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Remnant cholesterol and risk of aortic aneurysm and dissection: a prospective cohort Study from the UK biobank study and mendelian randomization analysis

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Abstract

Aim This study aimed to examine the relationships between remnant cholesterol (RC) and the risk of aortic aneurysm and dissection (AAD).

Methods This prospective cohort study included 368,139 European adults from the UK Biobank. Additionally, the causal relationship between RC and AAD was investigated using Mendelian randomization (MR) analyses.

Results During a median follow-up of 13.65 years, 1,634 cases of abdominal aortic aneurysm (AAA), 698 cases of thoracic aortic aneurysm (TAA), and 184 cases of aortic dissection (AD) were identified. Elevated RC levels were associated with an increased risk of AAA compared to the reference group ([highest vs. lowest RC levels]: adjusted hazard ratio (HR) = 1.65, 95% CI: 1.36–1.99). However, no significant association was observed between high RC levels and the risk of either TAA or AD. Two-sample MR analyses supported a significant causal effect of RC on AAA risk (odds ratio (OR) = 2.08, 95% CI: 1.70–2.56). The association between RC and AAA persisted after adjusting for the effects of RC-associated genetic variants on low-density lipoprotein cholesterol (LDL-C). In contrast, MR analyses did not indicate any causal associations between RC and TAA or AD.

Conclusions Elevated RC was linked to a greater risk of developing AAA, with MR analyses confirming a causal relationship. These findings suggest that RC may function as a new biomarker for AAA and could be integral to strategies aimed at preventing AAA.

Keywords Remnant cholesterol, Abdominal aortic aneurysm, Aortic dissection, Thoracic aortic aneurysm, Mendelian randomization analysis

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Introduction

Aortic aneurysm and dissection (AAD) affect 1.3–8% of individuals and are associated with high mortality rates due to acute aortic syndromes [1, 2]. AAD includes thoracic aortic aneurysm (TAA), abdominal aortic aneurysm (AAA), and aortic dissection (AD), is commonly associated with smoking, hypertension and dyslipidemia [3]. Prior to rupture, AAD is often asymptomatic, making timely diagnosis and treatment challenging. However, once rupture occurs, mortality rates soar to 80% [4]. Consequently, early prediction of AAD is critical for improving survival outcomes and enhancing patient prognosis.

Research has indicated that the etiology of AAA and atherosclerotic cardiovascular disease (ASCVD) is heavily influenced by conventional lipid profiles, comprising low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) [5]. Remnant cholesterol (RC) is the cholesterol content of chylomicrons, chylomicron remnants, intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL) [6]. In contrast to traditional lipid parameters, RC has been increasingly associated with ASCVD in recent studies, demonstrating its superior predictive capability in evaluating both the risk of development and the prognosis of ASCVD [7–9]. Preliminary evidence suggests that RC is deposited in arterial walls and accumulate in the intima and media, which promotes foam cell formation and the progression of atherosclerosis [10]. Studies have shown a connection between elevated levels of RC and increased risks of myocardial infarction, heart failure, ASCVD, and even mortality [9, 11–14]. Atherosclerosis has been shown to be strongly associated with the occurrence and progression of AAD, particularly aortic aneurysms, as both conditions share overlapping risk factors [2, 3, 15]. Mechanistically, RC may play a role in influencing the occurrence of AAD; however, current evidence remains inadequate to definitively establish a clear link between RC and AAD risk. Further exploration of the specific relationship between RC and AAD could yield valuable insights into risk assessment and management, ultimately enhancing the efficacy of AAD prevention strategies.

To explore the relationship between RC and incident AAD risk, a prospective cohort study was conducted using data from the UK Biobank, encompassing a large European adult population. Additionally, causal relationships between RC and AAD were validated through MR analysis.

Methods

UK Biobank cohort data

In the UK Biobank cohort, 502,389 individuals aged 40–69 years were registered between April 2006 and December 2010, a prospective population-based study [16]. The participants submitted comprehensive health data via touch-screen questionnaires and direct anthropometric assessments. Blood samples were obtained for genotyping and biomarker analysis. The research protocol and related data access information can be accessed online (http://www.ukbiobank.ac.uk/).

Participants in this research who had a baseline diagnosis of AAA, TAA, or AD (n = 332) or who did not have information on their lipid profiles (TC, triglyceride (TG), LDL-C, and HDL-C; n = 70,699) were not included in the analysis. Additionally, data on lost visits (n = 994) and other covariate-related data (n = 62,225) were excluded. Finally, our research comprised 368,139 individuals in total (Supplementary file 1, Figure S1).

LDL-C was determined using the Friedewald equation when TG levels were ≤ 4 mmol/L: LDL-C = TC − HDL-C − (TG/2.2). For TG levels > 4 mmol/L, LDL-C was directly measured [12, 17, 18]. RC was computed using the extensively used and verified techniques of earlier research, which were TC minus LDL-C minus HDL-C [8, 9]. To determine the effects of illnesses, the International Classification of illnesses Coding System (ICD-10) was used. The ICD-10 codes for AAA, TAA, and AD were taken from medical records [19, 20]. The codes and descriptions of the covariates were provided in Supplementary File 1, Table S1, and the Details of Covariates.

Genome-wide association study (GWAS) data

Data sources for exposures and outcomes

The MRC Integrative Epidemiology Unit (IEU) Open GWAS database provides GWAS summary statistics for RC, which include information from 115,082 people of European ancestry [21]. Simultaneously, how genetic instruments affect exposure to LDL-C was determined. LDL-C proxies were obtained from the Global Lipids Genetics Consortium (GLGC), which includes a sample of 173,082 people (http://lipidgenetics.org/) [22]. The GWAS data related to TAA, AAA, and AD patients were retrieved from the FinnGen consortium R12 release data (AAA, 4439 cases and 463,106 controls; TAA, 5108 cases and 463,106 controls; AD, 1150 cases and 463,106 controls).

Statistical analysis

Retrospective analysis and sensitivity analysis

Kurtosis and skewness measures were used in addition to normal probability plots to evaluate the normality of continuous data. Data that were nonnormally distributed and categorical are described as medians.

