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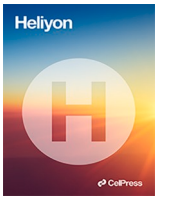

Research article

A potentially underestimated predictor of coronary artery disease risk: The ApoB/ApoA1 ratio

Bo Li [a,c,***,1], Xu Zhao [b,1], Yan Ding [c,**], Yi Zhang [a,*]

[a] Department of Endocrinology, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou, 362000, Fujian, China
[b] Emergency and Critical Care Center, Renmin Hospital, Hubei University of Medicine, No. 37 Chaoyang Middle Road, Shiyan, 442000, Hubei, China
[c] Hubei Key Laboratory of Embryonic Stem Cell Research, Biomedical Research Institute, Hubei University of Medicine, Shiyan, 442000, Hubei, China

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death worldwide, and statin therapy is the cornerstone of atherosclerotic cardiovascular disease. However, clinical practice is unsatisfactory, and there is significant interest in the risk of residual cardiovascular events. Traditional study methods make it difficult to exclude the crosstalk of confounding factors, and we investigated the impact of the ApoB/ApoA1 ratio on CVD using two-sample Mendelian randomization (MR) and multivariate Mendelian randomization (MVMR) methods.

Methods: Two-sample MR and MVMR analyses were performed using pooled statistics from genome-wide association studies (GWAS) of ApoB/ApoA1 ratio (BAR), lipoprotein (a) (Lp(a)), and triglyceride (TG) in Europeans to assess the causal relationship between BAR, Lp(a), and TG with coronary artery disease (CAD).

Results: The genetic prediction of BAR was significantly correlated with CAD (Inverse variance weighted (IVW) beta = 0.255; OR = 1.291; 95 % CI = 1.061–1.571; P = 0.011) in a two-sample MR analysis. MVMR studies showed that BAR (beta = 0.373; OR = 1.452; 95 % CI = 1.305–1.615; P = 7.217e-12), Lp (a) (beta = 0.238; OR = 1.269; 95 % CI = 1.216–1.323; P = 2.990e–28), and TG (beta = 0.155; OR = 1.168; 95 % CI = 1.074–1.270; P = 2.829e-04) were significantly associated with CAD. After further colinearity analyses of LASSO regressions, the results of multivariate analyses were similar for IVW, MR-Egger, MR-Lasso, and median methods.

Conclusion: BAR is causally related to coronary artery disease. BAR is an independent predictor of CAD risk, independent of routine lipid measurements and other risk factors. TG and Lp(a) may be causally related to CAD, subject to verification in clinical practice.

* Corresponding author.
** Corresponding author.
*** Corresponding author. Department of Endocrinology, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou, 362000, Fujian, China.
E-mail addresses: libo0305062022@163.com (B. Li), dyywzx@163.com (Y. Ding), zhayisn@163.com (Y. Zhang).
[1] These authors have contributed equally to this work.

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1. Introduction

CAD is the leading cause of death worldwide, with a heavy economic and social burden [1]. Low-density lipoprotein cholesterol (LDL-C) is associated with reduced cardiovascular events and mortality, and statin therapy status is unassailable [2]. The incidence of recurrent cardiovascular events remains high despite the promotion and iteration of hemodynamic reconstitution and the optimization of pharmacological treatment strategies [3]. The causal relationship between TG and CAD remains controversial [4]. Evidence suggests that high triglyceride lipids worsen CVD prognosis [5] and are associated with established CAD risk factors such as obesity, insulin resistance [6], LDL, and apolipoprotein B (ApoB) concentrations [7], but they do not appear to directly promote the atherosclerotic process [8]. The recent Phenome-wide MR study showed a causal relationship between plasma TG levels and CAD risk, consistent with previous findings [9].

High levels of Lp(a) are associated with an increased risk of CAD and atherosclerosis [10], and Lp(a) and LDL-C share a similar structure, but metabolic regulation appears to be relatively independent and functionally distinct [11]. Oxidized phospholipid Lp(a) acts as a preferred proinflammatory and proatherogenic lipoprotein carrier [12]. Studies have shown that Lp(a) as a risk factor for CAD is more pronounced in patients with high-density lipoprotein cholesterol (HDL-C) $\geq$35 mg/dL and non-obese patients [11]. Lp(a) and oxidized phospholipids apoB (OxPL-apoB) are associated with multiple coronary artery lesions, and Lp(a), OxPL-apoB, and OxPL-apo (a) are associated with cardiovascular events [13].

