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The potential protective effect of 3-Hydroxybutyrate against aortic dissection: a mendelian randomization analysis

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Abstract

Background 3-Hydroxybutyrate, also called β-hydroxybutyrate, is a significant constituent of ketone bodies. Previous observational and experimental studies have suggested that ketogenic diet, especially 3-hydroxybutyrate, may have a protective effect against cardiovascular disease. However, the relationship between ketone bodies, especially 3-hydroxybutyrate, and aortic dissection remains uncertain.

Materials and methods Publicly accessible data from genome-wide association study (GWAS) was utilized to obtain information on ketone bodies, including 3-hydroxybutyrate, acetoacetate and acetone as exposure respectively, while GWAS data on aortic dissection was used as outcome. Subsequently, two-sample Mendelian randomization (MR) analysis was conducted to examine the potential relationship between ketone bodies and aortic dissection. Then, reverse and multivariate Mendelian randomization analyses were performed. Additionally, sensitivity tests were conducted to assess the robustness of MR study.

Results The inverse-variance weighted (IVW) method of Mendelian randomization analysis of gene prediction observed a negative correlation between 3-hydroxybutyrate and risk of aortic dissection (OR 0.147, 95% CI 0.053–0.410). Furthermore, consistent findings were obtained through the implementation of the weighted median, simple mode, Mendelian randomization-Egger (MR-Egger), and weighted mode methods. After adjusting acetoacetate (OR 0.143, 95% CI 0.023-0.900) or acetone (OR 0.100, 95% CI 0.025–0.398), MR analysis of gene prediction still observed a negative correlation between 3-hydroxybutyrate and risk of aortic dissection. No indications of heterogeneity or pleiotropy among the SNPs were detected.

Conclusion The findings from the MR analysis demonstrated that genetically predicted 3-hydroxybutyrate exhibits a protective effect against aortic dissection.

Keywords 3-hydroxybutyrate, Aortic dissection, Genome-wide association study (GWAS), Ketone bodies, Mendelian randomization (MR)

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Introduction

Aortic dissection (AD) is a cardiovascular ailment characterized by significant morbidity and mortality. It represents a critical medical emergency wherein a disruption in the intimal layer of the aorta or hemorrhaging within the aortic wall leads to a dissection of said wall [1]. Over the past ten years, instances of aortic dissection have exhibited a substantial surge [2], and if left untreated, type A aortic dissection can result in a 30-day mortality rate as high as 90% [3]. Consequently, it is of paramount importance to identify the contributing factors associated with aortic dissection in order to facilitate early prevention measures. Aortic dissection is distinguished by its sudden onset and rapid progression, resulting in a significant mortality rate, which poses challenges in conducting clinical observational studies. Furthermore, such studies are vulnerable to the influence of reverse causality and confounding risk factors.

Ketogenic diet is a dietary pattern that has attracted wide attention in recent years. It stimulates the metabolic state of fasting through a dietary regimen that is high in fat, adequate in protein, and very low in carbohydrates, which leads to elevated levels of ketone bodies in the blood [4]. Ketone bodies mainly include 3-hydroxybutyrate, acetoacetate and acetone [5]. 3- Hydroxybutyrate, also known as β-hydroxybutyrate, constitutes a significant constituent of ketone bodies [6]. Emerging evidence indicates that a ketogenic diet can raise the levels of 3-hydroxybutyrate, thereby ameliorating various age-related ailments, including cardiovascular disease [7]. The chronic elevation of circulating ketones has been found to have a protective effect against the development of heart failure, which is attributed to the direct anti-inflammatory properties of β-hydroxybutyrate [8]. Additionally, 3-hydroxybutyrate has been shown to increase cardiac output through peripheral vasorelaxation and enhanced cardiac contractility [9]. In a study involving diabetic rats, moderately elevated levels of 3-hydroxybutyrate were associated with reduced aortic endothelial injury and increased production of vascular endothelial growth factor (VEGF) [10]. Based on these findings, it is hypothesized that 3-hydroxybutyrate may also play a protective role in aortic dissection. However, further research is needed to fully understand this potential relationship.

