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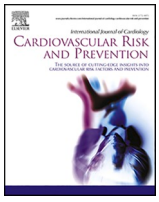

The associations between circulating amino acids and arterial aneurysms and dissection: A bidirectional Mendelian randomization study

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ABSTRACT

Background: Circulating amino acid levels can be altered in arterial aneurysms and dissection, but the relationships between them is unclear. The present study investigated the causal relationship between circulating amino acid levels and arterial aneurysms and dissection via bidirectional two-sample Mendelian randomization (MR).

Methods: A bidirectional two-sample MR analysis was used. Forward analysis was performed with amino acid levels as the exposure and arterial aneurysms and dissection as outcomes. Reverse analysis was performed with arterial aneurysms and dissection as exposures and circulating amino acid levels as outcomes. MR data were analyzed using five analytical methods: the inverse-variance weighted (IVW), MR−Egger, weighted median, simple, and weighted methods. IVW was used as the main analytical method, and the other methods were used for supplementary analyses. Heterogeneity was assessed using Cochran's Q test, and horizontal pleiotropy was assessed using intercepts from MR−Egger regression. The genome-wide association study (GWAS) data for circulating amino acids were obtained from the IEU open GWAS database and the GWAS Catalog database. The GWAS data for arterial aneurysms and dissection were obtained from the Finngen consortium database version R10.

Results: The tyrosine level was negatively correlated with other aneurysms (P = 0.00211, OR: 0.57, 95 % CI: 0.40, 0.82). Aortic dissection decreased the circulating glycine level (P = 0.00168, OR: 0.98, 95 % CI: 0.98, 0.99).

Conclusion: Through bidirectional MR analysis, we found that tyrosine level was negatively correlated with other aneurysms and that aortic dissection reduced circulating glycine. Our findings support a possible interaction between circulating amino acid levels and arterial aneurysms and dissection.

1. Introduction

According to the World Health Statistics 2023 of the World Health Organization (World health statistics 2023: monitoring health for the SDGs, sustainable development goals (who.int)), cardiovascular disease has become the number-one killer of humans among non-communicable diseases (NCDs), and arterial aneurysms and dissection rank first among these. The incidence of arterial aneurysms and dissection further increases with modernization of the diet and the growth of the middle-aged and elderly population. An aneurysm is

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defined as a pathological dilatation of the arterial wall [1,2], while arterial dissection is defined as a tear in the intima of an artery that separates from the arterial wall, resulting in blood flow impinging on the lumen between the torn intima and the residual arterial wall [3–5]. The rupture of an aneurysm or arterial dissection often results in arterial hemorrhage, quickly leading to death. Thus, the mortality rate for this group of patients is often very high [6]. How to detect or prevent arterial aneurysms and dissection from occurring and rupturing at an early stage is a tough clinical problem.

Circulating amino acids are involved in many metabolic processes in humans, including protein synthesis, enzyme catalysis, free radical scavenging, protein phosphorylation subunit reactions, and gene expression [7,8]. Circulating metabolites have been implicated in a variety of diseases. For example, plasma homocysteine has been implicated in a variety of diseases, including hypertension [9]. In recent years, plasma metabolite studies have shown that amino acid levels are associated with sepsis [10], deep vein thrombosis [11], chronic obstructive pulmonary disease [12], and myasthenia gravis [13]. All this suggests that circulating amino acids and their metabolism have the potential to influence certain pathophysiological processes in the human body [14]. A recent metabolomics study found changes in circulating amino acids in abdominal aneurysms and aortic dissection [15,16], providing evidence of a possible causal relationship between circulating levels of amino acids and arterial aneurysms and dissection.

Mendelian randomization (MR) analysis uses genetic variations (usually single-nucleotide polymorphisms (SNPs)) as instrumental variables to explore the relationship between exposure and outcome. It is better at avoiding confounding and reverse causation than commonly used observational experiments [17–19]. The MR method has a confidence level just below that of a randomized controlled trial [20]. MR analysis has been used for identifying risk factors, identifying drug targets, and predicting adverse events [21]. MR analysis has been increasingly used as an exploratory research method to investigate correlations between traits and as a complement to observational and randomized controlled trials.

The relationships between circulating amino acid levels and a variety of cardiovascular diseases, including coronary heart disease and venous thrombosis, has been investigated using MR analysis [22], but there have been no MR studies investigating the relationship between circulating amino acid levels and arterial aneurysms and dissection. Thus, in the present study, we used bidirectional, two-sample MR analyses to investigate the possible causal relationship between circulating amino acid levels and arterial aneurysms and dissection.

2. Data sources and methods

2.1. Data sources

In a genome-wide association study (GWAS) of amino acids from two different studies, Richardson TG et al. [23] studied data from the IEU Open GWAS (https://gwas.mrcieu.ac.uk/). Chen Y et al. [24] studied data from the GWAS Catalog database (https://www.ebi.ac.uk/gwas/). The arterial aneurysm and dissection data (including abdominal aortic aneurysm, thoracic aortic aneurysm, cerebral aneurysm (nonruptured), other aneurysm, aortic dissection, and dissection of cerebral arteries (nonruptured)) were derived from the R10 version of the Finngen consortium database (https://www.finngen.fi/fi). Specific GWAS data and download links can be found in Table 1. The study population in this study was European. All data are updated until April 1, 2024.