Previous studies have suggested that BAR is associated with CAD risk in patients with chronic kidney disease (CKD), but this association was not found in non-CKD patients [14]. However, earlier studies have shown that intracellular cholesterol levels are 2–5 times higher in serum cultures of human aortic intima subendothelial cells from CAD patients and that atherosclerotic potential was directly associated with BAR but not with total cholesterol, HDL-C, apoB, or apoA1 levels [15]. Holmes et al. showed that BAR treatment levels were the strongest predictor of coronary events [16]. INTERSTROKE showed that BAR was the best lipid predictor of ischemic stroke risk [17]. Based on existing studies, we attempted to elucidate the causal relationship between BAR and CAD using an MR method while analyzing the causal relationship between TG, Lp(a), and CAD.

2. Methods

2.1. Study design

We used a two-sample MR study designed to assess whether BAR is causally related to CAD. In this design, three hypotheses should be included [1]: instrumental variables (IV) of genetic variation are highly correlated with exposure (BAR) [2]; the IV used is not correlated with potential confounders [3]; IV is associated with the outcome only through selected exposures (BAR) and not through other pathways. IVW was used as the primary analysis method; weighted median (WM), simple mode, weighted mode, and MR-Egger regression were used as complementary analysis methods; MR-Egger and IVW were used for the heterogeneity test; MR-Pleiotropy Residual Sum and Outlier Method (MR-PRESSO) was used to eliminate outliers; MR-Egeer interpret was used for the pleiotropy test; and SNPs associated with confounders were further excluded using the PhenoScanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/). The robustness of the results was assessed using the Leaveoneout method, which examines whether there are SNPs that significantly affect the outcome. This MR study was based on published studies and public GWAS databases, and additional ethical approval or informed consent to participate was waived [18].

In addition, we used multiple MVMRs to analyze the causal relationship between Lp(a), TG, BAR, and CAD that may be associated with residual cardiovascular risk and to initially explore the causal relationship between multiple exposure factors and CAD. The TwoSampleMR package was used for MVMR analysis, the MV-LASSO method to exclude highly colinear exposure factors, the MR-LASSO method to further validate the MVMR results, and then the MendelianRandomization package was used to perform the multivariable inverse-variance weighted method, the multivariable MR-Egger method, the multivariable MR-Lasso method, and the multivariable median method to analyze the results.

2.2. Data sources

Summary-level genetic data for BAR were extracted from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk), including 12,321,875 single nucleotide polymorphisms (SNPs) from 115,078 European populations. Genetic data for TG included 12,321,875 SNPs from 441,016 European populations. GWAS data for Lp(a) contained 13,583,854 SNPs, and GWAS summary data for CAD included 8,597,751 SNPs in 141,217 European individuals from 42,096 CAD cases, all of which are available in the IEU OpenGWAS

Table 1
Summary of the GWAS included in this study.

Variables	ID	Population	Sample size	Number of SNPs	Sex	Year
Coronary artery disease	ebi-a-GCST003116	European	141,217	8,597,751	NA	2015
BAR	met-*d*-ApoB_by_ApoA1	European	115,078	12,321,875	Males and Females	2020
TG	ieu-b-111	European	441,016	12,321,875	Males and Females	2020
Lp(a)	ukb-*d*-30790_irnt	European	NA	13,583,854	Males and Females	2018

Abbreviations: BAR, Ratio of apolipoprotein B to apolipoprotein A1; TG, triglycerides; Lp(a), Lipoprotein A.

database (https://gwas. mercies.ac.uk/). Detailed information is provided in Table 1. Genetic instrumental variables and outcome data were extracted online from the IEU platform via the extract_instruments and extract_outcome_data functions of the TwoSampleMR package, respectively.

2.3. Select the instrumental variables

SNPs significantly associated with the BAR exposure factor were selected based on a genome-wide significance threshold of $P < 5 \times 10^{-8}$. The clump parameters were set to $r^2 > 0.001$ and the clump window <10000 kb to remove IVs with linkage disequilibrium (LD) and retain the SNP with the lowest P value associated with BAR. The F statistic was calculated to ensure a strong relationship with exposure, and $F \geq 10$ indicated a strong correlation between the selected IVs and BAR. Based on the above criteria, 73 BAR-associated SNPs were extracted from the GWAS dataset. A total of 69 BAR-associated IVs were obtained after combining exposure and outcome data by coordinating effects. Four outlier SNPs were excluded using MR-PRESSO. Given that hypertension, diabetes, hyperlipidemia, statin use, BMI, WHR, and obesity are established risk factors or relevant for CAD, we looked at each SNP in the online Phenoscanner [19] to identify SNPs associated with the above confounders. Using the default p-value threshold $p < 1 \times 10^{-5}$ and LD proxy search ($r^2 = 0.8$) [20], if the phenotype is associated with one of the SNPs or nearby variants, the phenotype may have a potential pleiotropic effect in MR analysis. In addition, SNPs associated with CAD-related routine lipid measurements (HDL, LDL, and TG) were also removed, while SNPs associated with apoA and apoB characteristics were not detected. Exclude SNPs from MR analysis and observe if there are differences in MR analysis results before and after rejection.

