry of all participants was European. SNP, single nucleotide polymorphism.

ISSN 0022-9040. Кардиология. 2025;65(2). DOI: 10.18087/cardio.2025.2.n2796

Statistical analysis

Multivariate analysis

This study mainly used the inverse variance weighted (IVW) method to evaluate the causal relationship between ApoB and aortic aneurysm [9, 10]. Egger, lasso, median, and robust methods were used for the sensitivity analysis. The Q statistic was used to evaluate the heterogeneity. When heterogeneity was present, a random-effects model was used; otherwise, a fixed-effects model was used. ApoB, ApoA1, and triglycerides were included in the multivariate analysis model to evaluate the OR value, 95% CI, and p-value after adjusting for the other two confounding factors.

Mediation effect analysis

The frailty index was used as a mediator, and mediation analysis was used to explore how ApoB-mediates aortic aneurysm through the proportion of frailty index. We used difference and multiplication methods to calculate the mediation effect and proportion. In the difference method, C is the total effect, C' is the indirect effect, and (C–C')/C is the mediation effect proportion. In the multiplication method, C is the total effect, B is the effect value of mediation on the outcome using multivariate MR analysis, and A is the effect value of exposure to mediation. The mediation effect is (A*B), and the mediation effect ratio is (A*B)/C. All studies selected European populations, and the corresponding analyses were performed using the two-sample MR [11] and R Mediation software packages in R (http://www.r-project.org).

Sensitivity analysis

Sensitivity analysis was performed from two aspects, horizontal pleiotropy [12] and the leave-one-out method [13], to test whether the conclusions were robust. Horizontal pleiotropy was determined based on whether the MR Egger intercept was 0 [10]. When the intercept was close to 0, this indicated that there was no horizontal pleiotropy, and a scatter plot was drawn to visualize the results of horizontal pleiotropy [14]. The leave-one-out method was used to eliminate individual SNPs individually to observe whether the effect value changed significantly, and a leave-one-out figure was drawn to visualize the results [15].

Results

The GWAS information for ApoA1, ApoB, triglycerides, aortic aneurysm, and frailty index is shown in Table 1. SNPs common to ApoA1, ApoB, triglycerides, and aortic aneurysm were combined to obtain 690 SNPs; 230 SNPs remained after removing duplicates. Mismatched alleles (rs2901285) and palindromic sequences of the neutral alleles (rs1194182, rs2001945, rs6029526, rs8053682) were removed, and 225 SNPs were obtained for MR analysis.

Figure 1. Schematic diagram of the research process. A is the effect size of exposure to the mediator. B is the effect size of the mediator on the outcome obtained by multivariate MR analysis. C is the total effect, and C' is the indirect effect

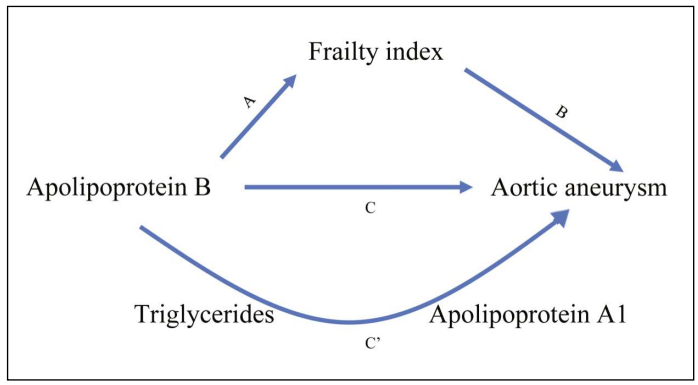


Figure 2. Multivariable ORs and 95% CIs for ApoB, ApoA1, and triglycerides (IVW method)