2.2. Methods

MR analysis mainly includes five methods: inverse variance weighted (IVW), MR−Egger, weighted median, simple mode, and weighted mode, with IVW as the main test ($P < 0.05$ indicates positive results). Heterogeneity was assessed using Cochran's Q test ($P > 0.05$

Table 1
Detailed information on the GWAS data.

trait	sample size	number of SNPs	Network link or download link	Author
Leucine level	115,078	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092891/	Richardson TG [23]
Isoleucine level	115,079	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092843/	
Valine level	115,052	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092995/	
Tyrosine level	114,913	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092993/	
Phenylalanine level	115,030	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092936/	
Glycine level	114,978	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092820/	
Alanine level	115,078	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092806/	
Histidine level	114,897	11,590,399	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092830/	
Cysteine level	8216	15,429,409	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200439/	Chen Y[24]
Methionine level	8222	15,429,509	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200391/	
Glutamate level	8287	15,432,170	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200412/	
Glutamine level	8253	15,430,860	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200419/	
Arginine level	8237	15,429,048	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200372/	
Lysine level	8250	15,430,464	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST	

(continued on next page)

Table 1 (*continued*)

trait	sample size	number of SNPs	Network link or download link	Author
			90201000/GCST90200402/	
Proline level	8257	15,431,336	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200411/	
Tryptophan level	8235	15,430,210	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200441/	
Serine level	8271	15,431,627	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200415/	
Threonine level	8245	15,430,624	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200432/	
Aspartate level	8253	15,430,779	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200370/	
Asparagine level	8245	15,430,003	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90200001-GCST90201000/GCST90200452/	
Abdominal aortic aneurysm	385,846	21,305,853	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_I9_ABAORTANEUR.gz	Finngen consortium
Thoracic aortic aneurysm	385,857	21,305,837	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_I9_THAORTANEUR.gz	
Cerebral aneurysm, nonruptured	377,415	21,305,609	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_I9_ANEURYSM.gz	
Other aneurysm	383,626	21,305,803	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_I9_OTHANEUR.gz	
Dissection of aorta	382,944	21,305,786	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_I9_AORTDIS.gz	
Dissection of cerebral arteries, nonruptured	374,839	21,305,564	https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_I9_DISCER.gz	

indicates no heterogeneity), horizontal pleiotropy was detected using intercepts from MR−Egger regression ($P > 0.05$ indicates no horizontal pleiotropy), and leave-one-out was used for sensitivity testing. Because we had multiple exposures and outcomes, we corrected the results for the false discovery rate (FDR) after performing a conventional MR analysis. In selecting the final positive result, not only must the P value derived from the IVW test for MR be less than 0.05, but the P value corrected using the FDR method (which we call adjustp) must also be less than 0.05. We regarded analyses with $p < 0.05$ using MR of IVW but corrected $p > 0.05$ using the FDR method as potentially causal.

In the forward MR analysis, amino acid levels were used as exposures, and arterial aneurysms and dissections (including abdominal aortic aneurysm, thoracic aortic aneurysm, cerebral aneurysm (nonruptured), other aneurysms, aortic dissection, and dissection of cerebral arteries (nonruptured)) were used as outcomes. The amino acid levels came from two different studies, so we divided our data into two main steps in selecting SNPs: SNPs that were significantly associated with amino acid levels and SNPs that were associated with exposure were selected by setting $P < 5 \times 10^{-8}$ from the GWAS data of Richardson TG et al. The data of Chen Y et al. were insufficient because of the small number of SNPs for setting $P < 5 \times 10^{-8}$, so $P < 5 \times 10^{-6}$ was chosen to screen for SNPs correlated with amino acid levels, and $r^2 = 0.001$ and kb $= 10000$ were set to remove chain imbalance. To ensure that SNPs were strongly correlated with exposure, we set F test values greater than 10 to remove weak instrumental variables. After filtering the SNPs that were strongly associated with exposure, the formula for the F value was F=R [2]/(1-R^2) × (N-2), where $R^2 = 2 \times (1\text{-MAF}) \times \text{MAF} \times \beta^2$, where N is the total number of samples, MAF is the minor allele frequency, and β is the beta coefficient of the exposure factor [25]. We then eliminated the SNPs that were strongly associated with outcome. Since SNPs are independent of confounding factors, we screened for SNPs potentially associated with aneurysms and arterial dissection from the PhenScanner GWAS database (http://phenoscanner.medschl.cam.ac.uk) and discarded these SNPs.

For reverse MR analysis, arterial aneurysms and dissection were used as the exposures, and amino acid levels were used as the outcomes. Because all our exposure data were from the Finngen consortium database, $P < 5 \times 10^{-6}$ was set to select SNPs associated with arterial aneurysms and dissection, and $r^2 = 0.001$ and kb $= 10,000$ were used to remove chain imbalance. An F test value > 10 was used to remove weak instrumental variables. After screening for SNPs strongly associated with exposure, SNPs associated with outcome were excluded. Finally, the PhenScanner GWAS database was screened for SNPs associated with amino acid levels, and these SNPs were discarded. All analyses in this study were performed in the R programming language (version 4.3.2) and RStudio (version 4.3.2) using the R package "TwoSampleMR".

3. Results

3.1. Forward MR analysis of the effect of amino acid levels on arterial aneurysms and dissection

In the forward MR analysis, we analyzed the effect of circulating amino acid levels on arterial aneurysms and dissection. Fig. 1 shows the MR results and the results of the heterogeneity and horizontal pleiotropy tests. We found that tyrosine level was negatively correlated with other aneurysms (p = 0.00211, odds ratio (OR): 0.57091, 95 % CI: 0.40, 0.82), the adjusted p (FDR-corrected p value) was 0.0422, the Cochran Q test did not show heterogeneity, and MR–Egger regression did not show evidence of pleiotropy. Figs. 2–4 show scatterplots, forest plots, and leave-one-out plots, respectively.