Mendelian randomization (MR) is an emerging epidemiological technique employed to examine the causal association between various traits by leveraging genetic variants. By utilizing genetic variables as instrumental variables to substitute exposures in assessing outcomes, the MR method offers enhanced causal inference capabilities for estimating causality [11]. Given that genetic variants are randomly assigned at birth, Mendelian randomization (MR) is less susceptible to confounding factors compared to observational studies [12]. In this study, our objective was to investigate the relationship between ketone bodies and aortic dissection utilizing the Mendelian randomization approach.

Materials and methods

Study design

Two-sample MR analysis and Multivariate MR were conducted to investigate the potential causal effects of ketone bodies on the risk of aortic dissection, as depicted in Fig. 1. The MR study adhered to three fundamental assumptions [13]. First, the single nucleotide polymorphisms (SNPs) variants were required to exhibit a strong association with exposure. Second, the SNPs had to be independent of other known confounders. Third, the SNPs were expected to solely influence outcome through their impact on exposure.

Data sources

The GWAS summary statistics for ketone bodies were derived from blood samples from the UK Biobank, measured by Nightingale Health using Nightingale's biomarker profiling technology in 2020. They were included in a GWAS dataset called met-d (https://gwas.mrcieu.ac.uk/datasets/). The ids of GWAS for ketone bodies were shown in Table 1. The GWAS summary statistics for aortic dissection came from FinnGen Release 5, an early personalised medicine programme designed to elucidate genotype-phenotype associations by aggregating and analysing genomic and health information from participants in the Finnish biobanks (https://www.finngen.fi/en). The specific characteristics of these traits are presented in Table 1. As all GWAS data were publicly available and had been approved by relevant ethical review boards, no further ethical approval was necessary for the analysis conducted in this study.

Selection and validation of instrumental variables

Instrumental variables (IVs) were employed in the MR analysis as mediators between exposure and outcome, aiming to investigate the causal relationship between exposure and outcome. Instrumental variables, specifically single nucleotide polymorphisms (SNPs), are commonly employed in genetic studies. SNPs that exhibit a significant association with exposure at a genome-wide significance level ($p<5\times10^{-8}$) are selected. These SNPs are further grouped based on linkage disequilibrium (LD), with an r2<0.001 within 10,000 kb windows. The F statistic is then utilized to confirm a strong association between the instrumental variables and the exposure, with a selection criterion of an F statistic greater than 10 [14]. The formula for calculating F is $F=R^2(n-2)/(1-R^2)$, where $R2=2\times(1-EAF)\times EAF\times beta^2$. EAF stands for effect of allele frequency, and n stands for sample size.