The follow-up duration, used as the time scale in the Cox proportional hazards model, was defined as the

interval between the enrollment date at the assessment center and the occurrence of the outcome event or death. The lowest quintile served as the reference group for the prospective analysis, which evaluated correlations between the RC quintiles, other variables, and the incidence of AAD using the Cox proportional hazards model. The unadjusted Cox regression was represented as a univariate analysis in Model 1. Model 2 was adjusted for sex, age, and ethnicity. In addition, Model 3 was further adjusted for common confounders associated with cardiovascular diseases, such as smoking status, drinking status, body mass index (BMI), education, activity, LDL-C, diabetes, hypertension, stroke, healthy diet, coronary atherosclerosis (CAD), coronary heart disease (CHD) and peripheral vascular disease (PVD). These covariates were identified on the basis of their relevance to the outcomes of interest or their potential to influence the effect estimate by more than 10%. Hazard ratios (HRs) and the associated 95% confidence intervals (CIs) were presented as outcomes. Prior to constructing the model, the covariance between RC and the covariates was evaluated via linear regression equations, and the variance inflation factors (VIFs) pertaining to RC and each covariate were determined.

Subgroup analyses were performed, and interaction variables were included in the adjusted model to explore any changes in the relationship between AAA risk and RC quintiles. Age (≥65 or < 65 years), sex (male or female), BMI (≥25 or < 25 kg/m^2), smoking status (yes or no), diabetes status (yes or no), hypertension status (yes or no), CHD status (yes or no), and LDL-C level (≥2.6 or < 2.6 mmol/L) were among these categories.

Owing to the strong collinearity among antihypertensive medications, antidiabetic drugs, and cholesterol-lowering agents, this study only considers including antihypertensive medications in the multivariable adjustment model for sensitivity analysis. Additionally, a regression analysis was performed with RC as a continuous variable against AAD.

Mendelian randomization and sensitivity analysis

Genetic instrument selection

For the construction of genetic instrument variables (IVs), genetic proxies were delineated as single-nucleotide polymorphisms (SNPs) correlated with RC exposure and individual lipoproteins characterized by the highest RC content, including medium- and large-density lipoproteins (M-VLDLs), small-density lipoproteins (S-VLDLs), medium-density lipoproteins (L-VLDLs), and intermediate-density lipoproteins (IDLs). Genetic instruments for RC traits were constructed from GWASs using variants in linkage equilibrium. Using the 1000 Genomes reference panel, the genetic variants were consolidated using a linkage disequilibrium threshold ($r^2 < 0.001$, distance = 10 mb). A genome-wide criterion of P < 5E-08 was established for the selection of genetic variants strongly associated with the exposures. Additionally, the efficacy of the instrument was determined by the F statistic, and weak instruments with F statistics < 10 were removed. This study utilized publicly accessible GWAS data, all originating from original studies that had obtained approval from the respective ethical review committees.

Two-sample MR analysis

For all the statistical studies, the R packages "Two Sample MR" and "Mendelian Randomization" were used. Inverse-variance weighting (IVW), MR–Egger, the weighted median (WM), weighted mode and simple mode were used to address the possible influence of pleiotropy bias to determine whether there is a causal relationship between the genetic predisposition to exposure and the result. Because of its effectiveness and dependence on relevant IVs, the IVW approach was chosen for the main MR study [23]. The Cochrane's Q test was used to assess any possible heterogeneity [24]. If significant heterogeneity (P < 0.05) was observed, a random-effects IVW model was applied [25]. To determine the horizontal pleiotropy of the genetic variations, the MR–Egger intercept was used (P < 0.05 was regarded as evidence of horizontal pleiotropy). Furthermore, the impact of IVs identified through MR-PRESSO tests was examined in an additional distortion analysis. Any outliers with a P < 0.05 in this analysis were excluded, and the causal estimates were re-evaluated [26]. To ascertain whether particular variations were responsible for the findings, leave-one-out analysis was also carried out [27].

To enhance the robustness of the association between RC and AAA, additional sensitivity analyses were performed. Using the FUMAGWAS database, all RC-related SNPs were examined for their biological functions and nearby genes, and SNPs associated with confounding factors such as age, sex, education, smoking, alcohol consumption, BMI, cardiovascular disease, and diabetes were excluded. To avoid horizontal pleiotropy of RC-related genetic instruments and ensure that SNPs influence AAA solely through RC, this study selected SNPs from genes directly involved in RC metabolism or lipid pathways (*PSK9, APOB, APOE, LDLR, HMGCR*) for further analysis [28, 29]. Furthermore, given that variants in the fatty acid desaturase (FADS) gene cluster are major determinants of multiple metabolic traits, including lipid fractions, FADS variants were excluded from enhancing robustness by mitigating the risk of pleiotropy through alternative metabolic pathways. And SNPs with the largest effect sizes on RC were removed to assess whether these variants disproportionately influenced the observed

associations. Finally, Steiger filtering method was used to detect reverse causation.

Mediation Analysis

A mediation analysis was performed using multivariable MR (MVMR) to estimate the direct effect of RC on the outcome [30], after accounting for the mediating effect of LDL-C. The total effect was directly obtained from the univariable MR analyses, and the indirect effect was calculated as the total effect minus the direct effect. IVs were filtered using the criteria of P < 1E-05 and linkage disequilibrium (LD) $r^2 < 0.001$ within 10 mb. Variants substantially linked with the outcomes were then eliminated. No sensitivity analyses were conducted for the MVMR model, as it was not the primary estimation of interest, and pleiotropy-robust sensitivity models for MVMR are not yet well established.

R version 4.3.0 (R Foundation for Statistical Computing) was used for all the statistical analyses. The results were deemed statistically significant if the P value with two tails was less than 0.05.

Results

Baseline characteristics of the participants

This research included 368,139 individuals in total. There were 1634 incident AAA cases, 698 incident TAA cases, and 184 incident AD cases, with a median follow-up of 13.65 years. Among the participants, 53% were female, and the median age was 58 years. Table 1 displays the participants' initial characteristics for each of the RC quintiles. Participants in higher RC quintiles were more likely to be male, had higher mean BMI, and were more likely to smoke, engage in unhealthy activity, follow an unhealthy diet, and have lower educational attainment compared to those in lower RC quintiles. They were also more prone to comorbidities. Supplementary file 1, Table S2 displays the quintile distributions of RC levels among the participants, and Supplementary file 1, Table S3 presents the differences in baseline characteristics between individuals who developed AAD during follow-up and those who did not.