After the results of analyses that showed a clear causal relationship, Fig. 5 shows the MR results with possible causal effects as well as the results of the heterogeneity and horizontal pleiotropy tests. The following factors may have causal effects: glycine levels (P = 0.04110, OR: 0.79, 95 % CI: 0.63, 0.99), glutamate levels (P = 0.00527, OR: 0.76, 95 % CI: 0.63, 0.92) versus abdominal aortic aneurysm, valine levels (P = 0.01557, OR: 0.57, 95 % CI: 0.36, 0.90) versus thoracic aortic aneurysm, glutamine levels (P = 0.02576, OR: 0.75, 95 % CI: 0.59, 0.97), cysteine levels (P = 0.03053, OR: 1.17166, 95 % CI: 1.01498, 1.35252) versus cerebral aneurysm (nonruptured), alanine levels (P = 0.02191, OR: 0.60144, 95 % CI: 0.39, 0.93) versus other aneurysms, leucine levels (P = 0.03709, OR: 0.42, 95 % CI: 0.19, 0.95) and valine levels (P = 0.03887, OR: 0.50, 95 % CI: 0.26, 0.97) versus aortic dissection, tyrosine levels (P = 0.00321, OR: 0.22, 95 % CI: 0.08, 0.60), glutamine levels (P = 0.04281, OR: 0.41, 95 % CI: 0.17, 0.97), aspartate levels (P = 0.0129, OR: 2.75, 95 % CI: 1.24, 6.08) and glutamate levels (P = 0.01132, OR: 2.75, 95 % CI: 1.26, 6.03) versus dissection of cerebral arteries (nonruptured). In the forward analyses, we did not find an association between isoleucine, phenylalanine, proline, tryptophan, serine, asparagine, lysine, arginine, or histidine and arterial aneurysms or dissection. OR > 1 meant that exposure had a positive effect on outcome and vice versa (95 % CI: 95 % confidence interval).

3.2. Inverse MR analysis showing the effects of arterial aneurysms and dissection on amino acid levels

In a reverse MR analysis, we analyzed the effect of arterial aneurysms and dissection on circulating amino acids. Fig. 6 shows the MR results and the results of the heterogeneity and horizontal pleiotropy tests. We found that aortic dissection may reduce circulating glycine levels (p = 0.00168, OR: 0.98, 95 % CI: 0.97, 0.99), and the adjusted false discovery rate (FDR)-corrected p value was 0.03351. The Cochran Q test did not show heterogeneity, and MR–Egger regression did not show evidence of pleiotropy. Figs. 7–9 show scatterplots, forest plots, and leave-one-out plots.

In addition to the results of the appeal, Fig. 10 shows the MR results with possible causal effects as well as the results of the heterogeneity and horizontal pleiotropy tests. We found that abdominal aortic aneurysms may be causally related to with tyrosine level (P = 0.04823, OR: 1.01, 95 % CI: 1.00, 1.03), other aneurysms to glycine level (P = 0.02713, OR: 1.02, 95 % CI: 1.00, 1.03), and aortic dissection to methionine level (P = 0.00624, OR: 1.05, 95 % CI: 1.01, 1.08). In the reverse analysis, we did not find a relationship between any circulating amino acid levels and thoracic aortic aneurysm, cerebral aneurysm (nonruptured), or cerebral artery dissection (nonruptured).

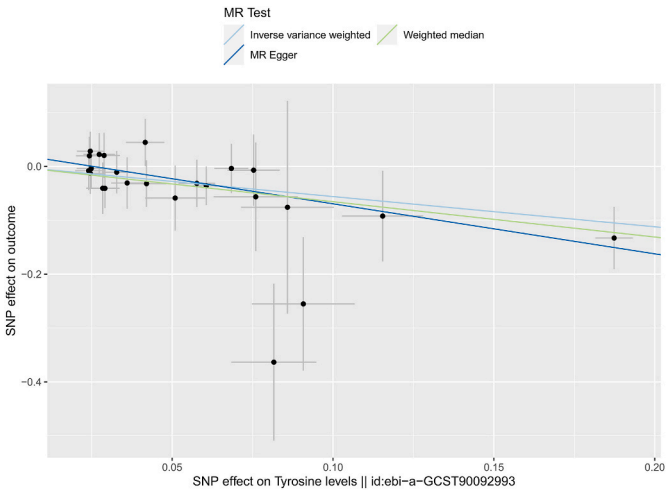

Fig. 2. Scatterplot of MR analysis of tyrosine levels in patients with other aneurysms. Horizontal axis: SNP associations with tyrosine level; vertical axis: SNP associations with other aneurysms (only IVW, MR–Egger and weighted median analyses).