MVMR used the same criteria to screen for SNPs significantly associated with exposure factors (Lp(a), TG, and BAR). We extracted SNPs significantly associated with TG, Lp(a), and BAR ($p < 5 \times 10^{-8}$) in online European populations using the TwoSampleMR package and used the same criteria to remove LD (R2 = 0.001, clumping distance = 10,000 kb), SNPs with incompatible alleles, and mid-frequency palindromic SNPs. We extracted CAD data from online European populations using the extract_outcome_data function and coordinated exposure and outcome data through the mv_harmonise_data function. Finally, we performed MVMR analysis using multiple multivariate R packages.

2.4. Statistical analyses

IVW was used as the key MR analysis method to estimate the causal effect of BAR on CAD [21]. We also conducted four different methods (WM, simple mode, weighted mode, and MR-Egger regression) as sensitivity analyses. WM was used to provide consistent causal estimates, assuming that more than 50 % of the weights were from valid instrumental variables [22]. The MR-Egger regression method was used for the horizontal pleiotropy assessment, with a P value < 0.05 for the MR-Egger intercept indicating directional multiplicity [23]. In addition, MR-Egger and IVW were used for heterogeneity testing, MR-PRESSO was used to identify horizontal multiplicity outliers, and new estimates were generated after removing multiplicity outliers [24].

Finally, we performed a leave-one-out analysis to assess the impact of the remaining SNPs on the results after omitting each SNP. This method will identify SNPs that may have a significant impact on results by phasing out each SNP, calculating the meta-effect of the remaining SNPs, and observing whether the results change after each SNP is excluded. After each SNP is excluded, the overall error bars do not change much (all error bars are 0 to the right or all error bars are 0 to the left), indicating that the results are reliable. Cochran's Q statistic was used to assess SNPs heterogeneity. All statistical analyses were performed by the TwoSampleMR and MRPRESSO packages in R software (version 4.2.2). MVMR was performed by the TwoSampleMR package, the MRPRESSO package, and the Mendelian randomization package of R.

Table 2
Details of the 17 eligible SNPs in the two-sample randomization analysis and the F-statistic values.

SNP	EAF	*P*-value	beta	SE	R^2	F
rs10145740	0.244938	1.55E-08	−0.0268609	0.00474915	0.000266876	15
rs112001035	0.059725	2.62E-11	0.0583006	0.00874529	0.000381757	22
rs142791556	0.030647	1.09E-08	−0.0676508	0.0118352	0.000271923	16
rs164641	0.049028	9.80E-09	−0.0543787	0.00948321	0.00027574	16
rs17001244	0.174486	2.29E-11	0.0357842	0.00535206	0.000368891	21
rs190651665	0.033075	2.00E-11	−0.0760558	0.0113418	0.000369988	21
rs198325	0.22016	7.01E-09	−0.0283911	0.00490293	0.000276782	16
rs2104616	0.540082	9.34E-12	−0.0277919	0.00407725	0.000383713	22
rs241777	0.485229	1.76E-09	−0.0245588	0.00408083	0.000301304	17
rs2517671	0.41912	2.21E-10	0.02607	0.00410832	0.000330931	19
rs59347135	0.045804	2.60E-11	0.0667113	0.0100051	0.000389018	22
rs59781045	0.068064	1.08E-12	−0.0576708	0.00810003	0.000421935	24
rs61805076	0.334061	3.80E-10	0.0269586	0.00430499	0.000323359	18
rs643884	0.157991	8.68E-11	0.0362817	0.00559187	0.000350231	20
rs72631343	0.129021	3.65E-11	−0.0401553	0.00606785	0.000362396	21
rs72823020	0.130419	1.64E-08	−0.0342425	0.00606482	0.000265957	15
rs77960347	0.013239	2.72E-14	−0.135212	0.0177656	0.00047767	28

Abbreviations: SNP, Single Nucleotide Polymorphisms; EAF, effect allele frequency; SE, standarderror; F: F-statistics.

3. Results

3.1. Screening results for valid SNPs

A total of 12,321,875 BAR-associated SNPs were obtained from the GWAS database. 75 BAR-associated SNPs were extracted based on filtering conditions (Table S1), and 2 SNPs were excluded based on LD. 8597751 CDA-associated SNPs were obtained from the GWAS database. 69 SNPs were obtained after coordinating and combining exposure and outcome data, and the MR-PRESSO package excluded four outliers, leaving 65 SNPs. Online Phenoscanner was searched for each SNP, and a total of 47 SNPs associated with CAD confounders and those directly associated with CAD were excluded. The palindrome SNP "rs1110088" with moderate allele frequency was removed from the dataset. Finally, 17 SNPs (Table 2) were included as valid IVs for the final MR analysis, and all SNPs had an F-statistic >10, indicating a strong correlation with BAR.