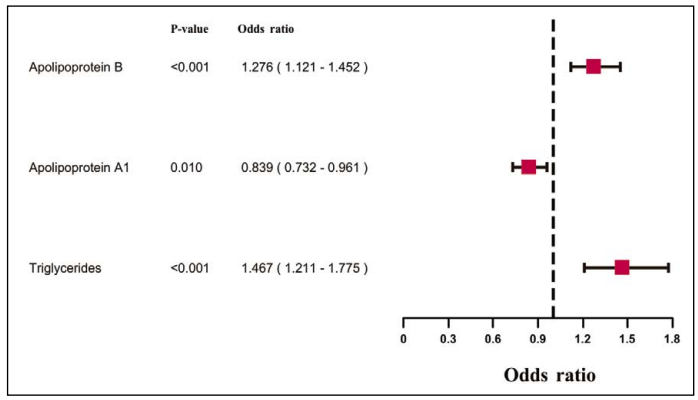
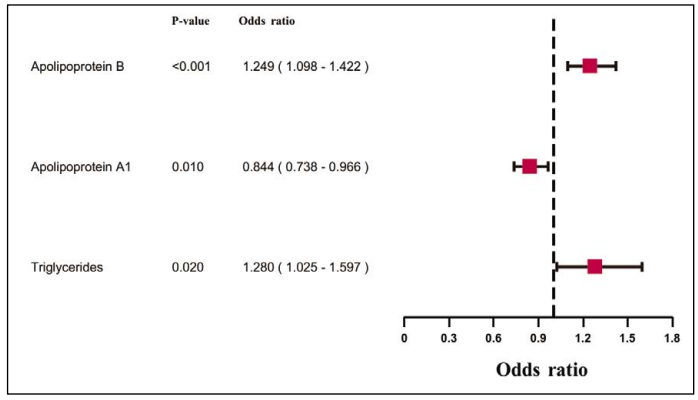


Figure 3. Multivariable ROs and 95% CIs for ApoB, ApoA1, and triglycerides (Egger method)



Multivariate and mediation results

A schematic of the multivariate MR in the IVW method is shown in Figure 1. The results showed that, after adjusting for ApoA1 and triglycerides, ApoB had a positive causal relationship (OR = 1.276, 95% CI = 1.121–1.452, p<0.001), as shown in Figure 2. The F statistics for ApoB, ApoA1, and triglycerides were 193.5, 155.4, and 25.47, respectively. The results of multivariate MR analysis using the Egger, lasso, median, and robust methods (Figure 3–6) showed

Figure 4. Multivariable ORs and 95% CIs for ApoB, ApoA1, and triglycerides (Lasso method)

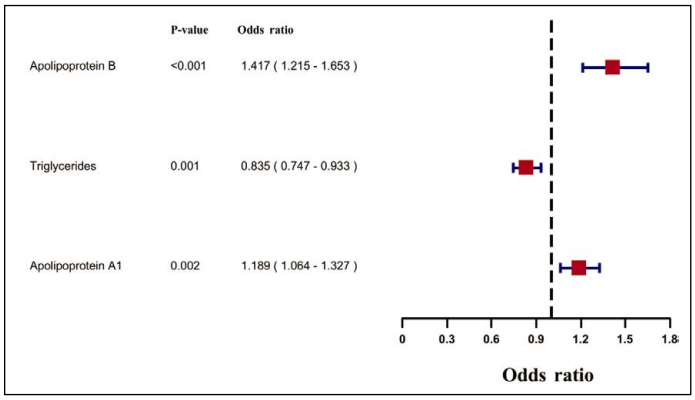


Figure 5. Multivariable ORs and 95% CIs for ApoB, ApoA1, and triglycerides (Median method)

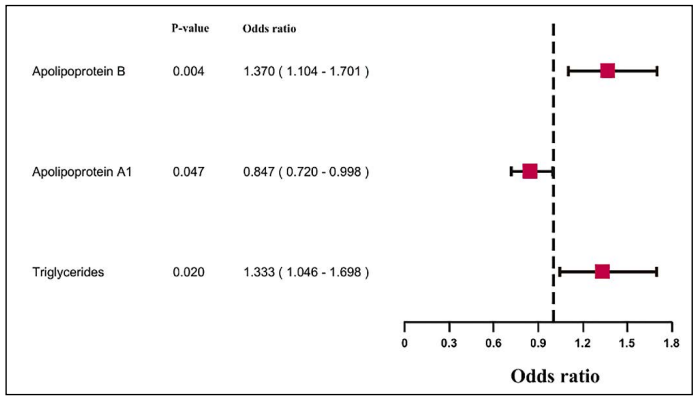


Figure 6. Multivariable ORs and 95% CIs for ApoB, ApoA1, and triglycerides (Robust method)