RC and AAD in the UK Biobank

Figure 1 displays the results of the multivariate Cox regression analysis with respect to RC and AAD. A positive does-gradient association between RC and AAA was identified, with the degree of correlation remaining stable. There was no covariance detected among the independent variables (Supplementary file 1, Table S4). Upon controlling for prevalent risk variables in Model 3, it was discovered that individuals in the following quintiles—the second (HR = 1.30, 95% CI 1.07–1.60), third (HR = 1.31, 95% CI 1.08–1.59), fourth (HR = 1.39, 95% CI 1.15–1.69), and fifth (HR = 1.65, 95% CI 1.36–1.99) quintiles—had a notably higher risk of AAA (P value < 0.01). There were modest associations between RC and TAA and AD in Model 1. After adjusting for covariates, there was no association between RC quintiles and the risk of AAA or AD. Additionally, when RC was treated as a continuous variable, each 1 mmol/L increase in RC was significantly associated with a 39% higher risk of incident AAA in Model 3 (HR = 1.39, 95% CI 1.22–1.58; P value < 0.01). And RC was not connected with TAA risk (Supplementary file 1, Figure S2). However, each 1 mmol/L increase in RC was associated with a 38% lower risk of incident AD. To further investigate the relationship between RC and AAA, the results showed the cumulative incidence of AAA events across RC quintile groups, with higher RC quintiles associated with a higher incidence of AAA (Fig. 2).

Subgroup analyses considering sex, age, BMI, LDL-C, hypertension, diabetes, CHD, and smoking revealed significant interactions between RC and age, smoking, LDL-C, and hypertension (Fig. 3). The results showed that, regardless of whether individuals were above or below 65 years of age, higher RC levels were associated with an increased risk of AAA. Furthermore, both smokers and individuals with hypertension presented a stronger association between elevated RC levels and a higher risk of AAA. Additionally, compared with individuals with LDL-C levels below 2.6 mmol/L, those with LDL-C levels above 2.6 mmol/L had an even greater risk of AAA.

The sensitivity analyses produced results consistent with the primary outcomes for both the adjusted models for medications (Supplementary file 1, Figure S3-S4) and continuous RC levels (Supplementary file 1, Figure S2).

Effect of genetic instruments, SNPs, on RC levels

A total of 50 independent SNPs correlated with RC were designated as IVs to evaluate the impact of RC on AAA, AD and TAA. All the SNPs were strongly associated with RC (P < 5E-08). Supplementary file 1, Table S5 provides a complete list of the SNPs used in the genetic instruments. F statistics of RC (Supplementary file 1, Table S6), which ranged from 29.79–2778.31, were all over 10, indicating a low chance of mild instrument bias. Supplementary file 1, Table S7 provides an overview of the research cohorts.

According to Table 2, the genetic score revealed a statistically significant association (OR = 2.08, 95% CI, 1.70–2.56; P = 2.28E-12) between total RC and an elevated risk of AAA, as determined by the IVW method. Additionally, a robust causal relationship between LDL-C and AAA was observed (OR = 1.95, 95% CI, 1.59–2.37; P = 5.57E-11) (Fig. 4). However, five MR methodologies failed to demonstrate a significant association between genetic susceptibility to RC and

Table 1 Description of baseline characteristics for the overall participants and for the groups by RC quintiles

Characteristics	Total participants (*n* = 368,139)	RC quintiles					P
		Quintile 1 (*n* = 73,753)	Quintile 2 (*n* = 73,613)	Quintile 3 (*n* = 73,568)	Quintile 4 (*n* = 73,600)	Quintile 5 (*n* = 73,605)	
Sex (%)							< 0.001
Female	195,782 (53.18)	49,555 (67.19)	44,581 (60.56)	39,874 (54.20)	34,545 (46.94)	27,227 (36.99)	
Male	172,357 (46.82)	24,198 (32.81)	29,032 (39.44)	33,694 (45.80)	39,055 (53.06)	46,378 (63.01)	
Age (median [IQR])	58.000 [50.000, 63.000]	54.000 [47.000, 61.000]	58.000 [50.000, 63.000]	59.000 [51.000, 64.000]	59.000 [52.000, 64.000]	58.000 [51.000, 63.000]	< 0.001
Ethnic (%)							< 0.001
Others	17,952 (4.88)	4860 (6.59)	3674 (4.99)	3222 (4.38)	3106 (4.22)	3090 (4.20)	
White	350,187 (95.12)	68,893 (93.41)	69,939 (95.01)	70,346 (95.62)	70,494 (95.78)	70,515 (95.80)	
Smoking (%)							< 0.001
No	200,359 (54.42)	44,349 (60.13)	42,074 (57.16)	40,324 (54.81)	37,895 (51.49)	35,717 (48.53)	
Yes	167,780 (45.58)	29,404 (39.87)	31,539 (42.84)	33,244 (45.19)	35,705 (48.51)	37,888 (51.47)	
Drinking (%)							< 0.001
No	181,136 (49.20)	32,988 (44.73)	35,268 (47.91)	36,806 (50.03)	37,798 (51.36)	38,276 (52.00)	
Yes	187,003 (50.80)	40,765 (55.27)	38,345 (52.09)	36,762 (49.97)	35,802 (48.64)	35,329 (48.00)	
Body mass index (%):							< 0.001
< 18.50	1875 (0.51)	1020 (1.38)	468 (0.64)	225 (0.31)	112 (0.15)	50 (0.07)	
18.50–24.99	120,507 (32.73)	40,768 (55.28)	30,344 (41.22)	22,790 (30.98)	16,139 (21.93)	10,466 (14.22)	
25.00–29.99	157,478 (42.78)	24,634 (33.40)	30,283 (41.14)	33,161 (45.08)	34,353 (46.68)	35,047 (47.61)	
> = 30.00	88,279 (23.98)	7331 (9.94)	12,518 (17.01)	17,392 (23.64)	22,996 (31.24)	28,042 (38.10)	
Lipid parameters, median [IQR], mmol/L							< 0.001
LDL-C	3.451 [2.811, 4.109]	3.189 [2.665, 3.757]	3.455 [2.856, 4.060]	3.546 [2.897, 4.193]	3.564 [2.872, 4.254]	3.555 [2.822, 4.267]	
TC	5.652 [4.908, 6.422]	5.254 [4.621, 5.936]	5.535 [4.845, 6.242]	5.676 [4.943, 6.399]	5.790 [5.025, 6.569]	6.085 [5.279, 6.894]	
TG	1.480 [1.043, 2.143]	0.790 [0.680, 0.880]	1.124 [1.044, 1.206]	1.480 [1.382, 1.584]	1.969 [1.823, 2.140]	2.944 [2.578, 3.559]	
HDL-C	1.401 [1.173, 1.677]	1.671 [1.426, 1.954]	1.531 [1.305, 1.790]	1.411 [1.207, 1.652]	1.298 [1.116, 1.511]	1.167 [1.012, 1.352]	
RC	0.672 [0.474, 0.967]	0.359 [0.309, 0.400]	0.511 [0.475, 0.548]	0.672 [0.628, 0.720]	0.892 [0.828, 0.967]	1.297 [1.161, 1.496]	
Education (%)							< 0.001
Low	58,386 (15.86)	8326 (11.29)	10,777 (14.64)	12,321 (16.75)	13,261 (18.02)	13,701 (18.61)	
Medium	186,508 (50.66)	36,079 (48.92)	37,063 (50.35)	37,292 (50.69)	37,691 (51.21)	38,383 (52.15)	
High	123,245 (33.48)	29,348 (39.79)	25,773 (35.01)	23,955 (32.56)	22,648 (30.77)	21,521 (29.24)	
Activity (%)							< 0.001
Healthy activity	255,045 (69.28)	53,730 (72.85)	52,289 (71.03)	51,090 (69.45)	49,591 (67.38)	48,345 (65.68)	
Unhealthy activity	113,094 (30.72)	20,023 (27.15)	21,324 (28.97)	22,478 (30.55)	24,009 (32.62)	25,260 (34.32)	
Diet (%)							< 0.001
Healthy diet	57,387 (15.59)	13,349 (18.10)	12,421 (16.87)	11,507 (15.64)	10,768 (14.63)	9342 (12.69)	
Unhealthy diet	310,752 (84.41)	60,404 (81.90)	61,192 (83.13)	62,061 (84.36)	62,832 (85.37)	64,263 (87.31)	
Peripheral vascular disease (%)							0.031
No	366,935 (99.67)	73,526 (99.69)	73,387 (99.69)	73,352 (99.71)	73,326 (99.63)	73,344 (99.65)	
Yes	1204 (0.33)	227 (0.31)	226 (0.31)	216 (0.29)	274 (0.37)	261 (0.35)	
Coronary heart disease (%)							
No	353,612 (96.05)	71,652 (97.15)	70,983 (96.43)	70,583 (95.94)	70,205 (95.39)	70,189 (95.36)	< 0.001
Yes	14,526 (3.95)	2101 (2.85)	2630 (3.57)	2985 (4.06)	3394 (4.61)	3416 (4.64)	
Coronary atherosclerosis (%)							< 0.001