4. Results of the two-sample MR analysis

We used the TwoSampleMR package (version 0.5.6) to coordinate and merge BAR data (GWAS ID:met-*d*-ApoB_by_ApoA1) and CAD data (GWAS ID:ebi-a-GCST003116). Four outliers were observed for MR-PRESSO ($p < 0.05$), and excluding four outliers (rs12740374, rs443401, rs821840, rs9295128) was necessary to obtain the two-sample MR results (Fig. S1: A-D). The main MR method (IVW) showed that BAR was significantly correlated with CAD (OR = 1.727; 95 % CI = 1.577–1.891; $p = 3.67e-32$); other complementary MR methods, including WM, MR-Egger regression, simple mode, and weighted mode, also confirmed similar results (Fig. S1E).

The online Phenoscanner excluded SNPs associated with CAD confounders and SNPs directly associated with CAD, and the remaining 17 SNPs were included in the final two-sample MR analysis, and BAR was still significantly associated with CAD (OR = 1.291, 95 % CI = 1.061–1.571, $p = 0.011$; MR-PRESSO Global Test p-value = 0.2159). As shown in Figs. 1 and 2, and S2.

Cochran's tests (MR-Egger $p = 0.245$; IVW = 0.293) and MR-Egger intercept tests (Egger-intercept = 0.004, $p = 0.697$) found no evidence of heterogeneity or directional pleiotropy (Fig. 3). We also performed a leave-one-out analysis and did not find that IVW estimates were substantially affected after the exclusion of an SNP (Fig. 4).

5. Results of MVMR analysis

We performed MVMR analysis using the TwoSampleMR package and found that TG (OR = 1.168, 95 % CI = 1.074–0.270, $p =$ 2.83E-04), BAR (OR = 1.452, 95 % CI = 1.305–1.615, $p = 7.22E-12$), and Lp(a) (OR = 1.269, 95 % CI = 1.216–1.323, $p = 2.99E-28$)

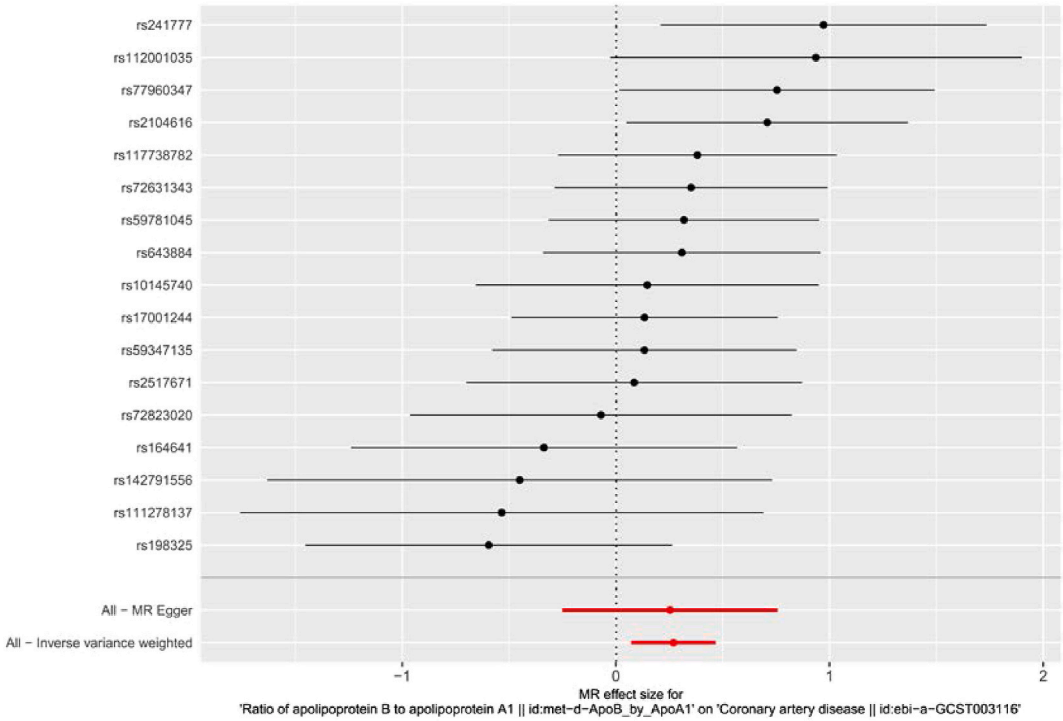

Fig. 1. Forest plot of causal effects of ApoB/ApoA1 ratio associated single nucleotide polymorphisms on coronary artery disease. The red dots represent the joint causal estimation used in a single tool using all SNPs, using two different methods (inverse variance weighted [IVW] random effects and MR-Egger).