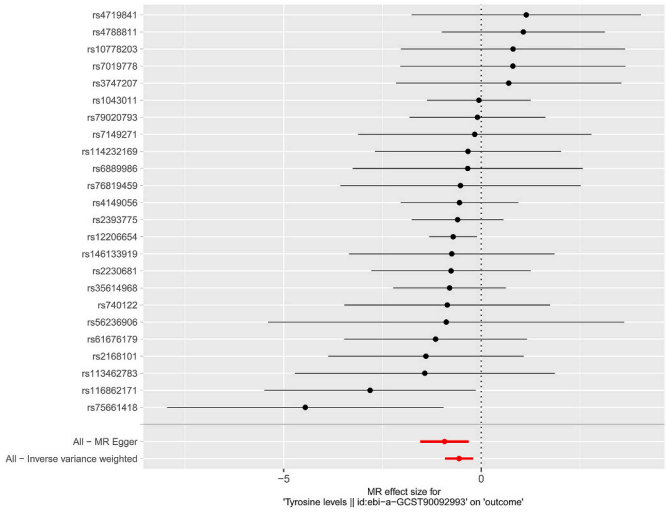

Fig. 3. Forest plot of tyrosine level versus MR analysis of other aneurysms.

exposure.outcome	method	nsnp	pval	P.heterogeneity.	P.pleiotropy.	adjustp	OR(95%CI)
Tyrosine levels & Other aneurysm	MR Egger	24	0.00729	0.9			0.39(0.21 to 0.73)
	Weighted median	24	0.00753				0.52(0.32 to 0.84)
	Inverse variance weighted	24	0.00211	0.85033	0.16404	0.0422	0.57(0.40 to 0.82)
	Simple mode	24	0.14837				0.53(0.23 to 1.22)
	Weighted mode	24	0.01319				0.51(0.31 to 0.83)

P<0.05 was considered statistically significant

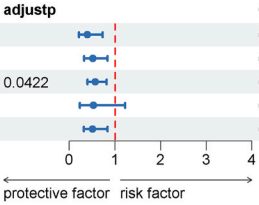

Fig. 1. Results of MR analysis of tyrosine levels and other aneurysms. $P_{heterogeneity}$ refers to the *P* value of the heterogeneity test; P > 0.05 means no heterogeneity; $P_{Pleiotropy}$ refers to the P value of the pleiotropy test, P > 0.05 means no horizontal pleiotropy; adjustp refers to the *P* value corrected by FDR; snp: single-nucleotide polymorphism; nsnp: number of SNPs; OR: odds ratio, 95 % CI: 95 % confidence interval.

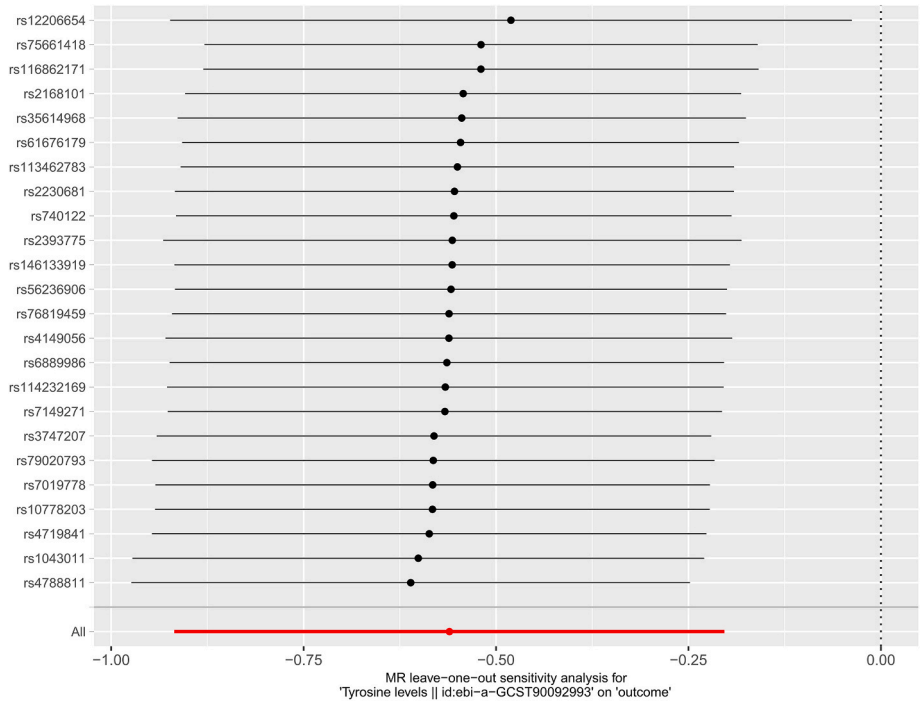

Fig. 4. Leave-one-out plot of tyrosine levels versus other aneurysms according to MR analysis (effect of individual SNPs on analysis).

4. Discussion

Aneurysms occur due to a variety of etiological factors, including inflammation of the arterial wall, degradation of the arterial wall matrix, cytokine regulation, protein hydrolyzing enzymes, and genetics [26–28]. The etiology of arterial dissection is controversial, but the basic causes include disruption of the structure of the arterial wall and an increase in pressure on the arterial wall leading to rupture of the arterial lining [29,30]. The relationship between circulating amino acids and cardiovascular disease has been noted before; for instance, the levels of amino acids and their metabolism are altered in cardiovascular diseases such as hypertension [31], atherosclerosis [32], peripheral vascular disease [33], and stroke [34], and there is much research on the underlying mechanisms involved. The vascular endothelium has important roles in the vascular system, including but not limited to the regulation of vascular tone, the regulation of the coagulation fibrinolytic system, the mediation of vascular inflammation, and the regulation of vascular shear [35], and it has been speculated that amino acid metabolism affects the biological functions of the vascular endothelium [36–38]. Some scholars have shown that glutamine may promote M2 polarization in macrophages and inhibit nitrative stress caused by excess nitric oxide (NO) [39], and some studies have shown that amino acid metabolism was associated with risk factors for cardiovascular disease (including diabetes, obesity, etc.) [40,41].