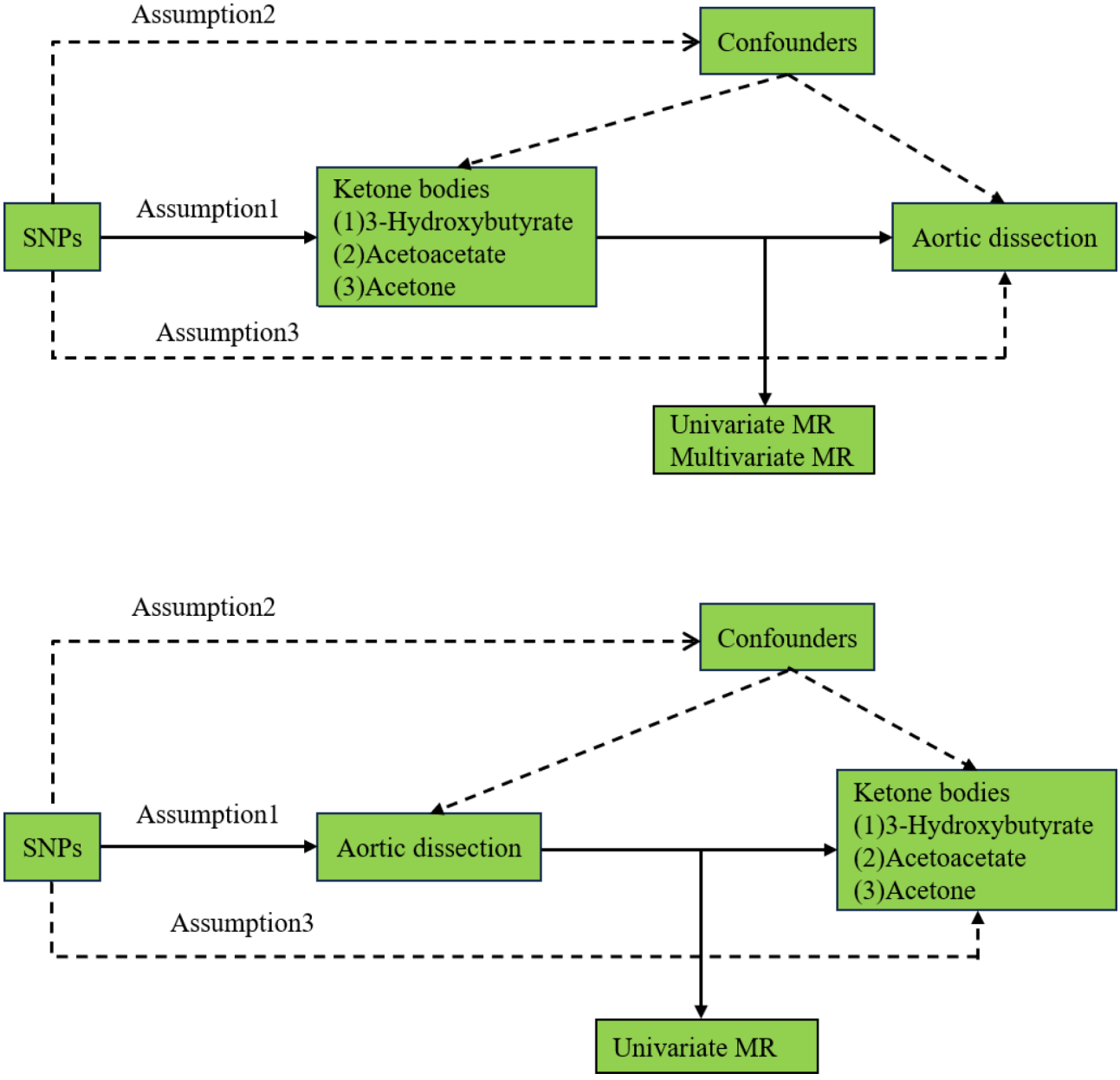

Fig. 1 Summary of MR

Table 1 Baseline characteristics of the genome-wide association studies included in the MR study

Trait	id	Year	Population	Sample size	nSNPs
3-Hydroxybutyrate	met-d-bOHbutyrate	2020	European	113,595	12,321,875
Acetoacetate	met-d-Acetoacetate	2020	European	115,075	12,321,875
Acetone	met-d-Acetone	2020	European	115,075	12,321,875
Aortic dissection	finn-b-I9_AORTDIS	2021	European	207,011	16,380,411

nSNPs, number of SNPs

To ensure the alignment of effect estimates for the same allele, the exposure and outcome SNPs were harmonized. MR pleiotropy residual sum and outlier (MR-PRESSO) test was performed to detect outlier SNPs (Nb Distribution = 3000, Significant Threshold = 0.05) using the MR-PRESSO packages in R software version 4.2.0.

Statistical analysis

The analysis was conducted using the TwoSampleMR R package and MR-PRESSO R package (R version 4.2.0). Five different MR analysis methods, namely Mendelian randomization-Egger (MR-Egger), weighted median, inverse-variance weighted (IVW), simple mode, and weighted mode, were employed to investigate the causal relationship between exposure and outcome. Bonferroni's correction was performed to adjust the *p*-values ($p < 0.0167 = 0.05/3$ for univariate MR analyses). Heterogeneity was assessed using the MR-Egger and IVW methods, and no heterogeneity was observed when $p > 0.05$. The pleiotropic effects of genetic variants were assessed using the MR-Egger and MR-PRESSO methods. A lack of horizontal pleiotropy was observed when the *p*-value exceeded 0.05. Additionally, a leave-one-out analysis was performed to determine if any individual SNP had a disproportionate impact on the outcome. Acetoacetate and acetone may be confounding factors affecting the risk of 3-hydroxybutyrate and aortic dissection. Multivariate Mendelian randomization (MVMR) analysis including acetoacetate or acetone as potential risks was performed to detect causal association between 3-hydroxybutyrate and aortic dissection. MVMR package of R (version 4.2.0) was used to perform all analyses [15].