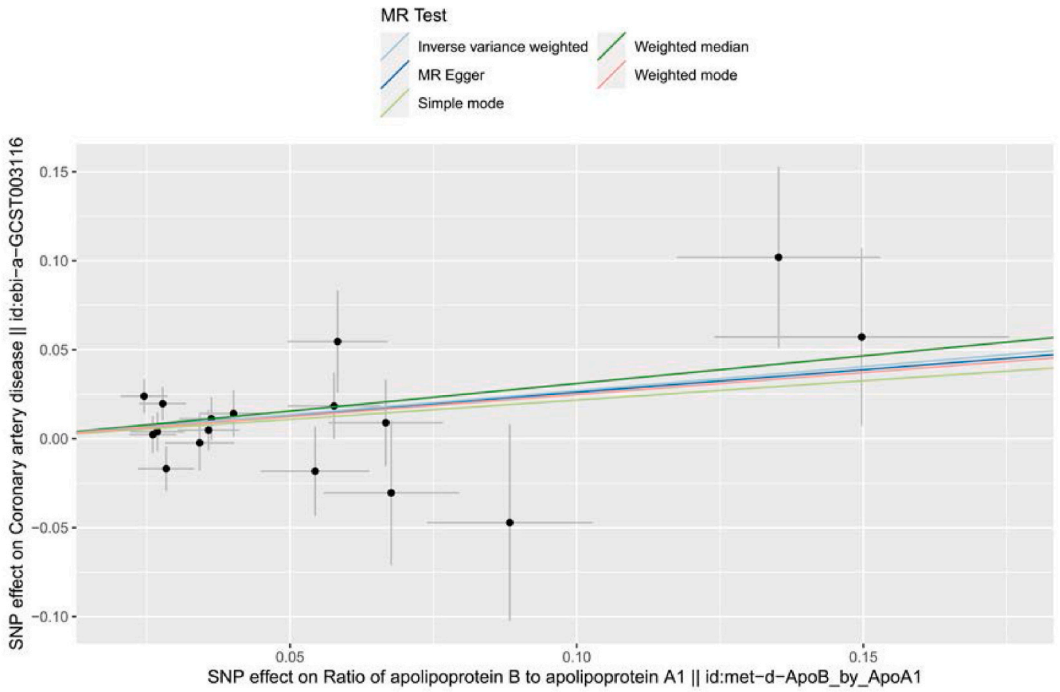

Fig. 2. Scatter plot of genetic association of ApoB/ApoA1 ratio with coronary heart disease. The slope of each line represents the causal association for each method.

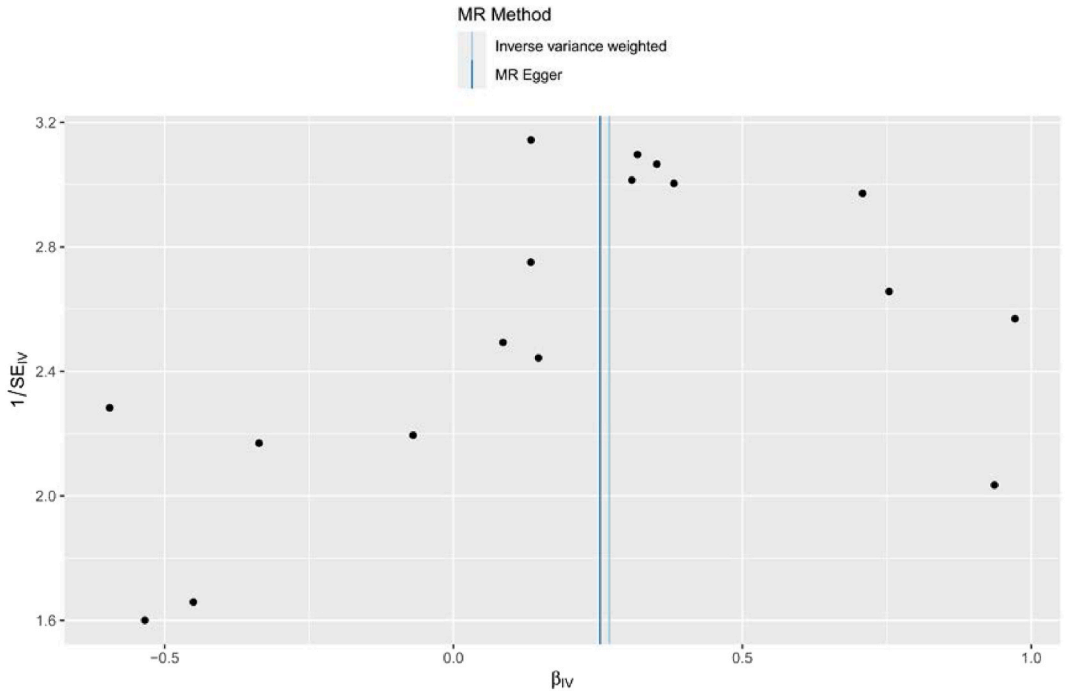

Fig. 3. Funnel plot assessing heterogeneity. The blue line represents the IVW estimate, and the dark blue line represents the Egger Mendelian randomization estimate.