In the forward MR study, we found that tyrosine levels were negatively associated with other aneurysms. Tyrosine is an aromatic amino acid and a gluconeogenic amino acid (converted to both sugar and ketone bodies). Two main metabolic pathways exist for tyrosine, the synthesis of catecholamine (including dopamine and the further conversion products epinephrine and noradrenaline) [42] and conversion to p-hydroxyphenyl pyruvic acid, uranyl acetic acid, and finally to fenugreek acid. Oxaloacetic acid and tyrosine are also precursors for the synthesis of thyroid hormones. These metabolic pathways suggest that circulating tyrosine may affect energy metabolism, neurotransmitter synthesis, and vascular function in humans [43,44]. As previously indicated, one of the crucial aspects in the pathogenesis of aneurysms is oxidative stress. One of the metabolic pathways of tyrosine involves its conversion into dopamine. Dopamine itself has the function of regulating the body's antioxidant system (reactive oxygen species, ROS) [45]. Based on previous literature, we hypothesize that dopamine activates the PI3K/AKT or ERK signaling pathways. This activation promotes the translocation of nuclear factor erythroid 2 - related factor 2 (Nrf2) into the nucleus, where it binds to the antioxidant response element (ARE). This binding event then facilitates the expression of various important antioxidant factors, including NAD(P)H and heme oxygenase - 1 (HO - 1) [45].

Recent metabolomics studies have demonstrated that tyrosine and tyrosine metabolism are altered in cardiovascular and cerebrovascular diseases and their risk factors, such as atherosclerosis [46,47], atherosclerotic cardiovascular disease [48,49], diabetes and its complications [50,51], atrial fibrillation [52], heart failure [53,54], stroke [55], and peripheral arterial disease [56]. As mentioned above, amino acids and their metabolism affect vascular endothelial function, and some researchers have found that tyrosine supplementation improves the contractility of skin microvessels (which are composed almost exclusively of vascular endothelial cells) [57]. According to Zho et al. [58], amino acid metabolism may not only affect vascular endothelial function but also regulate aortic inflammation by influencing aortic inflammatory cell activation and aggregation. Second, animal experiments have shown that tyrosine administration/ventricular injection reduces blood pressure in spontaneously hypertensive rats [59–61]. Yamaguchi et al. [62] reported a trend toward decreasing tyrosine levels in patients with metabolic syndrome, diabetes mellitus, dyslipidemia, and hypertension, and one possible explanation is the development of related diseases caused by decreasing tyrosine. These studies suggest that tyrosine has the potential to modulate aneurysm development and progression by lowering blood pressure. However, more recently, Anand et al. [63] found that higher tyrosine may be associated with atherosclerosis and higher cardiovascular risk.

In the inverse MR analysis, we found that aortic dissection reduced glycine. Glycine is a non-essential amino acid that is involved in protein synthesis, glutathione synthesis, purine and porphyrin production, one-carbon unit metabolism, conversion to serine, and oxidative energy supply [64]. Glycine is synthesized in the body mainly through three pathways. First, it can be synthesized via amino - acid conversion. Second, it is produced from the intermediates of sugar metabolism.