Table 1 (continued)

Characteristics	Total participants (*n* = 368,139)	RC quintiles					P
		Quintile 1 (*n* = 73,753)	Quintile 2 (*n* = 73,613)	Quintile 3 (*n* = 73,568)	Quintile 4 (*n* = 73,600)	Quintile 5 (*n* = 73,605)	
No	367,759 (99.90)	73,701 (99.93)	73,548 (99.91)	73,508 (99.92)	73,491 (99.85)	73,511 (99.87)	
Yes	380 (0.10)	52 (0.07)	65 (0.09)	60 (0.08)	109 (0.15)	94 (0.13)	
Stroke (%)							0.035
No	366,271 (99.49)	73,386 (99.50)	73,286 (99.56)	73,198 (99.50)	73,198 (99.45)	73,203 (99.45)	
Yes	1868 (0.51)	367 (0.50)	327 (0.44)	370 (0.50)	402 (0.55)	402 (0.55)	
Diabetes (%)							< 0.001
No	360,508 (97.93)	72,687 (98.55)	72,486 (98.47)	72,139 (98.06)	71,715 (97.44)	71,481 (97.11)	
Yes	7630 (2.07)	1066 (1.45)	1127 (1.53)	1429 (1.94)	1884 (2.56)	2124 (2.89)	
Hypertension (%)							< 0.001
No	162,789 (44.22)	43,675 (59.22)	36,151 (49.11)	31,452 (42.75)	27,315 (37.11)	24,196 (32.87)	
Yes	205,350 (55.78)	30,078 (40.78)	37,462 (50.89)	42,116 (57.25)	46,285 (62.89)	49,409 (67.13)	
Medication intake, n (%)							< 0.001
Antidiabetic drugs							
No	246,160 (99.30)	54,754 (98.98)	51,329 (99.42)	48,632 (99.38)	45,912 (99.41)	45,533 (99.37)	
Yes	1731 (0.70)	566 (1.02)	300 (0.58)	302 (0.62)	273 (0.59)	290 (0.63)	
Antihypertensive drugs							
No	246,160 (75.59)	54,754 (84.18)	51,329 (79.01)	48,632 (74.73)	45,912 (70.52)	45,533 (69.57)	
Yes	79,481 (24.41)	10,290 (15.82)	13,639 (20.99)	16,444 (25.27)	19,194 (29.48)	19,914 (30.43)	
Cholesterol-lowering drugs							
No	246,160 (79.16)	54,754 (86.38)	51,329 (82.24)	48,632 (78.68)	45,912 (74.61)	45,533 (73.68)	
Yes	64,788 (20.84)	8636 (13.62)	11,086 (17.76)	13,178 (21.32)	15,621 (25.39)	16,267 (26.32)	

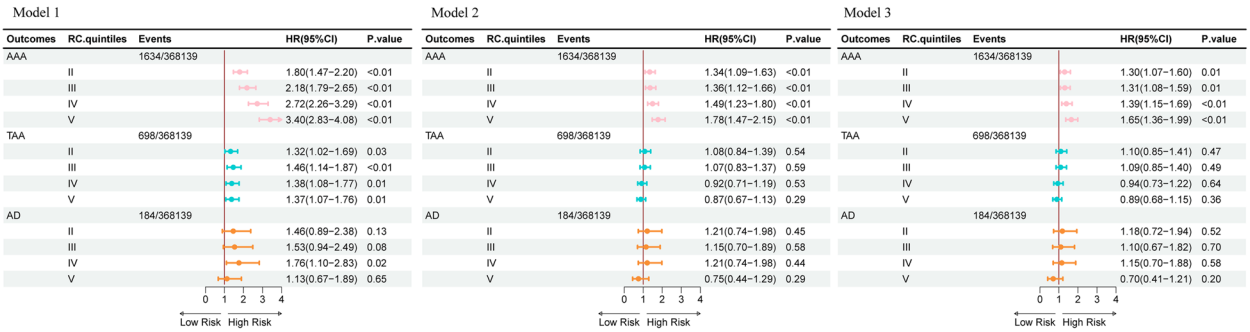

Fig. 1 Associations between remnant cholesterol (RC) quintiles (Qs) and the risk of aortic aneurysm and dissection (AAD). Model 1 was a univariate Cox regression model for RC and AAD. Model 2 was adjusted for age, sex, ethnicity and BMI. Model 3 was adjusted for age, sex, ethnicity, BMI, smoking status, drinking, education, activity, LDL-C, diabetes, hypertension, stroke, healthy diet, CAD, CHD and PVD. AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm; AD, aortic dissection; CAD, coronary atherosclerosis; CHD, coronary heart disease; PVD, peripheral vascular disease; HR, hazard ratio. II, RC quintile 2; III, RC quintile 3; IV, RC quintile 4; V, RC quintile 5

the likelihood of developing AD or TAA. MR analysis was further conducted to explore the causal associations between different RC components and AAA. The results showed that higher AAA risk was associated with L–VLDL–C (OR = 1.77, 95% CI, 1.40–2.24), M–VLDL-C (OR = 2.21, 95% CI, 1.80–2.72), and S–VLDL-C (OR = 2.00, 95% CI, 1.62–2.47).