were significantly associated with CAD. No collinear exposure factors were found in the MV-LASSO analysis, and the results were consistent with MVMR. MVMR sensitivity validation using MR-PRESSO and Mendelian randomization package yielded similar results (Table 3). Interestingly, the Mendelian randomization package analyzed showed heterogeneity (MR Egeer: heterogeneity test statistic

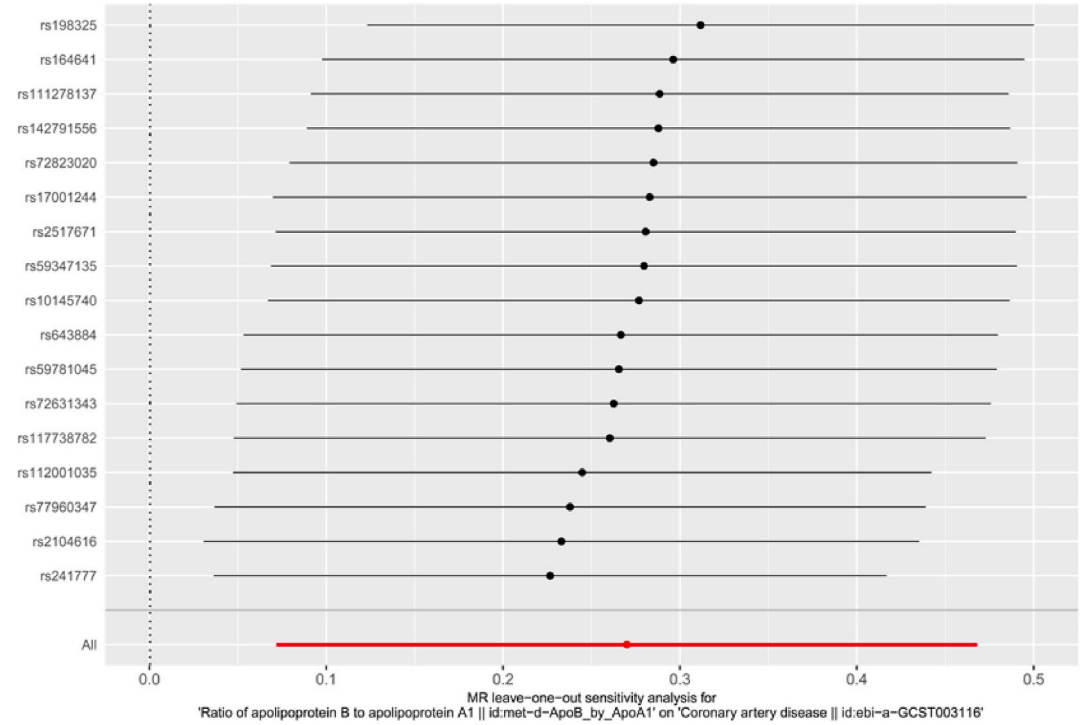

Fig. 4. Sensitivity analysis to investigate the possibility that causal association was driven by a unique single nucleotide polymorphism in coronary heart disease. Each black dot represents the IVW MR method used to estimate the causal effect of BAR on CAD after excluding this particular variant from the analysis. The red dots represent IVW estimates using all SNPs.

Table 3
The causal relationships between TG, BAR, Lp (a), and CAD were analyzed using four different MVMR methods.

MendelianRandomization	Phenotype	METHODS	Estimate	95 % CI	*P*-value
	TG	IVW	0.155	0.071–0.239	2.83E-04
		MR-Egger	0.057	0.052–0.165	3.04E-01
		MR-Lasso	0.163	0.090–0.236	1.28E-05
		MV-median	0.162	0.048–0.275	5.25E-03
	BAR	IVW	0.373	0.054–0.266	7.22E-12
		MR-Egger	0.354	0.248–0.460	6.50E-11
		MR-Lasso	0.366	0.261–0.472	1.06E-11
		MV-median	0.397	0.239–0.554	7.55E-07
	Lp(a)	IVW	0.238	0.196–0.280	2.99E-28
		MR-Egger	0.239	0.197–0.280	5.04E-29
		MR-Lasso	0.23	0.200–0.260	3.41E-51
		MV-median	0.234	0.199–0.268	1.72E-39
TwoSampleMR	Phenotype	nSNP	OR	95%CI	P
	TG	283	1.168	1.074–1.270	2.83E-04
	BAR	283	1.452	1.305–1.615	7.22E-12
	Lp(a)	283	1.269	1.216–1.323	2.99E-28
MV-LASSO	Phenotype	nSNP	OR	95%CI	P
	TG	283	1.168	1.074–1.270	2.83E-04
	BAR	283	1.452	1.305–1.615	7.22E-12
	Lp(a)	283	1.269	1.216–1.323	2.99E-28
MR-PRESSO	Phenotype	Estimate	Sd	T-stat	P
	TG	0.155	0.043	3.63	3.36E-04
	BAR	0.373	0.054	6.853	4.59E-11
	Lp(a)	0.238	0.022	11.022	1.05E-23

*TG, triglycerides; BAR, ratio of apolipoprotein B to apolipoprotein A1; Lp(a), lipoprotein a.