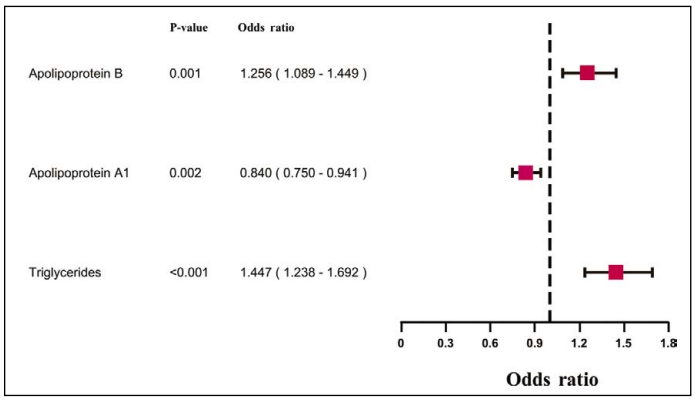


Figure 7. Multivariable ORs and 95% CIs for ApoB and triglycerides (IVW method)

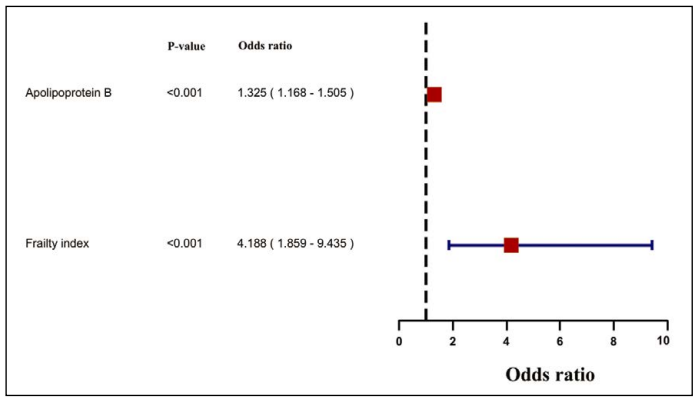
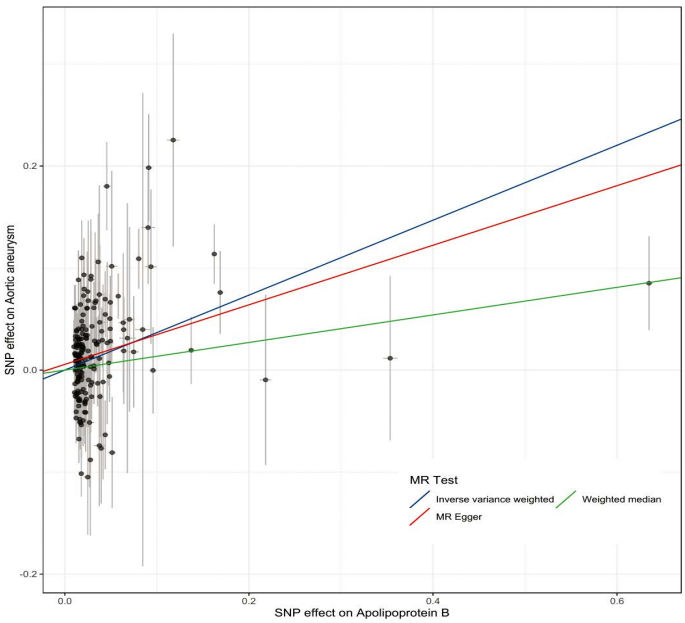


Figure 8. Scatter plot showing the relationship between ApoB and aortic aneurysm



Sensitivity analysis using three different MR methods is included: the inverse variance weighted (IVW) method (blue line), MR Egger regression (red line), and the weighted median method (green line). The individual points represent SNP effect estimates, with error bars indicating the variability of each estimate. The lines represent the estimated causal effects for each MR method.

that after adjusting for ApoA1 and triglycerides, ApoB had a positive causal relationship (egger OR = 1.249, 95% CI = 1.098–1.422, p<0.001); (lasso OR = 1.417, 95% CI = 1.215–1.653, p<0.001); (median-OR = 1.370, 95% CI = 1.104–1.701, p=0.004); (robust-OR = 1.256, 95% CI = 1.089–1.449, p=0.001). The results of multivariate MR of mediation analysis (Figure 7) showed that ApoB and aortic aneurysm: OR=1.323, 95% CI=1.168–1.505; frailty index and aortic aneurysm: OR=4.188, 95% CI=1.859–9.435. The mediation effect analysis used the difference and multiplication methods, and the frailty index mediated 23.1% and 20.1% of the effect of ApoB on the risk of aortic aneurysm, respectively.