Potential outliers among the IVs were identified. Following the exclusion of all outliers detected by the MR-PRESSO test (Supplementary file 1, Table S8), no significant directional pleiotropy was observed (Table 2). Notable heterogeneity was detected in the MR analysis, prompting the use of a multiplicative random effects model. Supplementary file 1,

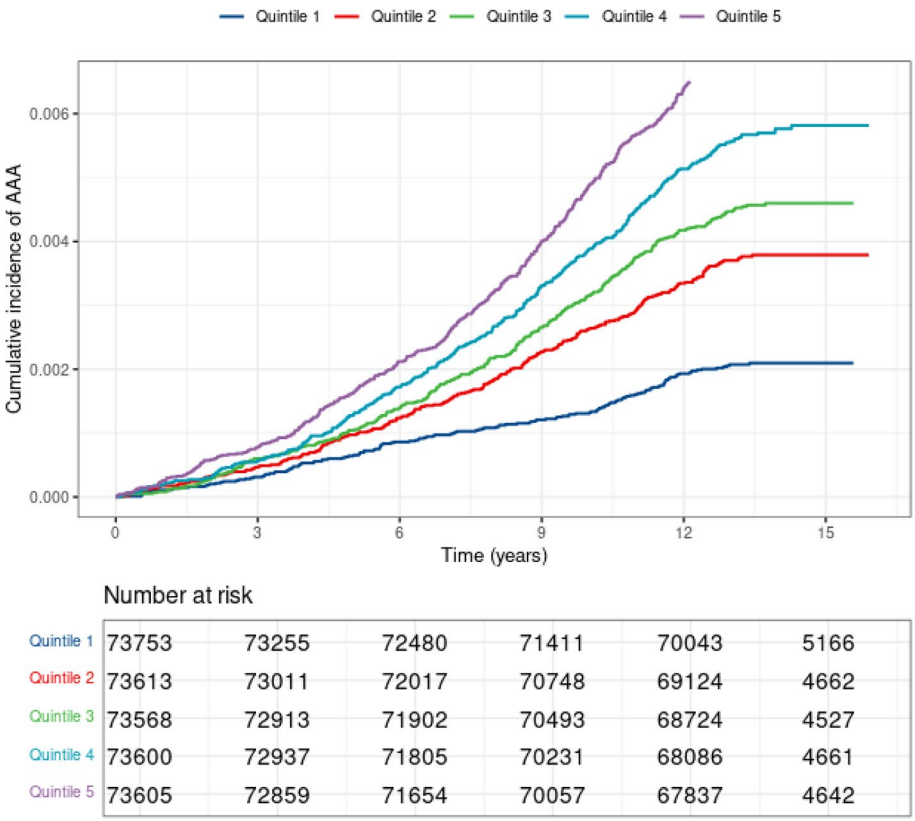

Fig. 2 The cumulative incidence of abdominal aortic aneurysm among remnant cholesterol quintile (Q) groups. AAA, abdominal aortic aneurysm

Figures S5–S8 illustrate the practical importance of each IV for RC using leave-one-out techniques, funnel plots, scatter diagrams and forest plots. Supplementary file 2, Tables S9-S11 showed the RC-related IndSigSNPs, along with the traits and nearest genes associated with each SNP. Supplementary File 2, Tables S12-S18, presented additional SNPs included in the sensitivity analysis and the corresponding two-sample MR results. The results indicated that after removing confounding-related SNPs, FADS-related SNPs, and the largest effect on RC, the association between RC and AAA remained consistent with the main findings of this study, with no evidence of horizontal pleiotropy or reverse causality.

Mediation analysis

Mediation analysis showed that the total effect was almost entirely driven by the direct effect of RC (Beta: 0.61; 95% CI, 0.33–0.88). Part of the effect of RC on AAA was mediated by the mediator LDL-C (Beta = 0.13; 95%CI, −0.22–0.47). (Supplementary file 1, Figure S9).

Discussion

This prospective cohort study and MR analysis revealed that RC was positively correlated with an elevated risk of AAA, but showed no significant correlation with the risk of TAA or AD. In the UK Biobank, participants in the higher quintile of RC demonstrated an increased risk of AAA incidence compared with those in the lower quintile. After adjusting for various covariates, RC was still independently related to the probability of AAA. Furthermore, two-sample MR analysis and mediation analysis further confirmed that the causal association between RC and AAA remains independent of LDL-C.

According to recent guidelines, dyslipidemia is intricately linked to both the occurrence and advancement of cardiovascular diseases [3]. A growing body of research has investigated the relationship between plasma lipids and AAA risk. One observational study found that LDL-C, TC, TG, and HDL-C were independently associated with an increased risk of AAA [31]. Similarly, a meta-analysis established a causal connection between conventional lipid parameters and AAA risk [5]. Domenico et al. reported that an intensified LDL-C lowering program could reduce the incidence of major vascular events and