Result

Univariate MR

In forward Mendelian randomization, 17 SNPs strongly associated with 3-hydroxybutyrate were selected. Subsequently, 16 SNPs were extracted from aortic dissection. Upon harmonizing the exposure and outcome SNPs, two SNPs were removed. Subsequently. Ultimately, 14 SNPs meeting the criteria of having F values exceeding 10 and passing the MR-PRESSO test were chosen for analysis. Seven SNPs strongly associated with acetoacetate were selected. Subsequently, 7 SNPs were extracted from aortic dissection. Upon harmonizing the exposure and outcome SNPs, no SNP was removed. Subsequently. Ultimately, 7 SNPs meeting the criteria of having F values exceeding 10 and passing the MR-PRESSO test were chosen for analysis. 12 SNPs strongly associated with acetone were selected. Subsequently, 11 SNPs were extracted from aortic dissection. Upon harmonizing the exposure and outcome SNPs, one SNP was removed. Subsequently. Ultimately, 10 SNPs meeting the criteria of having F values exceeding 10 and passing the MR-PRESSO test were chosen for analysis. The results of MR analysis were illustrated in Fig. 2. The IVW method of gene prediction observed a negative correlation between 3-hydroxybutyrate and risk of aortic dissection (OR 0.147, 95% CI 0.053–0.410). Consistency among the five MR methods was observed. The findings from IVW method indicated that genetically predicted acetoacetate and acetone were not significantly correlated with the occurrence of aortic dissection. In reverse Mendelian randomization, one SNP from aortic dissection was selected as instrumental variable. Wald ratio showed that genetically predicted relationship between aortic dissection and

exposure	outcome	nsnp	method	pval	OR(95% CI)
Aortic dissection	3−Hydroxybutyrate	1	Wald ratio	0.964	1.000 (0.987 to 1.013)
Aortic dissection	Acetoacetate	1	Wald ratio	0.715	0.998 (0.985 to 1.011)
Aortic dissection	Acetone	1	Wald ratio	0.971	1.000 (0.987 to 1.013)
3−Hydroxybutyrate	Aortic dissection	14	Inverse variance weighted	**<0.001**	0.147 (0.053 to 0.410)
		14	MR Egger	0.064	0.049 (0.003 to 0.888)
		14	Simple mode	0.102	0.145 (0.017 to 1.248)
		14	Weighted median	0.064	0.257 (0.061 to 1.082)
		14	Weighted mode	0.113	0.169 (0.022 to 1.311)
Acetoacetate	Aortic dissection	7	Inverse variance weighted	0.244	0.335 (0.053 to 2.114)
		7	MR Egger	0.817	0.422 (0.000 to 431.052)
		7	Simple mode	0.616	0.489 (0.035 to 6.927)
		7	Weighted median	0.501	0.521 (0.078 to 3.493)
		7	Weighted mode	0.482	0.449 (0.055 to 3.641)
Acetone	Aortic dissection	10	Inverse variance weighted	0.602	0.660 (0.139 to 3.143)
		10	MR Egger	0.311	6.114 (0.229 to 162.945)
		10	Simple mode	0.425	0.287 (0.015 to 5.373)
		10	Weighted median	0.562	0.596 (0.104 to 3.424)
		10	Weighted mode	0.433	0.432 (0.058 to 3.200)

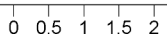

Fig. 2 The results of univariate MR

3-hydroxybutyrate was uncorrelated. Wald ratio method indicated that genetically predicted aortic dissection were not significantly correlated with acetoacetate and acetone. The results of MR analysis were illustrated in Fig. 2.

Heterogeneity and sensitive test

There was no observed evidence of heterogeneity and pleiotropy among the single nucleotide polymorphisms (SNPs) as indicated in Table 2. Furthermore, the leave-one-out analysis demonstrated that the association between ketone bodies and the risk of aortic dissection was not influenced by any individual SNP, as depicted in Fig. 3.