Sensitivity analysis results

The scatter plot of SNP effects on aortic aneurysm and Apolipoprotein B with sensitivity analysis using different MR methods is shown in Figure 8. The MR-Egger test results showed that the intercept terms of ApoB (intercept = –0.0005, p=0.101) were close to 0, p>0.05, indicating that there was no horizontal pleiotropy. The leave-one-out sensitivity analysis is shown in figure 9. After eliminating individual SNPs individually, the single SNP did not affect the overall results, and the effect line did not cross the ineffective line.

ISSN 0022-9040. Кардиология. 2025;65(2). DOI: 10.18087/cardio.2025.2.n2796

Discussion

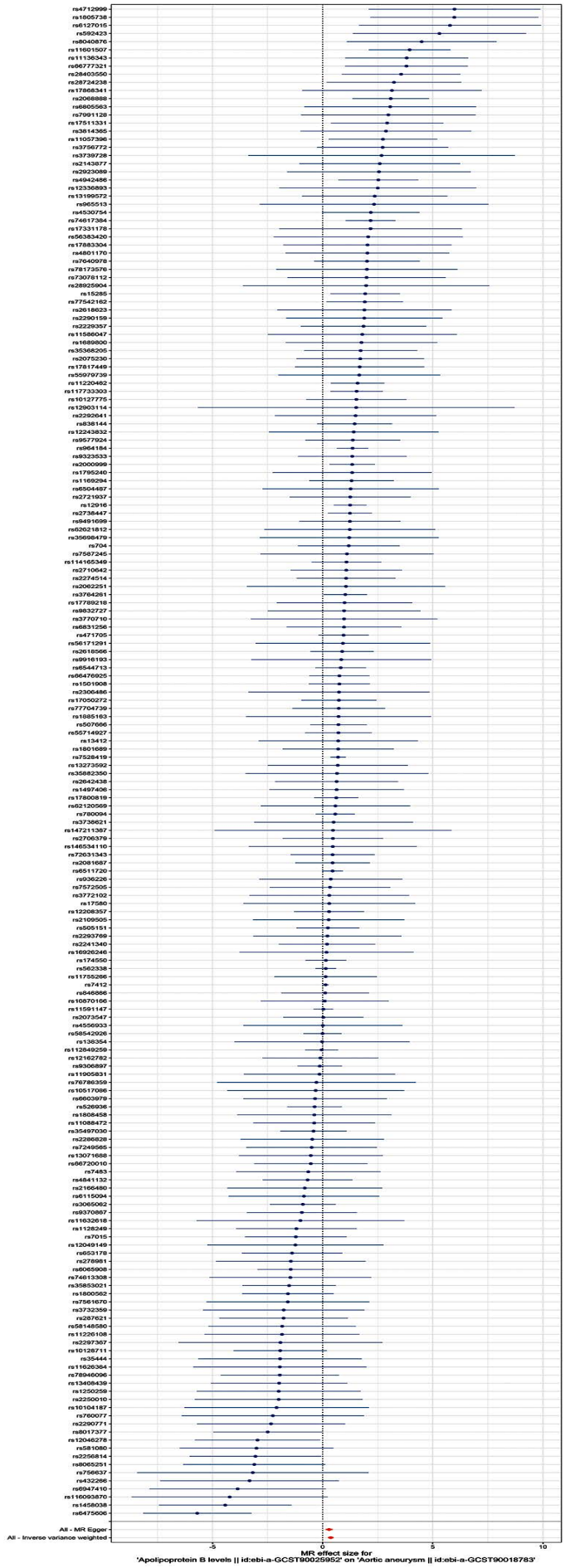
Aortic aneurysm is a common aortic disease, second only to atherosclerosis, and is associated with a substantial risk of sudden death, characterized by progressive and irreversible dilation of the affected section of the aorta [16].

Dyslipidemia describes an imbalance in plasma cholesterol and triglyceride concentrations [17]. Previous studies have demonstrated an association between dyslipidemia and atherosclerosis [18]. Another MR study showed that low-density lipoprotein cholesterol, total cholesterol, and triglycerides promote the occurrence of aortic aneurysms, whereas high-density lipoprotein cholesterol inhibits the occurrence of aortic aneurysms [19]. Currently, there is a lack of research on the relationship between apolipoproteins and aortic aneurysms. Long-term subcutaneous infusion of angiotensin II into mice is a common method for modeling aortic aneurysms, and lipoproteins containing ApoB help enhance Ang II-induced abdominal aortic aneurysms in male mice [3]. This finding suggests that ApoB may have a causal relationship with aortic aneurysm formation. Our multivariate MR study results also showed that after excluding the confounding factors of ApoA1 and triglycerides, multiple MR methods suggested that there was a positive causal relationship between ApoB and aortic aneurysm, and that higher apolipoprotein concentrations promote the occurrence of aortic aneurysm. In addition, lipoproteins containing ApoB have a variety of pro-inflammatory effects, including localized inflammation in the arterial walls as well as systemic activation of immune cells [20].