exposure.outcome	method	nsnp	pval	P.heterogeneity.	P.pleiotropy.	adjustp	OR(95%CI)
Glutamate levels & Abdominal aortic aneurysm	MR Egger	10	0.95057	0.91443			0.99(0.64 to 1.51)
	Weighted median	10	0.03315				0.76(0.59 to 0.98)
	Inverse variance weighted	10	0.00528	0.831	0.22342	0.10553	0.76(0.63 to 0.92)
	Simple mode	10	0.15075				0.75(0.52 to 1.07)
	Weighted mode	10	0.14934				0.76(0.54 to 1.07)
Glycine levels & Abdominal aortic aneurysm	MR Egger	29	0.04952	0.25535			0.65(0.43 to 0.98)
	Weighted median	29	0.03238				0.72(0.53 to 0.97)
	Inverse variance weighted	29	0.04110	0.24059	0.26956	0.41097	0.79(0.63 to 0.99)
	Simple mode	29	0.09576				0.66(0.41 to 1.06)
	Weighted mode	29	0.01488				0.67(0.49 to 0.91)
Valine levels & Thoracic aortic aneurysm	MR Egger	7	0.37949	0.04834			0.60(0.22 to 1.68)
	Weighted median	7	0.06014				0.69(0.47 to 1.02)
	Inverse variance weighted	7	0.01557	0.08258	0.90419	0.31137	0.57(0.36 to 0.90)
	Simple mode	7	0.39203				0.72(0.36 to 1.44)
	Weighted mode	7	0.12192				0.70(0.47 to 1.03)
Cysteine levels & Cerebral aneurysm, nonruptured	MR Egger	10	0.07401	0.26749			1.24(1.01 to 1.52)
	Weighted median	10	0.04502				1.23(1.00 to 1.50)
	Inverse variance weighted	10	0.03054	0.29699	0.46508	0.30536	1.17(1.01 to 1.35)
	Simple mode	10	0.19599				1.37(0.88 to 2.15)
	Weighted mode	10	0.03102				1.25(1.05 to 1.48)
Glutamine levels & Cerebral aneurysm, nonruptured	MR Egger	8	0.44775	0.29538			0.81(0.49 to 1.35)
	Weighted median	8	0.09795				0.76(0.55 to 1.05)
	Inverse variance weighted	8	0.02576	0.38779	0.76127	0.5153	0.75(0.59 to 0.97)
	Simple mode	8	0.10342				0.57(0.31 to 1.03)
	Weighted mode	8	0.09477				0.59(0.35 to 1.01)
Alanine levels & Other aneurysm	MR Egger	22	0.41718	0.76026			0.61(0.19 to 1.95)
	Weighted median	22	0.25003				0.69(0.37 to 1.29)
	Inverse variance weighted	22	0.02191	0.80866	0.97076	0.21915	0.60(0.39 to 0.93)
	Simple mode	22	0.72545				0.82(0.28 to 2.43)
	Weighted mode	22	0.58006				0.81(0.39 to 1.69)
Valine levels & Dissection of aorta	MR Egger	7	0.36122	0.44196			0.50(0.13 to 1.94)
	Weighted median	7	0.11369				0.52(0.23 to 1.17)
	Inverse variance weighted	7	0.03887	0.57093	0.9979	0.38866	0.50(0.26 to 0.97)
	Simple mode	7	0.10330				0.23(0.05 to 1.03)
	Weighted mode	7	0.17632				0.51(0.22 to 1.20)
Leucine levels & Dissection of aorta	MR Egger	9	0.16786	0.22935			0.24(0.04 to 1.48)
	Weighted median	9	0.07975				0.44(0.17 to 1.10)
	Inverse variance weighted	9	0.03709	0.26886	0.52105	0.74184	0.42(0.19 to 0.95)
	Simple mode	9	0.69555				1.52(0.20 to 11.44)
	Weighted mode	9	0.19778				0.45(0.15 to 1.37)
Tyrosine levels & Dissection of cerebral arteries, nonruptured	MR Egger	23	0.02939	0.84987			0.13(0.02 to 0.72)
	Weighted median	23	0.01889				0.19(0.05 to 0.76)
	Inverse variance weighted	23	0.00321	0.86081	0.45055	0.06411	0.22(0.08 to 0.60)
	Simple mode	23	0.10619				0.13(0.01 to 1.39)
	Weighted mode	23	0.02994				0.17(0.04 to 0.76)
Glutamate levels & Dissection of cerebral arteries, nonruptured	MR Egger	10	0.13955	0.45824			4.45(0.75 to 26.48)
	Weighted median	10	0.07318				2.77(0.91 to 8.45)
	Inverse variance weighted	10	0.01132	0.52457	0.57316	0.11317	2.75(1.26 to 6.03)
	Simple mode	10	0.47509				1.88(0.36 to 9.87)
	Weighted mode	10	0.22578				2.56(0.62 to 10.57)
Glutamine levels & Dissection of cerebral arteries, nonruptured	MR Egger	8	0.17922	0.6464			0.27(0.05 to 1.45)
	Weighted median	8	0.50165				0.67(0.21 to 2.15)
	Inverse variance weighted	8	0.04281	0.71793	0.60413	0.21407	0.41(0.17 to 0.97)
	Simple mode	8	0.73402				0.71(0.11 to 4.59)
	Weighted mode	8	0.77077				0.77(0.14 to 4.20)
Aspartate levels & Dissection of cerebral arteries, nonruptured	MR Egger	12	0.20515	0.19838			4.42(0.52 to 37.92)
	Weighted median	12	0.06128				2.48(0.96 to 6.43)
	Inverse variance weighted	12	0.01290	0.24588	0.6481	0.086	2.75(1.24 to 6.08)
	Simple mode	12	0.04287				6.09(1.30 to 28.58)
	Weighted mode	12	0.23048				2.06(0.67 to 6.29)

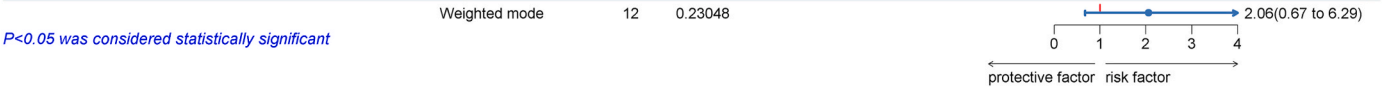

Fig. 5. Other potentially causal results in forward MR analyses ($P_{heterogeneity}$ refers to the *P* value of heterogeneity test; $P>0.05$ means no heterogeneity; $P_{Pleiotropy}$ refers to the P value of pleiotropy test; $P>0.05$ means no horizontal pleiotropy; adjustp refers to the *P* value corrected by FDR; snp: single-nucleotide polymorphism; nsnp: Number of SNPs; OR: odds ratio, 95 % CI: 95 % confidence interval).

Finally, in the liver, glycine can be synthesized by other substances through transamination and other reactions. For example, glyoxylate can react with glutamate and other amino acids under the action of transaminase to form glycine. Of the three methods, hepatic synthesis is the most important [65]. By analyzing the sources and metabolic pathways of glycine, we found that patients with aortic dissection are in a state of stress [66], which not only leads to a significant increase in energy expenditure, but also reduces the activity of various enzymes involved in glycine synthesis, which leads to a decrease in glycine synthesis. In particular, patients with aortic dissection often suffer from hepatic dysfunction [67], which is likely to further significantly inhibit glycine synthesis.