Multivariate mendelian randomization

In the MVMR analyses, gene prediction observed a negative correlation between 3-hydroxybutyrate and risk of aortic dissection after adjusting acetoacetate (OR 0.143, 95% CI 0.023-0.900) or acetone (OR 0.100, 95% CI 0.025–0.398), which was similar to the two sample MR result. The results of MVMR analysis were illustrated in Fig. 4.

Discussion

In the present study, an investigation was conducted to examine the potential correlation between ketone bodies and aortic dissection. Utilizing Mendelian analysis, gene prediction observed a negative correlation between 3-hydroxybutyrate and risk of aortic dissection.

3-Hydroxybutyrate, alternatively known as β-hydroxybutyrate, is a naturally occurring metabolite in humans, synthesized from adipose tissue within the liver [16]. This compound serves as a prominent constituent of ketone bodies, facilitating energy conservation by substituting glucose as a circulating energy source throughout the body. Moreover, it is generated during periods of intermittent fasting and dietary restriction [17]. During periods of intermittent fasting and dietary restriction, 3-hydroxybutyrate serves as both a source of energy and a potent signaling molecule. It possesses the ability to effectively diminish inflammatory factors and regulate various systemic metabolic processes, thereby enhancing cardiovascular risk factors [18]. Our study revealed a significant correlation between elevated levels of 3-hydroxybutyrate and a reduced risk of aortic dissection. Conversely, heightened concentrations of 3-hydroxybutyrate were also observed in association with cardiovascular diseases [19, 20]. Based on the aforementioned supporting studies, it is postulated that the utilization of 3-hydroxybutyrate may potentially mitigate the occurrence of aortic dissection by attenuating the risk factors associated with cardiovascular disease. Numerous investigations have demonstrated the involvement of cytokines and inflammation in the management of aortic dissection [21, 22]. Additional research endeavors propose that 3-hydroxybutyrate may exert a direct influence on aortic dissection. Specifically, 3-hydroxybutyrate has been found to impede the formation of plaques and lipid deposits within atherosclerotic arteries [23]. It has been identified as an anti-aging metabolite, exhibiting significant efficacy in mitigating cardiovascular aging [24]. Research has demonstrated its ability to reduce the senescence-associated secretory phenotype and senescent vascular cells in mammals [25]. However, additional experimental investigations are warranted to elucidate the mechanisms by which 3-hydroxybutyrate attenuates aortic dissection.

In our Mendelian randomized study examining the relationship between ketone bodies and aortic dissection, we observed no significant association between acetoacetate and aortic dissection, as well as between acetone and aortic dissection. Acetoacetate is produced through the oxidation of fatty acids, leading to the formation of acetone and hydroxybutyrate [26]. While our Mendelian randomization study did not identify a correlation between acetoacetate and aortic dissection, elevated levels of acetoacetate and 3-hydroxybutyrate induced by sodium-glucose cotransporter 2 inhibitors may have a beneficial effect on left ventricular dilation and endothelial function in individuals with type 2 diabetes. This potential mechanism could play a role in protecting against left ventricular diastolic dysfunction [27]. Body fat undergoes decomposition and combustion processes to produce acetone, an organic compound present in the bloodstream [28]. Acetone serves a multifaceted function as a natural element of metabolic processes [29]. The breakdown of acetoacetate into acetone aids in the preservation of pH buffering capabilities [30]. While neither 3-hydroxybutyrate nor acetoacetate have demonstrated anticonvulsant properties, acetone exhibits anticonvulsant effects at physiological and nearly physiological nontoxic levels [31].

Table 2 Tests of heterogeneity and pleiotropy of univariate MR

		Heterogeneity test				Pleiotropy test		
		MR Egger		IVW		MR Egger		MR-PRESSO
Exposure	Outcome	Cochran's Q	pValue	Cochran's Q	pValue	Egger intercept	pValue	Global pValue
3-Hydroxybutyrate	Aortic dissection	12.622	0.397	13.291	0.426	0.056	0.441	0.459
Acetoacetate	Aortic dissection	9.658	0.086	9.667	0.139	-0.011	0.948	0.198
Acetone	Aortic dissection	10.312	0.244	13.156	0.156	-0.112	0.176	0.209