Frailty is a dynamic syndrome characterized by decreased body homeostatic reserves and increased vulnerability to external stress [21], which can lead to an increased risk of cardiovascular disease and death [22]. The results of an epidemiological study showed that, after adjusting for multiple variables, such as baseline data and medications, remnant cholesterol (RC), the ratio of RC to TC, and the ratio of RC to LDL–C were positively correlated with frailty [5]. This indicates an association between dyslipidemia and frailty, and that higher dyslipidemia increases the risk of frailty. Although direct epidemiological evidence linking serum circulating ApoB concentrations to frailty is lacking, the results from this MR study highlight the role of elevated ApoB in inducing frailty.

We used difference and multiplication methods to calculate the mediation effect, and the results showed that frailty played a mediating role in the impact of ApoB on aortic aneurysm, accounting for 23.1%. In addition, the higher the triglyceride-glucose index value, the greater is the risk of frailty [23], which also suggests that abnormal glucose and lipid metabolism disorders are risk factors for frailty.

Figure 9. The leave-one-out sensitivity analysis



The association of frailty with vascular disease has rarely been studied, and the current study is the first to demonstrate a causal relationship between frailty and aortic aneurysm. For patients undergoing EVAR, frailty and sarcopenia significantly increased the 30-day and long-term mortality in EVAR patients [6]. A previous study showed that frailty was associated with a significantly increased risk of 30-day mortality in patients undergoing vascular surgery. This risk was also observed in patients undergoing abdominal aortic aneurysm repair and lower extremity revascularization [24], suggesting a possible relationship between frailty and aortic aneurysm-related disease. In a study of systemic inflammation and osteoporosis, frailty played a mediating role [25]. Chronic inflammation is a risk factor for frailty [26]. Cross-sectional and longitudinal studies have shown a positive correlation between increased inflammation and the risk of frailty [27–29]. The results were also consistent in the age and sex subgroups [25].

This study has several limitations. First, the data we investigated came from five large-scale GWAS, lacking specific demographic baseline data and clinical information of the study population, making it impossible to conduct statistical and subgroup analyses of the population data. Second, because the study population was European, the conclusions should be interpreted with caution when applied to other ethnic groups, and more studies should be conducted to confirm our results. Nevertheless, we provide evidence that ApoB may contribute to the development of aortic aneurysms through frailty.

In conclusion, our findings demonstrate that apolipoprotein B (ApoB) exhibits dual mechanistic pathways in the pathogenesis of aortic aneurysms. Primarily, ApoB directly mediates inflammatory cascades that contribute to aneurysm formation. Additionally, ApoB facilitates aneurysm development through an indirect pathway by perpetuating chronic systemic inflammation, which leads to elevated frailty index scores, a validated metric independently associated with increased aortic aneurysm susceptibility. These mechanistic insights suggest that maintaining physiological ApoB concentrations may serve as a promising preventive strategy against aortic aneurysm development. Moreover, our data identify ApoB as a potential therapeutic target in aneurysm prevention and intervention strategies, underscoring the clinical significance of stringent lipid management in reducing cardiovascular morbidity. The elucidation of these ApoB-mediated pathways not only advances our understanding of aneurysm pathobiology but also provides a foundation for developing targeted therapeutic interventions aimed at improving clinical outcomes in patients at risk for aortic pathologies.

Ethics approval and consent to participate

Prior ethics approval and consent to participate were not applicable. However, this study is consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, and all methods were performed in accordance with relevant guidelines and regulations.

Availability of data

Publicly available datasets were analyzed in this study. These data are available at https://gwas.mrcieu.ac.uk/.

Authors' contributions

TXZ and KYD contributed to the study concept and design. YJL and YZJ performed the statistical analysis and data interpretation. YPZ and HHL were responsible for the quality control of the data and algorithms. HYL performed the literature research and data extraction. XYL and DLC assisted in the experimental procedures and data collection. JFW and LX contributed to the manuscript revision and provided critical feedback. All authors contributed to the writing of the manuscript and approved the final version for submission.

No conflict of interest is reported.

The article was received on 27/10/2024

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