In a metabolomics study, Wang et al. [16] examined the changes in amino acid profiles during aortic dissection and reported that glycine

exposure.outcome	method	nsnp	pval	P.heterogeneity.	P.pleiotropy.	adjustp	OR(95%CI)
Dissection of aorta & Glycine levels	MR Egger	13	0.00972	0.49778			0.97(0.95 to 0.99)
	Weighted median	13	0.17557				0.99(0.98 to 1.00)
	Inverse variance weighted	13	0.00168	0.33415	0.10463	0.03351	0.98(0.98 to 0.99)
	Simple mode	13	0.82499				1.00(0.98 to 1.02)
	Weighted mode	13	0.58513				0.99(0.98 to 1.01)

P<0.05 was considered statistically significant

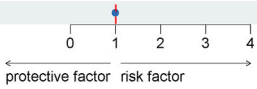

Fig. 6. MR results for aortic dissection and glycine level. $P_{heterogeneity}$ refers to the P value of the heterogeneity test; $P > 0.05$ means no heterogeneity; $P_{Pleiotropy}$ refers to the P value of the pleiotropy test; $P>0.05$ means no horizontal pleiotropy; adjustp refers to the P value corrected by FDR; snp: single-nucleotide polymorphism; nsnp: number of SNPs; OR: odds ratio, 95 % CI: 95 % confidence interval.

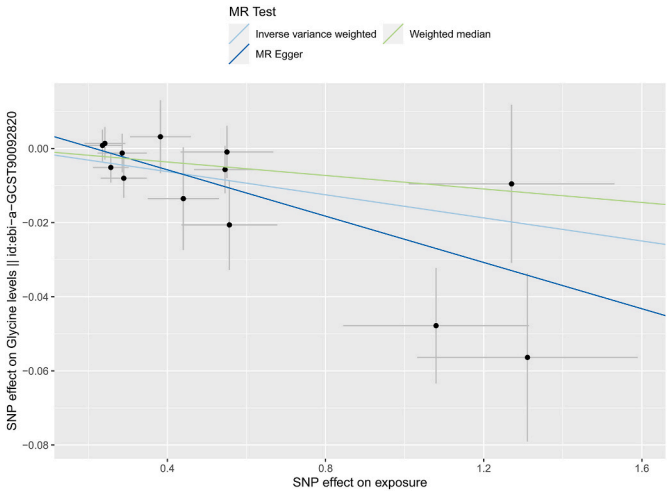

Fig. 7. Scatterplot of MR analysis of dissection of the aorta with glycine level. The horizontal axis represents the association of SNPs with aortic dissection, and the vertical axis represents the association of SNPs with glycine level (only IVW, MR−Egger and weighted median analyses).

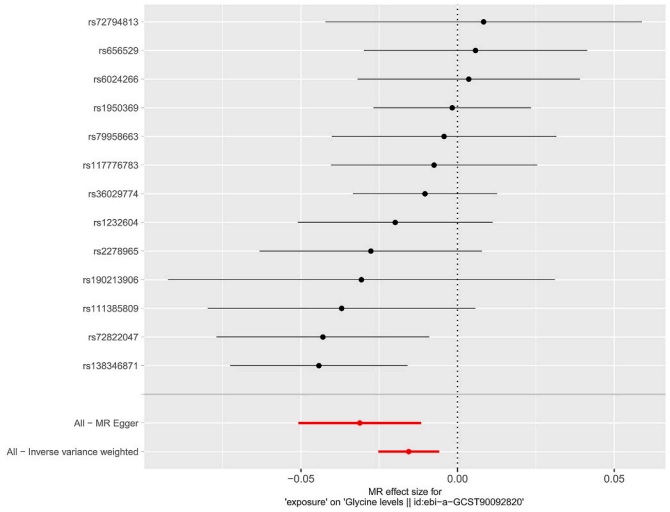

Fig. 8. Forest plot of aortic dissection with MR effect size for glycine level.

was reduced in humans with acute aortic dissection, and Wang et al. hypothesized that the change in glycine levels may be due to aortic dissection affecting vascular endothelial function, resulting in lower glycine levels. Some scholars, using MR to analyze the relationship between circulating amino acids and blood pressure, have found that higher blood pressure is causally associated with lower glycine [68]. We did not find any other studies on glycine and glycine metabolism in arterial dissection, but we did find studies on changes in other amino

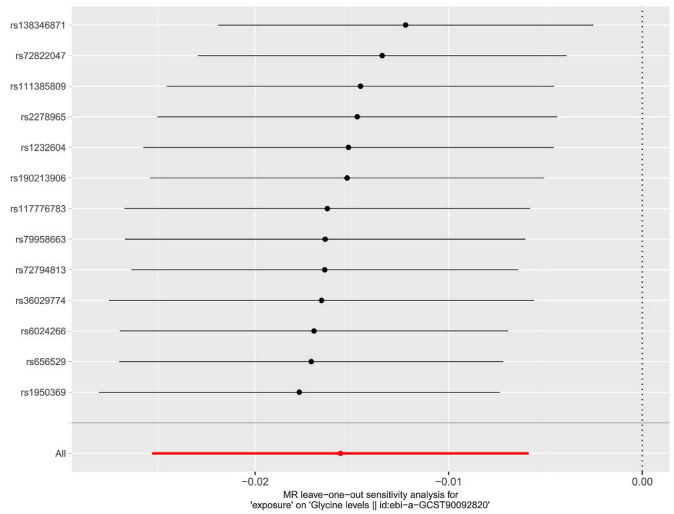

Fig. 9. "Leave-one-out" plot of MR analysis of aortic dissection versus glycine level (effect of individual SNPs on the results of the analysis).

acids in arterial dissection. A study by Fan et al. [69] found abnormalities in the tricarboxylic acid cycle and arginine and proline metabolism in patients with acute aortic dissection. Yu et al. [70] found that disturbances in the metabolism of branched-chain amino acids may affect the phenotypic transformation and inflammatory response of vascular wall smooth muscle cells leading to thoracic aortic dissection and that disturbances in the metabolism of branched-chain amino acids lead to an increase in their local concentration, whereas disturbances in the metabolism of branched-chain amino acids lead to an increase in their local concentration, although their study did not cover glycine. Their findings suggest to us that aortic dissection might affect amino acid levels in this way.