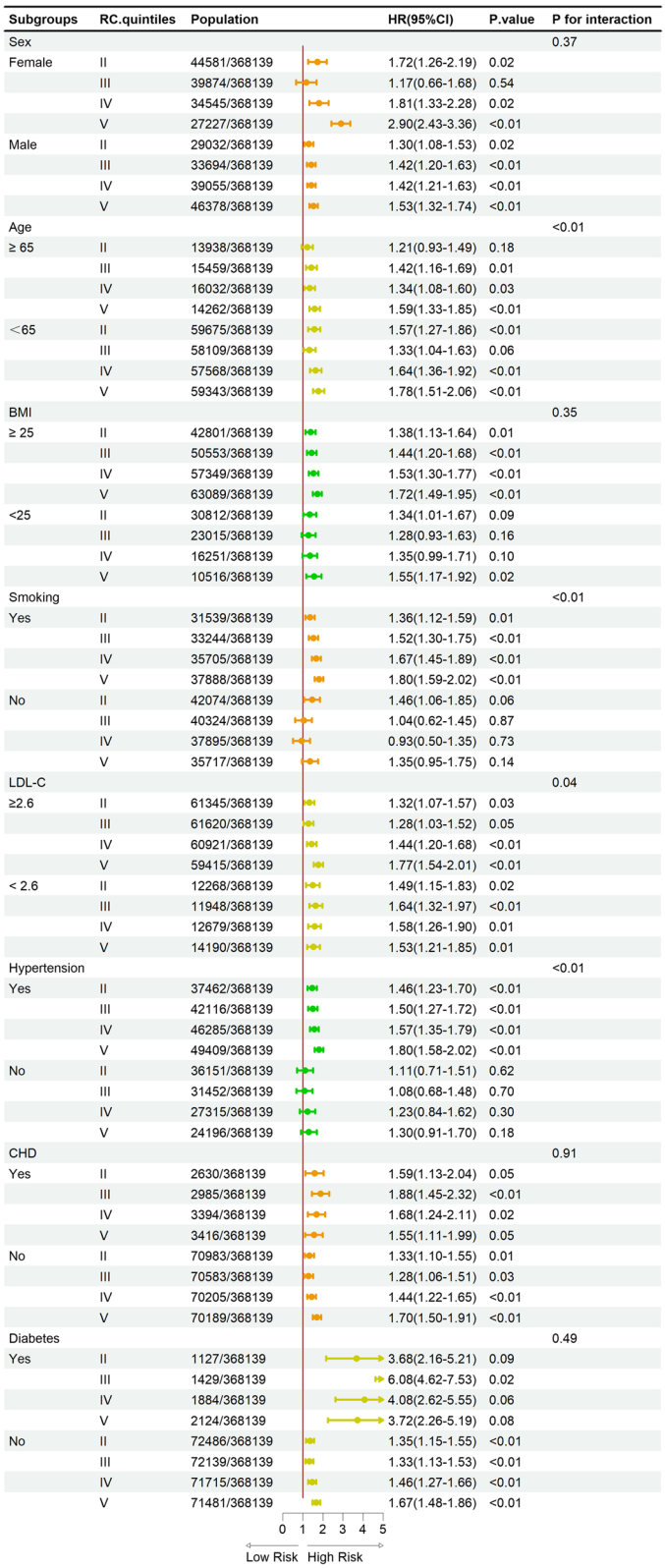

Fig. 3 Subgroup analysis results for the associations between remnant cholesterol (RC) quintiles (Qs) and the risk of AAA. BMI indicates, body mass index; LDL-C, low-density lipoprotein cholesterol; CAD, coronary atherosclerosis; HR, hazard ratio; Age, years; BMI, kg/m.^{3}; LDL-C, mmol/L; and HR = log (exp(estimate)). II, RC quintile 2; III, RC quintile 3; IV, RC quintile 4; V, RC quintile 5

Table 2 Mendelian randomization results of the effect of RC on the risk of AAD, along with tests for heterogeneity and horizontal pleiotropy

Outcome	MR method	No. of SNP	OR	OR (95% CI)	P for association	P for MR-Egger intercept	P for heterogeneity test
AAA	IVW	50	2.08	2.08(1.70–2.56)	2.28E-12	0.65	< 0.01
	MR Egger		1.97	1.97(1.42–2.73	1.87E-04		
	Weighted mode		1.77	1.77(1.40–2.24)	1.64E-05		
	Weighted median		1.81	1.81(1.43–2.28)	5.71E-07		
	Simple mode		2.24	2.24(1.22–4.10)	1.00E-02		
TAA	IVW	50	1.08	1.08(0.94–1.23)	2.80E-01	0.96	0.01
	MR Egger		1.08	1.08(0.88–1.33)	4.80E-01		
	Weighted mode		1.25	1.25(1.05–1.49)	2.00E-02		
	Weighted median		1.28	1.28(1.08–1.52)	0.40E-02		
	Simple mode		1.07	1.07(0.76–1.51)	6.90E-01		
AD	IVW	50	1.24	1.24(0.99–1.56)	6.00E-02	0.75	0.42
	MR Egger		1.19	1.19(0.83–1.70)	3.60E-01		
	Weighted mode		1.52	1.52(1.04–2.23)	4.00E-02		
	Weighted median		1.51	1.51(1.05–2.16)	3.00E-02		
	Simple mode		1.24	1.24(0.57–2.70)	5.90E-01		

AAA abdominal aortic aneurysm, *TAA* thoracic aortic aneurysm, *AD* aortic dissection, *OR* odds ratio, *Ple* pleiotropy, *Het* heterogeneity

peripheral vascular events in individuals with asymptomatic AAA [32]. Although dyslipidemia is found in AD patients and is correlated with increased mortality [33, 34], an MR study illustrated that genetically influenced serum lipid levels did not contribute to the risk of AD [35]. Furthermore, Allara et al. reported no significant associations between LDL-C, HDL-C, or TG levels and TAA risk [36].

RC represents the cholesterol found in TG-rich lipoproteins and serves as a precursor to the formation of atherogenic small dense LDL-C, which is known for its potent atherogenic effects [37, 38]. As a novel lipid marker, RC has shown a stronger association with cardiovascular disease compared to conventional lipid parameters [8, 9, 39]. In addition, multiple MR studies have established a genetically driven causal relationship between RC and atherosclerotic cardiovascular conditions [7, 40]. Collectively, these findings suggest that RC may function as an independent predictor of AAD. However, the number of studies addressing the connection between RC and AAD remains minimal. This research used a large-scale prospective cohort and MR analysis to examine the connection between RC and AAD for the first time. The results demonstrated a robust causal association between RC and AAA, supporting the notion that RC may serve as a novel predictor for AAA.

LDL-C, a well-established lipid marker, has long been recognized as a significant risk factor for cardiovascular diseases. Nevertheless, recent studies have indicated that residual cardiovascular risk persists even after LDL-C reduction treatments [41–43], with RC playing a key role in this risk [9]. To investigate whether RC could independently predict the occurrence of AAA, multivariable Cox regression analysis and mediation analysis were performed as part of this study. Both approaches revealed that RC was independently associated with an increased risk of AAA, indicating that RC can predict AAA development regardless of LDL-C level.