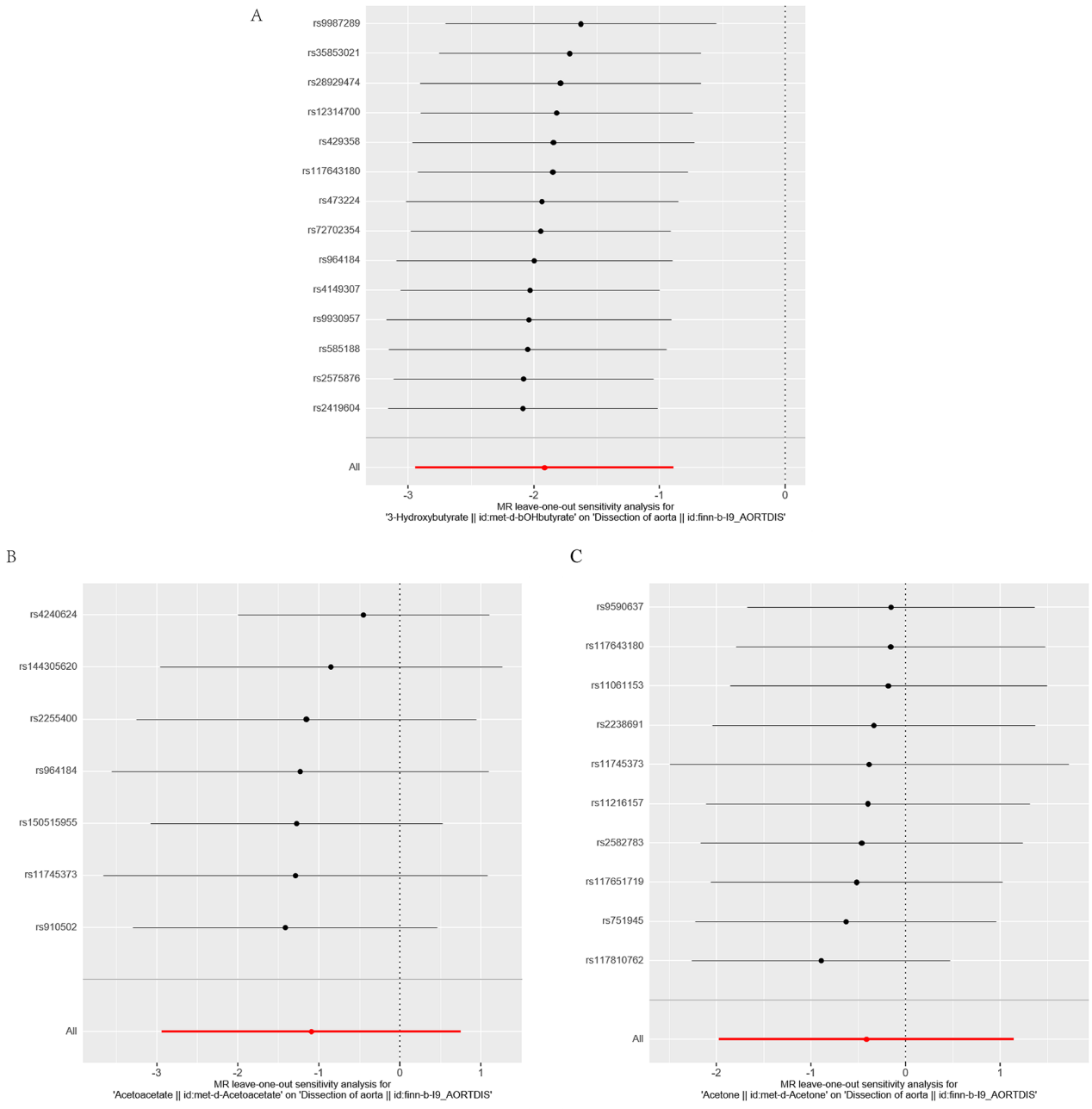

Fig. 3 The leave-one-out analysis plot of SNPs associated with ketone bodies and aortic dissection. **A:** 3-Hydroxybutyrate; **B:** Acetoacetate; **C:** Acetone

exposure	outcome	nsnp	method	pval	OR(95% CI)
3−Hydroxybutyrate,adjusting acetoacetate	Aortic dissection	16	IVW	**0.038**	0.143 (0.023 to 0.900)
3−Hydroxybutyrate,adjusting acetone	Aortic dissection	20	IVW	**0.001**	0.100 (0.025 to 0.398)
Acetoacetate,adjusting 3−hydroxybutyrate	Aortic dissection	16	IVW	0.616	1.949 (0.143 to 26.528)
Acetone,adjusting 3−hydroxybutyrate	Aortic dissection	20	IVW	0.339	2.322 (0.413 to 13.046)