Combining the results of previous metabolomics and basic research, we used MR analysis to provide evidence for the interaction between circulating amino acids and arterial aneurysms and dissection. We found that circulating amino acids can be used as a detection indicator in the process of arterial aneurysms and dissection or to delay the development of arterial aneurysms and dissection by regulating the levels of circulating amino acids. Since early detection and treatment of arterial aneurysms and dissection are relatively homogeneous in clinical practice, the use of circulating amino acids to detect or delay the development of arterial aneurysms and dissection would greatly reduce the waste of medical resources, and the modulation of circulating amino acids could be used as a therapeutic tool for patients who are unsuitable for, or who refuse, surgical treatment.

There are several limitations to this study. First, it included only European populations, and we were unable to determine whether the findings could be generalized to other populations. Second, we found some heterogeneity in the sensitivity analyses (including valine and abdominal aortic aneurysm, alanine and aortic dissection, and glutamine and thoracic aortic aneurysm in the positive analyses); however,

exposure.outcome	method	nsnp	pval	P.heterogeneity.	P.pleiotropy.	adjustp	OR(95%CI)
Abdominal aortic aneurysm & Tyrosine levels	MR Egger	38	0.41803	0.00785			1.01(0.98 to 1.05)
	Weighted median	38	0.15191				1.01(1.00 to 1.03)
	Inverse variance weighted	38	0.04823	0.01052	0.99383	0.96456	1.01(1.00 to 1.03)
	Simple mode	38	0.39029				1.01(0.98 to 1.04)
	Weighted mode	38	0.40787				1.01(0.99 to 1.04)
Other aneurysm & Glycine levels	MR Egger	13	0.73853	0.30564			0.99(0.95 to 1.03)
	Weighted median	13	0.11297				1.01(1.00 to 1.03)
	Inverse variance weighted	13	0.02713	0.27016	0.25476	0.54267	1.02(1.00 to 1.03)
	Simple mode	13	0.36374				1.02(0.98 to 1.05)
	Weighted mode	13	0.34103				1.02(0.98 to 1.05)
Dissection of aorta & Methionine levels	MR Egger	16	0.02625	0.75771			1.10(1.02 to 1.18)
	Weighted median	16	0.12400				1.04(0.99 to 1.09)
	Inverse variance weighted	16	0.00624	0.68201	0.18975	0.06243	1.05(1.01 to 1.08)
	Simple mode	16	0.30355				1.04(0.96 to 1.13)
	Weighted mode	16	0.29005				1.04(0.97 to 1.12)

P<0.05 was considered statistically significant

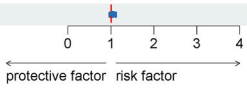

Fig. 10. Results of other reverse MR analyses that may be causally related. $P_{heterogeneity}$ refers to the P value of the heterogeneity test; P>0.05 means no heterogeneity; $P_{Pleiotropy}$ refers to the P value of the pleiotropy test; P>0.05 means no horizontal pleiotropy; adjustp refers to the P value corrected by FDR; snp: single-nucleotide polymorphism; nsnp: number of SNPs; OR: odds ratio, 95 % CI: 95 % confidence interval.

the presence of heterogeneity does not mean that the results of the analyses are not credible, as only abdominal aortic aneurysm affected tyrosine levels in our positive results, whereas the other results showed a small amount of heterogeneity in the negative results, which had a small impact on the overall results of our study. Finally, we only corrected one type of arterial aneurysm and dissection as a group when performing FDR correction.

5. Conclusion

In our bidirectional two-sample MR analysis, we found that tyrosine level was negatively correlated with other aneurysms and that aortic dissection reduced circulating glycine. Our findings support a possible interaction between circulating amino acid levels and arterial aneurysms and dissection.

CRediT authorship contribution statement

Xiaodong Li: Writing – original draft, Software, Resources, Methodology, Formal analysis. **Yarong Ma:** Writing – review & editing, Visualization, Resources, Data curation. **Qiulin Jiang:** Visualization, Resources. **Huizhi Zhan:** Visualization, Software, Resources. **Xiaolei Sun:** Writing – review & editing, Validation, Supervision, Investigation, Funding acquisition, Conceptualization.

Informed consent statement

Not applicable.

Abbreviations

BMI	Body mass index
CI	Confidence interval
EAF	Minor allele frequency
FDR	False discovery rate
GWAS	Genome-wide association studies
MR	Mendelian randomization
NCDs	Noncommunicable diseases
NO	Nitric oxide
OR	Odds ratio
SNP/snp	Single-nucleotide polymorphism

Data availability statement

All GWAS data were obtained from public databases. Detailed information on the GWAS data can be found in Table 1 in the Supplementary Information.

Ethics statements

All data in this study were obtained from public databases and were exempt from informed consent and ethical review.

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Declaration of competing interest

The authors declare no conflicts of interest.

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