= 563.33, degrees of freedom = 279, *p*-value <0.001; Ivw: heterogeneity test statistic = 578.63, degrees of freedom = 280, *p*-value <0.001) and horizontal pleiotropy (MR-Egger intercept = 0.004, *p*-value = 0.006).

6. Discussion

The causal effect of BAR and CAD is still controversial, and the causal relationship between TG and CAD has been controversial for more than 10 years and remains unresolved. TG tends to be involved in the risk of CAD events under certain conditions, but not directly in the pathogenesis of atherosclerosis. Lp(a) has been a hot topic of major guideline recommendations in recent years, suggesting that it may be significantly associated with residual cardiovascular events in CAD. Our findings suggest a significant causal relationship between BAR and CAD, and sensitivity analysis confirms very robust results. MVMR analysis showed a causal relationship between TG, Lp(a), and CAD as well, but MR-Egger analysis had horizontal pleiotropy.

Dyslipidemia is a major cause of cardiovascular and cerebrovascular atherosclerosis. The INTERSTROKE analysis of the association between lipoproteins and apolipoproteins in stroke subtypes showed [17] that elevated ApoB was significantly associated with large vessels and stroke of uncertain etiology; HDL-C and apoA1 were negatively associated with ischaemic stroke; but BAR was more strongly associated with ischaemic stroke (OR = 1.26, 95 % CI 1.21–1.31/SD) and was considered to be the best lipid predictor of ischaemic stroke. ApoB and apoA-1 both have the potential to penetrate the arterial wall, and a dynamic balance of lipid transport processes underpins the maintenance of arterial structure and function; an imbalance in BAR may contribute to atherogenesis and increase the risk of clinical events [25,26]. The Swedish AMORIS cohort study showed [27] that apoB levels and BAR were positively associated with major cardiovascular events and subgroup risk and were independent of sex and age; BAR covered a broader population at risk of dyslipidemia than apoB; and an imbalance between apoB and apoA1 resulting in increased BAR was an earlier predictor of MACE and was associated with subgroups of cardiovascular event outcomes. The ARIC study [14] showed that BAR was associated with CAD risk in patients with CKD (HR = 1.22, 95 % CI = 1.01–1.46), and no significant difference was found in patients without CKD, suggesting that BAR may be associated with renal function and that there was no significant association with CAD risk in non-CKD patients. A study on lipid metabolism in early and late-stage diabetes-related CKD showed [28] that ApoA1 and HDL-C concentrations were reduced and BAR (adj $p = 0.04$) and LDL-TG concentrations were increased in late-stage CKD compared to early CKD (adj $p = 0.01$), and that altered lipid metabolic profiles may be associated with increased cardiovascular risk in late-stage CKD. The analysis of the IDEAL trial [16] on cardiovascular events in patients with CAD during statin therapy showed that BAR was the strongest predictor of major coronary events in patients during statin therapy, suggesting that BAR is a major predictor of the risk of residual cardiovascular events with statin therapy. In our study, after excluding SNPs associated with confounding and outcomes strictly according to the screening criteria of the MR design, BAR still showed a significant causal relationship with CAD, and no heterogeneity or horizontal pleiotropy was detected, with good statistical efficacy.