Fig. 4 The results of MVMR

Through the application of Mendelian randomization, our study has revealed that 3-hydroxybutyrate exhibits a significant potential in mitigating the occurrence of aortic dissection, thus highlighting its crucial role in preventive measures. As the principal constituent of ketone bodies, the augmentation of 3-hydroxybutyrate can be achieved through the implementation of a ketogenic diet. Notably, the ketogenic diet has been employed as a metabolic therapy for well over a century, with its ability to induce ketone body production being initially observed by Woodyatt et al. in 1921, either through periods of starvation or the consumption of a diet characterized by a high fat-to-carbohydrate ratio [32]. The ketogenic diet has been extensively utilized for weight loss and the management of various metabolic disorders, such as polycystic ovarian disease, diabetes mellitus, and neurologic disorders like epilepsy and Alzheimer's disease [33]. However, due to the necessary modifications in dietary habits, adhering to and sustaining the ketogenic diet can present challenges. Consequently, exogenous ketone supplements in the form of ketone salts or ketone esters have been formulated as a substitute for the ketogenic diet [34]. In individuals with a high risk of aortic dissection, prevention can be accomplished through the implementation of a ketogenic diet or the utilization of exogenous ketone supplementation.

Moreover, it is worth noting that empirical investigations have revealed a decreased susceptibility to thoracic aortic dissection among individuals diagnosed with diabetes. This observation suggests the possibility that diabetes mellitus, or its corresponding therapeutic interventions, may confer a safeguarding influence against aortic dissection [35]. In instances of starvation or diabetes, elevated levels of ketone bodies, resulting from heightened fatty acid levels and diminished insulin production, have been observed [36]. Our recent Mendelian-mediated randomization analysis suggests that type 1 diabetes may protect against aortic dissection through the involvement of 3-hydroxybutyrate [37].

In this study, we employed the two-sample Mendelian randomization and MVMR approach to elucidate the causal impact of 3-hydroxybutyrate on the susceptibility to aortic dissection. Notably, this investigation represents the inaugural application of MR analysis in the context of 3-hydroxybutyrate and aortic dissection. Our study successfully satisfied several instrumental variable assumptions, and the instruments exhibited significant predictive capacity for exposure, as evidenced by both surpassing the F-statistics threshold and the number of single nucleotide polymorphisms. Importantly, Mendelian randomization effectively mitigates potential confounding factors, as alleles are essentially assigned randomly during conception [38, 39]. In order to mitigate population stratification, the scope of this study was limited to individuals of European descent. Our analysis revealed no indications of heterogeneity or pleiotropy within our study. The validity of the results obtained through Mendelian randomization analysis was confirmed. Nonetheless, certain limitations persisted in our study. Provided that specific criteria are met, naturally occurring genetic variation can serve as a valuable instrument for evaluating causality in the design of Mendelian randomization studies [40, 41]. Given the predominant focus on individuals of European ancestry in our study, it is imperative to corroborate the findings in diverse populations.

In summary, our Mendelian randomization study provides evidence supporting the notion that 3-hydroxybutyrate serves as a protective factor against aortic dissection from gene prediction. Individuals with a high susceptibility to aortic dissection may effectively prevent its occurrence by adopting a ketogenic diet or utilizing exogenous ketone supplementation. These findings warrant consideration in future investigations and the development of public health initiatives aimed at preventing aortic dissection.

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Author contributions
Shi Qiu was responsible for the conception and initial drafting of the manuscript. Zhen Liu was responsible for the study design. Chun-ting Wang prepared the figures. Xiao-di Sun prepared the tables. Zeng-qiang Liu analyzed the data. Wen Liu contributed to the study design and approved the final version of the manuscript. Shi Qiu is the first author, and Wen Liu is the corresponding author. All authors have read and agree to the published version of the manuscript.All authors reviewed the manuscript.

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

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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