Although the exact mechanism underlying the strong correlation between RC and AAA remains unclear, it may involve inflammation and atherosclerosis. RC particles are capable of traversing arterial walls and being absorbed by smooth muscle cells and macrophages. Since human cells can typically breakdown TGs but not cholesterol, the accumulation of RC in the arterial wall may contribute to atherosclerosis, similar to LDL-C [44]. Despite carrying approximately 40 times more cholesterol than LDL-C particles, RC particles exhibit comparable atherogenic potential [45]. Thus, unsurprisingly, RC content has been linked to cardiovascular diseases in both observational and genetic studies [44, 46, 47]. Additionally, prior research has highlighted shared pathogenic mechanisms between atherosclerosis and AAA, with atherosclerosis being a well-established risk factor for AAA [3, 48]. This study provides new evidence for the causal relationship between RC and AAA susceptibility. In general, RC was strongly correlated with atherosclerosis risk, laying a theoretical foundation for its potential role in

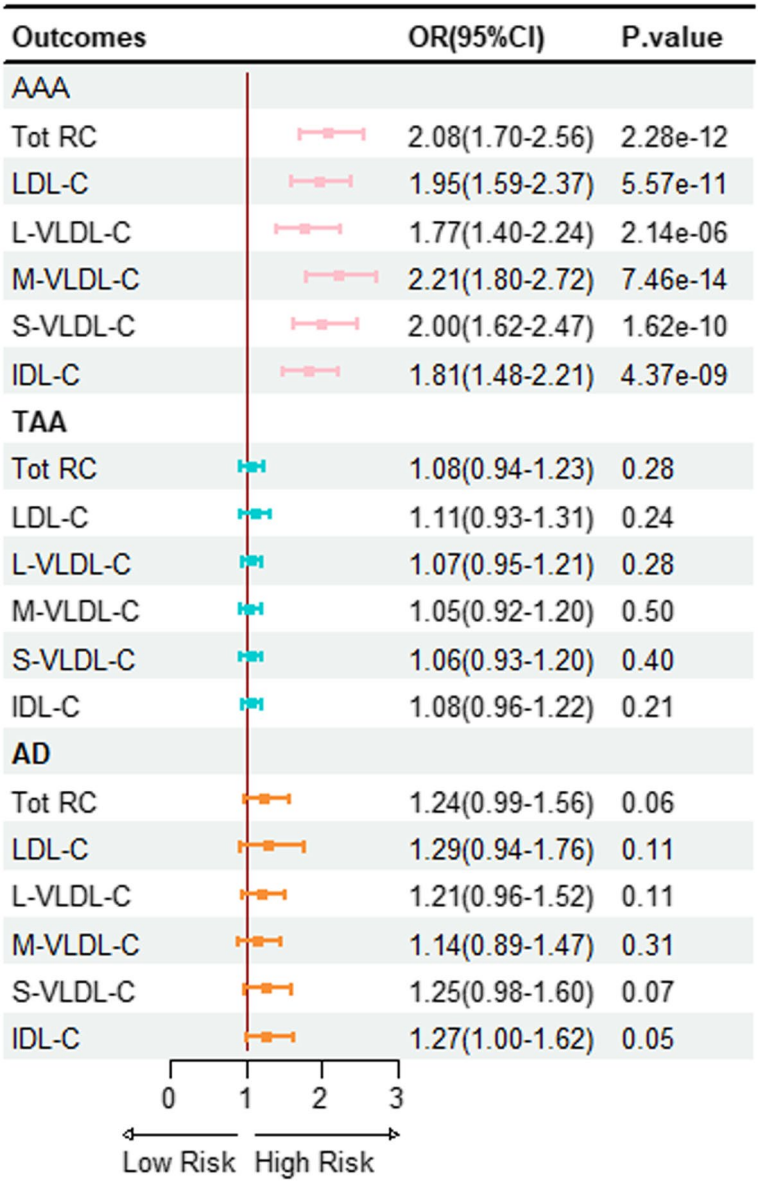

Fig. 4 Mendelian randomization results of the effects of remnant cholesterol (RC) and its most represented subfractions, as well as low-density lipoprotein cholesterol (LDL-C), on the risk of abdominal aortic aneurysm (AAA), thoracic aortic aneurysm (TAA), and aortic dissection (AD). VLDL, very low-density lipoprotein; IDL-C, intermediate-density lipoprotein cholesterol; L-VLDL-C, large VLDL cholesterol; M-VLDL-C, medium VLDL cholesterol; S-VLDL-C, small VLDL cholesterol; Tot RC, total remnant cholesterol; and. AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm; AD, aortic dissection; OR, odds ratio

AAA progression. Furthermore, recent studies indicate that heightened RC levels may exacerbate inflammatory processes in arterial tissues [49, 50], with chronic inflammation being a key factor in the pathogenesis of AAA [51]. Therefore, RC may facilitate the development of AAA.

This study found no significant correlation between RC levels and TAA or AD from either an epidemiological or genetic perspective. Although RC shows a statistically significant negative correlation with AD when treated as a continuous variable, this association disappears after stratifying by RC quintiles. This could be due to the relatively small number of AD cases, which may result in lower statistical power. Studies have shown that the most common risk factor for AAA is atherosclerosis, whereas the most common risk factors for TAA were connective tissue diseases and bicuspid aortic valves [52]. While TAA and AAA share several pathogenic similarities,

along with these notable distinctions, there are additional variations in predisposing gene mechanisms of inheritance and population prevalence. Thoracic aortic disease is caused by single-gene mutations, whereas AAA typically does not demonstrate this genetic pattern [53]. Pathogenic genes that lead to a high risk of thoracic aortic disease are identified in the genetic risk of TAA. Importantly, these genes generally do not increase the risk of AAA. This might explain the differing results between the TAA and AAA patients in this study. Although observational studies revealed a correlation between in-hospital mortality in AD patients and dyslipidemia [33, 34], an MR investigation showed that blood lipid levels inherited genetically did not influence the probability of AD development [35]. The findings of the MR analysis and the prospective cohort research in this investigation indicated that there did not seem to be a significant correlation between the prevalence of AD and RC.

Given the limited reporting on RC and AAD, further clinical trials and basic research are soon needed to investigate their relationships and underlying mechanisms.

Strengths and limitations

This research has numerous advantages. This study utilized a large cohort with an extended follow-up period and applied MR analysis to establish the genetic association between RC and AAA, effectively addressing the limitations of observational studies in accounting for confounding factors and reverse causation. Moreover, for the first time, this study thoroughly explored the relationship between RC and AAD risk, offering robust epidemiological evidence to predict the influence of RC on AAA development, with MR analysis providing further validation at the genetic level. Finally, various sensitivity analysis methods were employed in the MR study, including heterogeneity tests, pleiotropy tests, MR-PRESSO, and the removal of confounding SNPs using FUMAGWAS, among other approaches, ensuring the stability and reliability of the findings.