Conventional lipid profile measurements include plasma levels of total cholesterol (TC), LDL-C, HDL-C, and TG to predict CVD risk [29], but apolipoprotein (apo) and ratio measurements may be associated with CAD and broader CVD independently of conventional lipids and may be significantly associated with the risk of residual cardiovascular events beyond LDL-C [30]. In individuals at high residual cardiovascular risk, the incidence of recurrent cardiovascular events remains high even when LDL-C levels are significantly reduced, prompting more attention to lipid markers other than LDL-C [31,32]. Clarke et al. [33] showed that apolipoprotein subtypes correlate with CAD independently of conventional risk factors and lipids, may reflect lipoprotein particle concentration and composition, and provide additional information that can help guide individualized therapeutic approaches. Epidemiological data suggest that increasing circulating ApoC2 levels may reduce cardiovascular risk [34]. Lp(a) is a complex consisting of Apo(a) covalently bound to LDL [35]; Apo(a) contains a variable number of Kringle-IV type 2 repeats associated with variability in measured levels of Lp(a); high levels of Lp(a) are associated with CAD risk [36]; and previous MR analyses have shown a causal association between Lp (a) and CAD risk [37]. Burgess et al. [36] showed that the clinical benefit of each approximately 2.6 mmol/L reduction in Lp (a) may achieve a similar reduction in CAD risk as a 1 mmol/L reduction in LDL-C. Apolipoprotein profile assessment analysis [33] evaluated 13 of 4 lipoproteins, with plasma Lp(a) levels highly correlated with Apo(*a*)-KR peptide and Apo(*a*)-CR peptide and not with other apolipoproteins; ApoB was highly correlated with LDL-C levels, moderately correlated with ApoC2 and ApoC3, and weakly correlated with others; TG levels were positively correlated with ApoC2, ApoC3, and ApoE, and negatively correlated with HDL-C. Quantitative analysis of apolipoproteins and CAD risk showed [33] that CAD was slightly more correlated with ApoB compared to conventional LDL-C levels and remained higher with correction for conventional lipids (OR = 1.98, 95 % CI = 1.19–3.22); apolipoproteins carrying TG (ApoC1, ApoC3, ApoE) were strongly correlated with CAD independent of conventional lipid measurements; ApoA4 and ApoM levels were negatively correlated with CAD. Refined apolipoprotein typing may be more useful for identifying residual cardiovascular risk and may better explain variability in TG-CAD correlation studies and variability in Lp(a) tests, but it is still in the early stages of research with small sample sizes, pending the results of larger multicenter, multiracial RCT studies.

Our findings are in high agreement with recent studies, and we are reasonably confident that BAR is an independent predictor of CAD risk and can be used synergistically with LDL-C to assess cardiovascular risk stratification, with equal or greater value than LDL-C in individuals at high residual CVD risk and independently of other lipid and other cardiovascular risk factors.

MR studies are valuable for using existing large-scale GWAS data to reveal potential causal associations between modifiable factors and diseases, including rare diseases. However, RCT studies, which require long-term follow-up with large samples, may not be suitable for all situations. In addition, MR studies can investigate exposure factors that negatively affect disease risk, a type of research that may be unethical or impractical to conduct as an RCT. Moreover, RCTs are limited by research time and funding, often focusing on short-term effects, while MR studies can provide a broader and longer-term perspective on the impact of risk factors [38].

It should be noted that there were some limitations to our research. As the study was based on a European database, it is difficult to

apply the findings to the entire population. In addition, although sensitivity analyses were carried out, the potential for horizontal pleiotropy could not be completely eliminated. Finally, using a strict threshold to evaluate the causal relationship between BAR and CAD may reduce the number of false positives, but it may not be comprehensive enough. In addition, while MR studies can provide important clues about the possible causal effects of BAR on CAD risk, MR findings should be interpreted in conjunction with evidence from other sources, such as traditional observational and experimental studies, to ensure the reliability and accuracy of the findings.

7. Conclusion

Our study provides statistical clues for a causal association between BAR and CAD risk, suggesting that BAR may be an independent predictor of CAD risk, independent of conventional lipid measurements and other risk factors, and may be recommended as a key indicator of CAD risk stratification. Assessment of BAR during treatment may be an important risk factor for residual cardiovascular risk. However, the effect value obtained by MR is only the effect of this part of the exposure variant on the outcome determined by instrumental variables, while the effect of exposure variants on the outcome determined by other non-genetic factors cannot be obtained by MR models. The estimated effect of exposure on MR results cannot be fully equivalent to the true causal effect. MR analysis provides a theoretical basis for future more definitive experimental research and mechanism exploration. The true causal relationship should be discussed in conjunction with the biological mechanism of the disease, complete experimental and clinical research results, and other evidence. No single research method can fully clarify the causal relationship.

Data availability statement

The publicly available data sets were analyzed in this study. These data can be found at the following websites: https://gwas.mrcieu.ac.uk/.

Ethics approval and consent to participate

Primary studies from each country's genome-wide association studies (GWASs) have previously received ethical consent, and the current analysis is based on publicly available abstract-level data that does not require additional approval.

Consent for publication

All authors have given their approval for publication of this manuscript.

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CRediT authorship contribution statement

Bo Li: Writing – original draft, Software, Methodology, Conceptualization. **Xu Zhao:** Visualization, Resources, Investigation, Data curation. **Yan Ding:** Writing – review & editing, Validation, Supervision. **Yi Zhang:** Writing – review & editing, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32084.

Abbreviations

GWAS	genome-wide association study
MR	Mendelian randomization
MVMR	multi-variable Mendelian randomization

BAR	the ApoB/ApoA1 ratio
Lp(a)	lipoprotein (a)
TG	triglyceride
CAD	coronary artery disease
LDL-C	Low-density lipoprotein cholesterol
CKD	chronic kidney disease
IVW	Inverse variance weighted
MR-PRESSO	MR-Pleiotropy Residual Sum and Outlier Method
IV	instrumental variables
WM	weighted median
SNP	single nucleotide polymorphism
TC	total cholesterol
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol

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