However, this work is not without its limitations. In the UK Biobank data, the definition of AAD relies solely on ICD-10 diagnostic codes, leading to a limited number of cases, and future studies should consider broader definitions of outcomes, such as including patients undergoing endovascular aneurysm repair procedures, to increase case numbers and improve the reliability of research findings. The definition of medication use among participants is also restricted to only two specific codes, which likely underestimates baseline medication use rates; while adjustment for antihypertensive drug use did not alter the conclusions, the potential roles of lipid-lowering and antidiabetic drugs remain unaddressed, necessitating further investigations into the effects of these three common drug classes on RC-induced AAA. Additionally, the populations included in both the UK Biobank clinical data and MR summary data are predominantly of European ancestry, which may limit the generalizability of the findings to other populations. Moreover, due to the potential genetic correlations between exposures, it is difficult to identify SNPs that are independently associated with RC and not confounded by other lipid markers. Although this study used summary-level data, future research could utilize individual-level data to reconstruct genetic risk scores for specific SNPs, potentially providing more comprehensive insights. Considering the strong correlations between RC and lipid markers such as LDL-C, HDL-C, TC, and TG, along with the potential multicollinearity among the components of the lipid profile, this study did not include additional lipid parameters in the MVMR analysis. Although only LDL-C was included as a mediator, the statistical power of the analysis may still be limited.

Conclusions

Prospective cohort research and MR analysis revealed an independent causal relationship between RC levels and the risk of AAA, whereas there was no association between RC levels and TAA or AD. These findings, along with additional evidence in the field, suggest that RC should be viewed as an independent marker of AAA risk and that early detection of RC may prevent the development of AAA.

Abbreviations

RC	Remnant cholesterol
AAD	Aortic aneurysm and dissection
MR	Mendelian randomization
AD	Aortic dissection
AAA	Abdominal aortic aneurysm
TAA	Thoracic aortic aneurysm
LDL-C	Low-density lipoprotein cholesterol
VLDL	Very low-density lipoprotein
IDL-C	Intermediate-density lipoprotein cholesterol
L-VLDL-C	Large VLDL cholesterol
M-VLDL-C	Medium VLDL cholesterol
S-VLDL-C	Small VLDL cholesterol
Tot RC	Total remnant cholesterol
IVW	Inverse-variance weighted
HDL-C	High-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglyceride
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary atherosclerosis
CHD	Coronary heart disease
PVD	Peripheral vascular disease
GWAS	Genome-wide association study
SNPs	Single-nucleotide polymorphisms
ORs	Odds ratios
HR	Hazard ratio
IVs	Instrumental variables
MVMR	Multivariable Mendelian randomization

BMI Body mass index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02466-0.

Supplementary Material 1: Table S1. UK Biobank Codes and the details of covariates. Table S2. RC quintile (mmol/L). Table S3. Baseline characteristics of the AAD population.. Table S4. The variance inflation factors (VIFs) of RC and each covariate. Table S5. SNPs associated with exposures. Table S6. F statistics for remnant cholesterol (RC) as an instrumental variable (IV). Table S7. Mendelian randomization study cohorts. Table S8. MR-PRESSO analysis for the associations between exposures and outcomes. Figure S1. Flowchart for selection of the analyzed study sample from the UK Biobank study. Figure S2. Associations between residual cholesterol (RC) continuous variables and the risk of aortic aneurysm and dissection (AAD). Figure S3. Cox regression modeling between remnant cholesterol (RC) and AAD after adjusting for antihypertensive drugs. The model was adjusted for age, sex, ethnicity, BMI, smoking status, drinking, education, activity, LDL-C, diabetes, hypertension, stroke, healthy diet, CAD, CHD, PVD and antihypertensive drugs. Figure S4. Cox regression modeling between residual cholesterol (RC) continuous variables and AAD after adjusting for antihypertensive drugs. The model was adjusted for age, sex, ethnicity, BMI, smoking status, drinking, education, activity, LDL-C, diabetes, hypertension, stroke, healthy diet, CAD, CHD, PVD and antihypertensive drugs. Figure S5. Mendelian randomization leave—one—out sensitivity analysis for the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S6. Funnel plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S7. Scatter plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S8. Forest plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S9. Multivariate Mendelian analysis disentangled the multivariate effects of remnant cholesterol (RC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) on the risk of abdominal aortic aneurysm (AAA)Figure S5. Mendelian randomization leave—one—out sensitivity analysis for the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S6. Funnel plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S7. Scatter plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S8. Forest plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S9. Multivariate Mendelian analysis disentangled the multivariate effects of remnant cholesterol (RC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) on the risk of abdominal aortic aneurysm (AAA)Figure S5. Mendelian randomization leave—one—out sensitivity analysis for the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S6. Funnel plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S7. Scatter plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S8. Forest plot of the effect of remnant cholesterol (RC) on the risk of abdominal aortic aneurysm (AAA). Figure S9. Mediation analysis.

Supplementary Material 2: Table S9. Gwascatalog of RC related SNPs. Table S10. IndSigSNPs of RC related SNPs. Table S11. NearestGene of RC related SNPs. Table S12. Non-confounder-SNPs used in two-sample MR. Table S13. RC metabolism-related gene SNPs used in two-sample MR. Table S14. Two-sample MR results after excluding confounding SNPs. Table S15. Two-sample MR results after excluding FADS-related SNPs. Table S16. Two-sample MR results for RC metabolism-related gene SNPs. Table S17. Two-sample MR results after excluding the SNP with the largest effect on RC. Table S18. Steiger filtering results.

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Authors' contributions
ZT, LWH, and YBY contributed to the conceptualization and design of the study. LY, and HWH gathered and examined the information. LSY engaged in UKB data analysis and statistical work. HZY, XNJ, LZH and YF carried out the MR statistical work. The writing of the manuscript included ZT, LWH, and YBY. During the critical review of the article, LJF, LZH and LSY made substantial contributions to the core ideas. After carefully reading the paper, all the writers agreed on the final draft.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Northwest Multicenter Research Ethics Committee (11/NW/0382) granted ethical clearance to the UK Biobank, and informed permission was given by each participant. The current studies were carried out using application number 93913 from the UK Biobank. Publicly accessible genome-wide association study (GWAS) data were utilized to generate the genetic data. There was no requirement for fresh ethical clearance, and no new data were gathered.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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